ENCYCLOPEDIA OF PHARMACY PRACTICE AND CLINICAL PHARMACY

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Pharmacy Practice Research Methods

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CONTENTS OF ALL VOLUMES

VOLUME 2

VOLUME 3A

VOLUME 3B

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His other work includes *Economic Evaluation of Pharmacy Services*, *Pharmaceutical Prices in the 21st Century*, *Pharmaceutical Policies in Countries With Developing Healthcare Systems*, and *Pharmacy Practice Research Methods*. Published by Elsevier and Adis/Springer, the books are used in curriculum design, policy development, and for referral all around the globe. Professor Babar is also the Editor-in-Chief of *BMC Journal of Pharmaceutical Policy and Practice* and can be contacted at z.babar@hud.ac.uk.

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Ahmed Awaisu

Dr. Ahmed Awaisu is an Associate Professor of Clinical Pharmacy and Practice in the College of Pharmacy at Qatar University. He received his Bachelor of Pharmacy degree from Ahmadu Bello University Zaria, Nigeria in 1999, his masters and PhD degrees in Clinical Pharmacy from Universiti Sains Malaysia (USM) in 2004 and 2009, respectively. He is also a licensed pharmacist and has practiced in the hospital setting since 1999. Dr. Awaisu has a unique privilege of past academic experiences in international pharmacy degree programs. He has made substantial and tremendous contributions that impact teaching and learning, research, curriculum design, as well as professional development of students and healthcare practitioners in Qatar and other countries. He received the Qatar University Merit Award for Outstanding Faculty for 2016–17 Academic Year. He is a member of the American College of Clinical Pharmacy (ACCP), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), among others.

Professor Awaisu has extensive experience in the conduct of pharmacy practice and clinical research involving various types of study designs including case-control and cohort studies, quantitative surveys, mixed-methods designs, randomized control trials, and systematic reviews mostly on diabetes, cardiovascular diseases, tobacco dependence, and other chronic diseases. He has published over 100 peer-reviewed articles in internationally reputable pharmacy and healthcare journals and 10 book chapters related to the field of pharmacy. He has successfully supervised several postgraduate and undergraduate research projects, including MSc and PhD.

His research interest includes pharmacy practice especially pharmacists' expanded scope of practice, outcome-based research, pharmacoepidemiology and medication safety, and health promotion. Dr. Ahmed Awaisu has conducted training sessions and workshops on research methodology and biostatistics, drugs in sports, developing cognitive pharmacy services, and responding to symptoms in pharmacy practice. He presents regularly at continuing professional development programs for healthcare professionals in Qatar and other countries.

Timothy Chen

Professor Timothy Chen is a registered pharmacist and Professor of Medication Management, School of Pharmacy, The University of Sydney, Australia. Tim is nationally and internationally renowned for his research in medication management review and strategies to reduce medication related harm. Tim's research directly informed the Australian Government funded Home Medicines Review programme (MBS Item 903). Tim is an experienced educator and health services researcher, with experience in both community pharmacy and hospital pharmacy practice. Tim leads a productive research team (>160 peer-reviewed papers) and has completed main supervision of 15 PhDs, amongst other postgraduates. Tim has delivered >70 invited presentations at conferences and meetings across the globe. Tim has received university and national awards (Australian Government) for teaching, is an International Pharmaceutical Federation (FIP) Fellow (2016), and is President of the Social and Administrative Pharmacy Section, FIP.

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Louise Curley is a pharmacist and Senior Lecturer in Pharmacy practice at the School of Pharmacy. Louise's area of research focuses on the effects of recreational drug use in humans. She began her research as an undergraduate by investigating the subjective and electrophysiological effects of the Party Pill drugs using electroencephalography (EEG) and graduated with a PhD in pharmacy in 2012. Her thesis investigated the effects of the main constituents of "Party Pills" benzylpiperazine (BZP) and trifluromethylphenylpiperazine (TFMPP) on executive functioning and reward using functional magnetic resonance imaging (fMRI). Currently, her focus is developing new fMRI paradigms to investigate different aspects of risk, specifically by comparing populations of dependent versus non-dependent participants. Louise also has an interest in pharmacy practice research including innovative methods of teaching undergraduate students using different technologies and evaluating the effects of these innovations. She has recently been awarded the Butland Teaching Award: Innovation in Teaching.

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Dr. Danijela Gnjidic (BSc PhD MPH) is an NHMRC Dementia Leadership Fellow and Senior Lecturer at the School of Pharmacy, Faculty of Medicine and Health, University of Sydney. Her research expertise is in clinical and geriatric pharmacology, clinical studies on polypharmacy, high risk prescribing, and deprescribing in older people, pharmacoepidemiology, and the quality use of medicines. Danijela's academic track record includes 115 publications, 3-book chapters, with over 2500 citations on Scopus and $4M in research funding. Danijela was awarded the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Denis Wade Johnson & Johnson New Investigator Award in 2012. Internationally, Danijela's contribution to the filed was recognized with the 2018 American Society of Clinical Pharmacology and Therapeutics William B. Abrams award in Geriatric Clinical Pharmacology. Danijela is an Associate Editor of the *Journal of Alzheimer's Disease* and Academic Editor of the *PloS One Journal*.

Arijana Meštrović

Dr. sc Arijana Meštrović, MPharm, FFIP has been working as a community pharmacist and she was responsible for education, services, and competency development in the biggest pharmacy chain in Croatia. She is now independent consultant and educator in Pharma Expert international agency, providing lectures and workshops in CPD programs for pharmacists, pharmacy technicians, medical representatives, implementing new services in pharmacy chains, and teaching Social Pharmacy and Pharmaceutical Care at universities in Croatia and Cyprus as Assistant Professor. Her Doctor's degree is in biomedical sciences—competency development in pharmacy. Arijana serves as member of the International Services Program Advisory Group the Accreditation Council for Pharmacy Education (ACPE, USA), member of PCNE (Pharmaceutical Care Network of Europe), ExCo member of FIP (Pharmaceutical International Federation) Academic section, and WHO international expert consultant in Pharmaceutical care field. She used to serve as Co-Chair of the FIP World Congress Programme Committee, Expert Member of the Board of Pharmacy Practice at FIP. In Croatia, she is a leader in Croatian Pharmaceutical Society and Croatian Chamber of Pharmacist as a Lecturer and Co-author of New services model in community pharmacy practice. Arijana is dedicated to promoting competency-based education in CPD cycle, so her teaching usually addresses all components of competencies—knowledge, experience, and motivation. In collaboration with ACPE International Services, she has founded and implemented SMART Pharmacy CPD model for pharmacists in more than 12 countries all over the world. She was invited speaker and consultant in more than 40 countries.

Kath Ryan

Kath is Professor of Social Pharmacy at the University of Reading, and Visiting Professor at Bournemouth University, United Kingdom. She has 45 years of experience as a pharmacist in the pharmaceutical industry, community practice, and academia. She has held posts at the University of Otago, New Zealand; Bournemouth University, United Kingdom; La Trobe University, Melbourne, Australia; and the University of Reading, United Kingdom. She also has experience in academic nursing and midwifery. Her research interests include extended roles for pharmacists, especially in general practice; application of the behavioral sciences to pharmacy practice; personal experiences of health and illness; and public and patient involvement, engagement and participation in research, and the education of health professionals. She has expertise in quantitative, qualitative, and mixed methods research. She also has an interest in infant feeding,

particularly breastfeeding research, promotion and support, from lay, professional, and academic perspectives. She has been a health advisor to La Leche League International and La Leche League New Zealand. Kath has been on Scientific Committees for the International Social Pharmacy Workshops and the Australasian Pharmaceutical Sciences Association. She has consulted for the National Institutes of Health, USA; Canadian Forces; Health Technology Assessment, NHS UK; and the NZ Ministry of Health.

Kath has over 100 publications in peer-reviewed journals and several book chapters and reports. She produced two multimedia, online resources for Health Talk: women's experiences of breastfeeding in the United Kingdom, and people's experiences of ageing in Australia. She was a Founding Co-Director of Health Talk Australia.

FOREWORD

This first edition of the Encyclopedia of Pharmacy Practice and Clinical Pharmacy is one-of-a-kind and the most comprehensive amalgamation of an inclusive range of topics relevant to the pharmacy profession brought together to ensure safe and effective provision of pharmaceutical care across the world. Professor Zaheer Babar is a Professor in Medicines and Healthcare at the University of Huddersfield and also a global expert in pharmacy practice and pharmaceutical policy. He has united over hundreds of researchers and practitioners from across the world in a collaborative endeavor to provide a unique insight into current best practice and strategies for the future for the profession of pharmacy and its practice.

As patient care becomes more complex with advances in medicines and new developments in practice, including pharmacogenomics and pharmacoeconomics, there is an ever-evolving demand for practice and policy to keep pace. This encyclopedia contains 180 chapters, from all fields of pharmacy practice and clinical pharmacy, providing an in-depth coverage of modern approaches to the practice of pharmacy and highlighting the directions that will enable advancement to continue.

This encyclopedia includes definitions, concepts, theories, and applications of clinical pharmacy and pharmacy practice, providing background knowledge of the area that will provide valuable information for students of pharmacy practice. By providing relevant and topical summaries on a broad range of subjects, this book is also an excellent resource for those seeking information beyond their specific areas of expertise. In addition, the information contained in this book and its communication is of importance to a range of stakeholders, such as physicians and other healthcare professionals, health regulatory authorities, and the pharmaceutical and health industry, in addition to patients and their caregivers.

This encyclopedia also provides an excellent insight into pharmacy practice research and methods, as well as pharmacovigilance, pharmacoeconomics, social and administrative pharmacy, public health pharmacy, pharmaceutical systems research, the future of pharmacy, and new interventional models of pharmaceutical care. In addition, new treatments, algorithms, standard treatment guidelines, and pharmacotherapies regarding diseases and disorders are also covered.

The six key strands around which this encyclopedia is arranged pay testament to the complex and broad nature of the topic and are key topics of interest in pharmacy today and drivers of change for the future, for the benefit of public health across the world.

1. Pharmacy practice
2. Pharmacy practice research methods
3. Clinical pharmacy education, professional standards, and workforce
4. Clinical pharmacy and pharmacotherapy
5. Pharmacoepidemiology and pharmacovigilance
6. Socio-behavioral and administrative pharmacy

Topics range from the education and training of pharmacists, technicians and assistants to counterfeit medicines, pharmaceutical pricing policies, and implementation of change. As pharmacy practice evolves to meet the ever-more-complex health and medicines needs of patients, practitioners need an understanding of the social, political, and economic contexts across the world, noting particular highlights and challenges in developing countries to reach high standards. While it is acknowledged that there are differences between countries in terms of legislation, regulations, and guidelines (as detailed in individual chapters), the vision for the profession must be for a world in which everyone can access safe, effective, and affordable medicines and pharmaceutical care. The chapters include many examples of innovation and best practice in delivering health

services for the future, embracing additional roles beyond the supply of medicines in a robust manner underpinned by scientific and evidenced practice. Quantitative, qualitative, and mixed methods of pharmacy practice research are presented alongside expanded and evolving roles for pharmacists and where technology may take us. More quality research and coordinating efforts will bring a range of theoretical concepts and an evidence-based practice to the forefront of our activities, to focus a global workforce to meet the challenges of this exciting new era for pharmacy practice. This timely volume exemplifies the willingness and ability of the profession to work collaboratively on global issues, representing an unprecedented opportunity to shape the future of pharmacy practice.

With ever-increasing demands on healthcare systems, alongside growing financial pressures, it is essential that we work collaboratively with other pharmacists and the wider public health workforce who have the expertise, opportunity, and capacity to support and inform development.

In this context, this encyclopedia is an important resource with far-reaching impact on global healthcare community, and I hope this will be well liked by students, researchers, and academics.

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March 2019

PREFACE

Encyclopedia of Pharmacy Practice and Clinical Pharmacy

This encyclopedia has 180 chapters in total and it covers all domains of pharmacy practice and clinical pharmacy, including pharmacy practice research, socio-administrative and behavioral pharmacy, pharmacy education, pharmacoepidemiology, and the pharmacotherapy. One main question being asked is the need for this work. *What encyclopedia of pharmacy practice and clinical pharmacy adds to the current body of literature and what it means for global pharmacy community?* The answer to that is, though there were a number of books available on pharmacotherapy, however, current landscape lacks material comprehensively covering aspects, such as pharmacy practice, pharmacy practice research, social pharmacy, pharmacoepidemiology, pharmacy education, and the linking of clinical pharmacy with the health system. This encyclopedia aims to provide a collection of chapters on the above-mentioned areas. It also developed, synthesized knowledge, and provided policy guidance in the areas where there were gaps in the literature. For example, filling the gaps and including chapters on health systems, pharmaceutical policy, evidence and impact in pharmacy practice research, and on pharmacy education.

Here is a brief summary of what is being covered in its three volumes: Volume 1, 2, and 3.

Volume 1 includes chapters on pharmacy practice and pharmacy practice research. The pharmacy practice section starts with the historical evolution of pharmacy practice, medicines management, expanded roles of pharmacists, cognitive pharmacy services, community, and ambulatory pharmacy practice, ethics and regulation, and the new models of pharmaceutical care. There are also chapters on prescribing standards, practices, and competencies, interpersonal communication, evidence-based medicine, models on patient counseling, innovative pharmacy services, technology in pharmacy practice, and the pharmacist's role in substance misuse. The case studies chapters include pharmacy practice in high, low, and middle-income countries; United Kingdom, Western Europe, Australia, New Zealand, China, India, Gulf States, Philippines, and Portugal.

It is vital to understand and discuss the quality of evidence in pharmacy practice research, for example, how the evidence is produced and how it could impact on health outcomes. This is a niche section in the encyclopedia covering chapters on quantitative and qualitative methods in pharmacy practice research, quality of qualitative research, philosophical perspective and theories applied in pharmacy practice research, meta-synthesis, mixed methods research, discrete choice experiments, and the use of network meta-analysis in pharmacy practice. There are also chapters on evolution and definition of practice research, evidence, impact, and gaps in pharmacy practice research in low- and middle- and high-income countries.

Volume 2 covers pharmacovigilance, pharmacoepidemiology, and the socio-behavioral and administrative aspects of pharmacy and medicines use. The knowledge regarding pharmacoepidemiology and pharmacovigilance significantly impacts on medicines safety. The chapters included are on definitions, principles, and application of pharmacoepidemiology, descriptive and drug utilization studies, case-control and cohort studies, methodological challenges in epidemiological studies, data sources, and the issues related to medicines safety and comparative effectiveness research.

The socio-administrative and behavioral pharmacy section covers two broad aspects, namely, social pharmacy and pharmacy administration. Social pharmacy section covers concepts, development, and theories related to social pharmacy, public and patient engagement, sociology for pharmacists, implementation of change in pharmacy practice, and the social perspectives in addiction. There are also chapters on medicines adherence, compliance, and concordance, medication narratives, investigating medicines use among elderly

from a sociological perspective, changing nature of pharmacy as a profession, the impact of culture and religion on medicine use, and the issues related to disease mongering.

The understanding of health system is vital when promoting access and the use of medicines, hence in this context understanding administrative aspects of pharmacy are crucial. This section explores the dynamics between public policy, pharmaceutical policy, pharmacy practice, health systems, and patient-health outcomes. It covers a range of pharmaceutical policy and health system issues including access to biosimilars, access to high-cost medicines, counterfeit medicines, factors influencing pharmaceutical policy implementation, funding mechanisms for community pharmacy services, generic drug policies, national medicine policies, essential medicines list, pharmaceutical company sponsored medication assistance programs, and the pharmaceutical pricing policies.

Volume 3 covers clinical pharmacy education and pharmacotherapy. Pharmacy education training and the workforce have a great impact on global health. There are 25 chapters or more on pharmacists' training, and certification exploring the relationship between education, regulation, and practice. This is one of the largest collection of chapters covering pharmacy education and regulation at the global level. This includes chapters on pharmacist workforce, competency standards for clinical pharmacists, quality assurance in the pharmacy education, developing and evaluating clinical skills, continuing professional development, experiential education, inter-professional learning, leadership in pharmacy education, and the needs-based education. There are also case studies chapters on clinical pharmacy professional standards in the United States of America, Canada, the European Union, and in the low- and middle-income countries.

The pharmacotherapy section covers over 70 chapters discussing standard treatment guidelines, pharmacist's role in the central nervous system, infectious diseases, cardiovascular disorders, skin and endocrine disorders, musculoskeletal disorders, neurology, gastrointestinal disorders, and the respiratory disorders. The other key chapters include clinical pharmacy concepts, history, and development, clinical governance principles, pharmacokinetics, therapeutic guidelines, end of life care, palliative care, long-term care, fundamentals of pharmaceutical care planning, health outcomes and quality of life, the role of the pharmacist in the military and prisons, and the pharmacotherapy and deprescribing.

It has been a challenging task to complete this encyclopedia within a short span of 2 years. However, I am very thankful to the support of my section editors, reviewers, and hundreds of authors from all over of the world to come together and to contribute to this exciting project.

I hope you will like this effort and it will serve its purpose.

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Editor-in-Chief
Encyclopedia of Pharmacy Practice and Clinical Pharmacy

March 2019

To Danyal Zaheer

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Pharmacy Practice and Its Research: Evolution and Definitions

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The Development of Pharmacy Practice Research

Pharmacy has traditionally been portrayed as a profession responsible for formulating and dispensing medicines. In the early 1900s, pharmacists were experts in apothecary, *secundum artem*, i.e. the art for empirical or medicinal use. As clinical pharmacy emerged as a speciality discipline, its development was influenced by the introduction of hospital pharmacy in the 1920s (Gregory, 2013). In the 1960s, clinical pharmacy started evolving and this aspect of the profession became patient-oriented rather than product-based. The significance and recognition of clinical pharmacy services were first documented in the 1970s and 1980s, respectively (International Pharmaceutical Federation, 2019; World Health Organization, 2006). This marked the beginning of the professional integration of pharmacists' roles and enhanced interactions with medical practitioners and other healthcare professionals such as nurses, physiotherapists, and dieticians (Pearson, 2007; Zermansky et al., 2006).

In 1991, Hepler proposed the concept of program evaluation for clinical pharmacy services and made useful suggestions to improve research designs (Hepler, 1991). In 1992, Ascione et al. made recommendations and provided insightful information on improving research in pharmaceutical care (Ascione et al., 1992). As pharmacy practice research continued to mature at its own pace, there was a paucity of literature in pharmaceutical care research. In 1998, Kennie et al. published a critical analysis of 12 pharmaceutical care research studies conducted between 1992 and 1998 (Kennie et al., 1998), and recommended that there was scope for improvement in study design, reporting of outcomes, and the associated relationships with structure and process, as defined by the Economic, Clinical and Humanistic Outcomes (ECHO) model (Strand et al., 1990).

The Nuffield Foundation was the first organization to advocate pharmaceutical sociology in 1986 (Deb, 1986). A few years later in 1994, Nick Mays explained that the sociological theory should be utilized to explain pharmacy practice research (Mays, 1994); however, it was not until 2001 that Bissell, Traulsen, and Haugbolle formally introduced the concepts of sociology and its importance in pharmacy practice research (Bissell et al., 2001). Morrall (2001) defined the discipline of sociology as one that reveals the nature of health and illness (Morrall, 2001). Health and illness have been identified as social phenomena and thus are susceptible to sociological analysis; for example, mortality and morbidity vary depending on the social differences such as age, gender, and ethnicity. There seems to be a social pattern associated with all forms of illness, and the analysis and elaboration of such patterns signify the importance of sociology in pharmacy practice research (Bissell et al., 2001).

Part of being diagnosed with an illness may involve taking medicines and there are many social aspects to the use and beliefs about medicines. Practice of pharmacists, use of medicines by patients, interactions between pharmacists and their patients, and the organizational and institutional structure of pharmacy services have the potential for an analysis through sociological theories (Bissell et al., 2001). Bissell et al. (2001) strongly believed that these theories directly contribute to strength, diversity, and dynamism of pharmacy practice research (Bissell et al., 2001).

Evolution of Pharmacy Practice Research and Its Literature

Pharmacy practice research continued to evolve after 2000s, particularly in the United Kingdom, the United States, Australia, Canada, and Scandinavia. In 2002, Felicity Smith published a book entitled *Research Methods in Pharmacy Practice* outlining how to conduct a practice project (Smith, 2002). These research interests also shifted from pharmacotherapy to pharmaceutical services involving education and medication advice (Fish et al., 2002). In 2015, Zaheer Babar edited *Pharmacy Practice Research Methods, an edition* that discusses theories, methodologies, models, and techniques (Babar, 2015).

In 2019, Austin and Sutton published *Research Methods in Pharmacy Practice Methods and Applications Made Easy*. This book explains basic concepts, as well as case studies outlining practice (Austin and Sutton, 2019). The current encyclopedia of pharmacy

practice and clinical pharmacy is comprehensive and has sections on pharmacy practice, covering qualitative, quantitative techniques, mixed methods approaches, meta synthesis, as well as the chapters on evidence and impact.

Definition and Evolution of Pharmacy Practice

The definition of pharmacy practice varies; in the context of this chapter, it is imperative to understand what activities or practices constitute pharmacy practice. In order to bridge this gap, a methodical and structured review of literature was performed. A summary of definitions of pharmacy practice and pharmacy practice research are presented in Table 1 and Table 2 respectively. In the process of searching for a clear and universal definition of pharmacy practice, we have identified 11 documents describing pharmacy practice published. These were all published between 1990 and 2019. The seven definitions (7/13) defined pharmacy practice as a discipline within pharmacy that involves health or pharmacy services delivery. The reason for incorporating health services provision in the definition of pharmacy practice could be increasing number of services provided by the pharmacists in both hospital and community settings.

Table 1 Summary of pharmacy practice definitions

Reference	*Relevance/ Context*	*Term used*	*Definition*	*Reference type*
Collett and Aulton (1990)	United Kingdom	Pharmaceutical practice	Pharmaceutical practice embraces the techniques of preparation and presentation of medicines, a knowledge of the biological fate of drugs and medicines, the symptomatic treatment of minor ailments, and the abilities to relate to and communicate with the patient, the prescriber, and other members of the healthcare team	Book (*Pharmaceutical Practice*)
World Health Organization (1996)	Global	Good Pharmacy Practice (GPP)	GPP is the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care. The potential contribution of pharmacists extends to all levels of planning and provision of services. The mission of pharmacy practice is to provide medications and other healthcare products and services and to help people and society to make the best use of them (Pharmaceutical Care [PC] and GPP are largely identical, where GPP could be the way to implement PC)	WHO Report
RPSGB (1997a)	United Kingdom	Pharmaceutical service/ pharmacy practice	Five main areas in which pharmacy makes major contributions to health outcomes are management of prescribed medicines, management of chronic conditions, management of common ailments, promotion and support of healthy lifestyles, and advice and support for other healthcare professionals	RPSGB Report
Horne (2001)	United Kingdom	Pharmacy practice	Pharmacy practice serves to facilitate the appropriate use of medicines	Book (*Pharmacy Practice*)
Taylor and Harding (2001)	United Kingdom	Effective pharmacy practice	Effective pharmacy practice requires an understanding of the social context within which pharmacy is practiced, recognizing the particular needs and circumstances of the users of pharmaceutical services, and of pharmacy's place within health service provision	Book (*Pharmacy Practice*)
FIP/WHO (2011)	Global	Pharmacy practice	WHO described the mission of pharmacy practice as being "to provide medicines and other healthcare products and services and to help people and society to make the best use of them"	WHO Technical Report (Joint WHO/FIP Guidelines on GPP)

Table 1 Summary of pharmacy practice definitions (*cont.*)

Reference	*Relevance/ Context*	*Term used*	*Definition*	*Reference type*
American Pharmacy Association Academy of Pharmaceutical Research and Science (1998)	United States	Pharmacy practice activity	The PPAC is focused primarily on activities of licensed, practicing pharmacists across the continuum of healthcare settings. The classification captures a range of activities from traditional dispensing to direct patient care services. These include ensuring appropriate therapy and outcomes, dispensing medication and devices, health promotion and disease prevention, and health systems management	Pharmacy Practice Activity Classification (PPAC, 2019) Project
Whalley (2008)	United Kingdom	Pharmacy practice	Pharmacy practice is a discipline within pharmacy that involves developing the professional roles of the pharmacist. The critical parts of the discipline are understanding healthcare systems and public health	Book (*Foundation in Pharmacy Practice*)
Council on Credentialing in Pharmacy (2009) and National Association of Boards of Pharmacy (NABP) (2019)	United States	Pharmacy practice	NABP defines the pharmacy practice as the interpretation, evaluation, and implementation of Medical Orders; the Dispensing of Prescription Drug Orders; participation in Drug and Device selection; Drug Administration; Drug Regimen Review; the Practice of Telepharmacy within and across state lines; Drug or Drug-related research; the provision of Patient Counseling; the provision of those acts or services necessary to provide Pharmacist Care in all areas of patient care, including Primary Care and Collaborative Pharmacy Practice; and the responsibility for Compounding and Labeling of Drugs and Devices, proper and safe storage of Drugs and Devices, and maintenance of required records. The practice of pharmacy also includes continually optimizing patient safety and quality of services through effective use of emerging technologies and competency-based training	Reports (Council on Credentialing in Pharmacy, 2009; National Association of Boards of Pharmacy, 2019)
Moullin et al. (2013)	Australia	Pharmacy service/ pharmacy practice	A professional pharmacy service is defined as "an action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population, or other health professional to optimize the process of care, with the aim to improve health outcomes and the value of healthcare"	Journal article
Almarsdottir et al. (2014)	Europe	Pharmacy practice	Pharmacy practice and social pharmacy are two important contemporary research areas within the field of pharmaceutical sciences, studying the role of medicines, patients, and pharmacists within the healthcare sector and society at large	Journal article
Fathelrahman et al. (2016)	Developing countries	Pharmacy practice	It is a description of what pharmacists normally do while acting in a professional context and it represents also the essential components and basic requirements for performing every job or action related to pharmacy, including where and how pharmacists do it	Book (*Pharmacy Practice in Developing Countries*)
Scahill and Babar (2017)	Global	Pharmaceutical Practice	Pharmaceutical practice encompasses everything, which is related to availability of medicines, access, and use at the individual and the population levels. This term encapsulates the research, development, formulation, distribution, access, and clinical use of medicines. It incorporates the human capital required to deliver pharmacy services and the impact on end users of pharmaceutical products and services	Journal article

Table 2 Summary of pharmacy practice research definitions

Reference	*Relevance*	*Term used*	*Definition*	*Reference Type*
Royal Pharmaceutical Society/King's Fund (RPSGB, 1997b)	United Kingdom	Pharmacy practice research	A useful definition of pharmacy practice research has been provided by the King's Fund (1997), which describes it as "research which attempts to inform and understand pharmacy and the way in which it is practiced, in order to support the objectives of pharmacy practice and to ensure that pharmacists' knowledge and skills are used to best effect in solving the problems of the health service and meeting the health needs of the population"	RPSGB Report
Smith (2010)	Global	Pharmacy practice research	Pharmacy practice research is used as an umbrella term for research into pharmacy services, medicines use, professional practice, and education. Research into the practice of pharmacy and the use of medicines is viewed as a branch of health services research	Book (*Conducting your Pharmacy Practice Research Project*)
Koster et al. (2014)/The Utrecht Pharmacy Practice network for Education and Research (2014)	Europe	Pharmacy practice research	Pharmacy practice research is necessary to generate evidence for further development of pharmacy services Pharmacy practice research can be divided in two main themes: (1) research related to the pharmacy as data source (e.g., studies regarding prescribing behavior or medication use) or (2) research related to the pharmacy as object of research (e.g., studies regarding internal pharmacy procedures, guideline adherence or quality of patient counseling)	Pharmacy Practice network for Education and Research Report
Almarsdottir et al. (2014)	Europe	Pharmacy practice research	Research within the field of pharmaceutical sciences, combining natural sciences with social and humanistic research to study the role of medicines, patients, and pharmacists within the healthcare sector and society at large	Journal article
Awaisu and Alsalimy (2015)	Global	Pharmacy practice research	"Pharmacy practice research" to be any research activity that pertains pharmacy practice or patient care, including, but not limited to, clinical and outcome research, health services research, and comparative effectiveness research	Journal article
Bond (2015)	Global	Pharmacy practice research	Pharmacy practice research, a sub-speciality within health services research, focuses on exploring how and why people access pharmacy services, the costs of pharmacy services, and the outcomes for patients as a result of these services, and comparison of these costs and outcomes compared to the same or similar services delivered by other providers	Book (*Pharmacy Practice Research Methods*)
Almarsdottir and Babar (2016)	Global	Pharmacy practice research	Many pharmacy practice researchers define their work as part of drug utilization research (DUR), clinical pharmacy, social pharmacy, pharmaceutical policy, health services research, or health economics	Journal article
Dolovich and Tsuyuki (2016)/Canadian Pharmacists Association/ Canadian Pharmacy Practice Research Group (2016)	Canada	Pharmacy practice research	Pharmacy practice research is defined as a component of health services research that focuses on the assessment and evaluation of pharmacy practice. It includes studies that evaluate pharmacists' roles in a variety of capacities. These studies include systems research, patient-centered research, and community-based research that encompasses a variety of determinants of health and their influence on patient outcomes and population health	Journal article and professional group
FIP Pharmacy Practice Research Special Interest Group (2019)	Global	Pharmacy practice research	Pharmacy practice research looks at the impact of the practice of pharmacy on healthcare systems, medicines use, and patient care. Its scope has expanded over the past 50 years to encompass aspects such as the clinical, behavioral, economic, and humanistic implications of the pharmacy practice, as well as change management and implementation	Special interest group

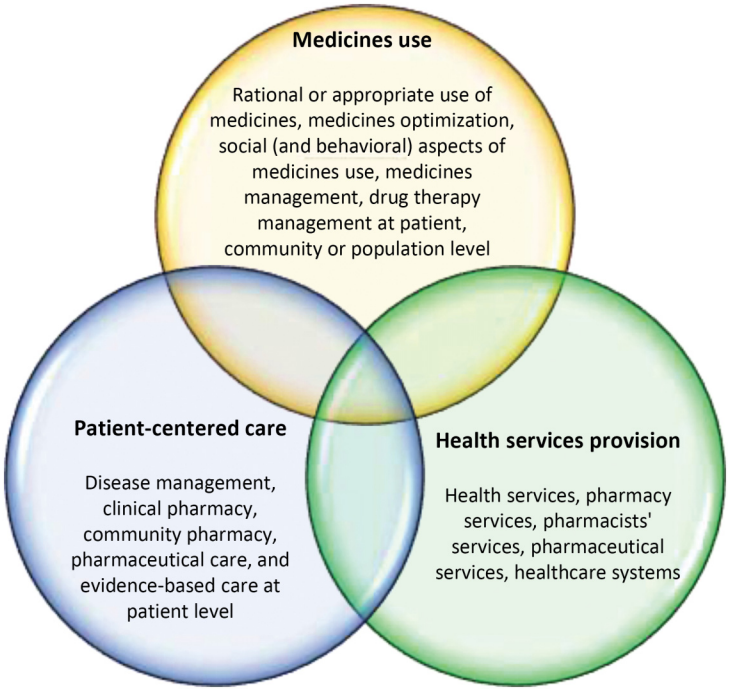

Figure 1 Diagrammatic representation of the different facets of pharmacy practice and its research.

The majority of the authors have used the term "pharmacy practice" except for a few (Collett and Aulton, 1990; Scahill and Babar, 2017) who used the term "pharmaceutical practice". The major difference between the two terms is the incorporation of pharmaceutical sciences in the definition of pharmaceutical practice.

The pharmacy practice definitions also vary according to who defines it and how they are being defined in a healthcare system. For example, in the United States, clinical pharmacy seems to be more a popular term or practice and is defined by the American College of Clinical Pharmacy as "*a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention*" (American College of Clinical Pharmacy, 2008). In the United Kingdom, 'health services delivery' and 'medicines optimization' are more commonly used. Health services and medicines management were adopted and are widely promoted by the World Health Organization. Fig. 1 presents the three major elements (themes) which contribute to pharmacy practice and pharmacy practice research, namely medicines use, patient-centered care and health services provision.

Conclusion

It is commendable that pharmacy practice research has gained recognition in the international arena. Moving forward, pharmacy practice research should be performed in a manner which captures quality evidence on the use of medicines, patient-centered care, and provision of health services. These goals provide all the more reason to collaborate with other healthcare professionals and initiate new health services, with input from stakeholders and supported by research evidence.

List of Abbreviations

ECHO	Economic, Clinical and Humanistic Outcomes
FIP	International Pharmaceutical Federation
GPP	Good Pharmacy Practice
NABP	National Association of Boards of Pharmacy
PC	Pharmaceutical Care
RPSGB	Royal Pharmaceutical Society of Great Britain

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Research Designs and Methodologies Related to Pharmacy Practice

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Learning Objectives

- Discuss the value of pharmacy practice research to evidence-based practice and policy.
- Describe the classifications and types of study designs commonly used in pharmacy practice research.
- Discuss the concepts and structure of common study designs used in pharmacy practice research including experimental, quasi-experimental, observational, qualitative, and mixed method designs.
- Discuss the important considerations for conducting pharmacy practice research in terms of study design, data collection, data analyses, and ethical considerations.

Introduction to Research Methodologies Used in Pharmacy Practice

The mission of pharmacy profession and the role of pharmacists in healthcare have evolved toward patient-centered care in the last few decades. Pharmacists with their expertise in drug therapy and accessibility to the public have unprecedented opportunities to assume increasing responsibility for direct patient care (Bond, 2006). New cognitive pharmaceutical services and new roles for pharmacists continue to emerge.

In the era of evidence-based practice and health services, it is not just adequate to propose those new pharmacy services or new roles without evidence of their benefit (Awaisu and Alsalimy, 2015; Bond, 2006). New pharmacy services and new roles must be proven to be feasible, acceptable, cost-effective, and increase health outcomes. Pharmacy practice research provides such evidence and can confirm the value of a new service, inform policy, and result in practice changes (Bond, 2006; Chen and Hughes, 2016). Research evidence should be used to identify new areas for improved health service delivery and rigorously

evaluate new services. The research used to generate such evidence should be grounded in robust and rigorous methodologies (Chen and Hughes, 2016). Traditionally, common quantitative and qualitative methods such as randomized controlled trials, cohort study, case control study, questionnaire-based surveys, and phenomenology using qualitative interviews have been used in pharmacy. However, in recent years, novel and more complex methods are being developed and utilized. Pharmacy practice researchers need to know how these old and new methodological approaches should be selected, applied, and interpreted in addressing research problems.

Various study designs, including, but not limited to experimental, quasi-experimental, observational, qualitative, and mixed method designs, have been used in pharmacy practice research. Furthermore, different classification systems (e.g., quantitative vs. qualitative, experimental vs. observational, descriptive vs. analytical study designs) have been used in the literature. The choice of a study design to answer a research question in pharmacy practice research is driven by several factors, including the type of the research question or the research hypothesis, expertise of the investigator, availability of data, and funding opportunities. Pharmacy practice researchers need to be competent in the selection, design, application, and interpretation of these methodological and analytical approaches. Today, many of the research methods used in pharmacy practice research have been adapted from fields such as sociology, anthropology, psychology, economics, and other disciplines. This paradigm shift has led to a greater emphasis on the appropriate choice of a specific research design or method to answer a specific research question (Chen and Hughes, 2016). Consequently, pharmacy practice researchers should place an emphasis on the reliability of the methods selected, the correct interpretation of their findings, the testing of a specific hypothesis, and the internal validity of their data, among other considerations. Novice and early career researchers should be familiar and have sound foundation in a variety of methods applied in pharmacy practice research, which will be covered in this chapter and other chapters in this Encyclopedia. We do believe that more experienced researchers should focus on certain methods in order to advance research in our discipline.

Core Quantitative and Qualitative Approaches Used in Pharmacy Practice Research

Traditionally, core quantitative approaches used in pharmacy practice research include nonexperiments, quasi-experimental designs, and true experimental designs such as prospective randomized controlled intervention trials. Nonexperiments also include observational study designs that are often described as pharmacoepidemiologic study designs such as case–control study, cohort study, nested case–control study, and cross-sectional study (Etminan, 2004; Etminan and Samii, 2004). In recent years, conventional qualitative approaches and their philosophical paradigms are increasingly been used in pharmacy. These include the five qualitative approaches to inquiry: narrative research, phenomenology, grounded theory, ethnography, and case study. These qualitative methods are often difficult for pharmacy practice researchers to comprehend, and researchers tend to describe the methods of data collection such as individual interviews and focus group discussions as qualitative methods of inquiry. These data collection methods are briefly described later in this chapter, among others. Furthermore, there is an increasing importance on the appropriate selection and use of mixed method approach (Hadi et al., 2013; Hadi and Closs, 2016a, 2016b), which are often designed and applied wrongly. Finally, it is worthwhile to be familiar with novel research methodologies such as discrete choice experiments, Delphi techniques, simulated client technique, and nominal group techniques, which fall between quantitative and qualitative approaches, often with no clear differentiation on where they belong. Although called "novel" in the context of this chapter, these methods are not new in other relevant disciplines, but new and not commonly used in pharmacy practice research.

Research Question and Selection of Study Design

Pharmacy practice researchers begin by conception of a research idea or identifying a research question and defining a hypothesis based on the question. The researcher then selects a study design that will be suitable to answer the research question. The study design should be appropriately selected prior to initiation of any research investigation. Selecting an inappropriate study design may potentially undermine the validity of a study in its entirety. Investigators are encouraged to critically think about the possible study designs to ensure that the research question is adequately addressed and should be able to adequately justify their choice. These study designs have been variously classified and one common classification system is quantitative vs. qualitative study designs. Study designs play a major role in determining the scientific value of research studies. Inappropriate choice of a study design is impossible to correct after completion of the study. Therefore, thorough planning is required to avoid unconvincing results and invalid conclusions. Good understanding of basic study design concepts will aid researchers in conducting robust and rigorous practice-based research. This chapter introduces the structure and the fundamentals of common study designs used in pharmacy practice research and discusses the important considerations for conducting pharmacy practice research in terms of study design, data collection, data analyses, and ethical considerations.

Classification of Research Methodologies Used in Pharmacy Practice

Various classifications for research designs and methods used in pharmacy practice have been used in the literature. The following are some of the approaches for the classification of research designs:

1. Classification based on time orientation: Retrospective vs. prospective designs

a. Retrospective design—A retrospective study design observes what has happened in the past. It begins and ends in the present. This design involves a major limitation as it looks to collect information about events that occurred in the past. An example of this design is retrospective case-control study.
Case example: Investigators were looking for the association between acute myocardial infarction and smoking status, type of tobacco, amount of smoke, etc. (Teo et al., 2006). Another example of a case–control study from published literature is the study investigating the association between the use of phenylpropanolamine and the risk of hemorrhagic stroke (Kernan et al., 2000).
b. Prospective design—A prospective study design begins in the present and progresses forward, collecting data from subjects whose outcomes lie in the future. An example of this design is prospective cohort study.
Case example: Investigators were interested to determine the long-term effectiveness of influenza vaccines in elderly people; they recruited cohorts of vaccinated and unvaccinated community-dwelling elderly (Nichol et al., 2007).

2. Classification based on study purpose: Descriptive vs. analytical designs

a. Descriptive design—A descriptive study describes a population/sample in terms of distribution of the variables, and frequency of outcomes of interest. Unlike analytical studies that include control (comparison) group, descriptive studies do not include a comparison group. Descriptive studies include case reports, case series reports, cross-sectional studies, surveillance studies, and ecological studies.
Case example: A case report was written by a physician who contracted Severe Acute Respiratory Syndrome (SARS) during an outbreak in Hong Kong (Wu and Sung, 2003). Another example is an ecological study examining diet and sunlight as risks for prostate cancer mortality (Colli and Colli, 2006). Chim et al. conducted a large population-based survey in Australia to determine what community members think about the factors that do and should influence government spending on prescribed medicines (Chim et al., 2017).
b. Analytical design—An analytical study identifies risk factors, associated factors, mediating factors, etc. Analytical studies are either experimental or observational. Case–control and cohort studies are types of observational studies.
Case example: A group of investigators carried out a study to establish an association between the use of traditional eye medicines (TEM) and corneal ulcers. In this case, both case–control and cohort study designs are applicable. In an example of a case control study, Archibugi et al. aimed to investigate the association between aspirin and statin exclusive and combined and pancreatic ductal adenocarcinoma occurrence (Archibugi et al., 2017). Another example of a cohort study is a study carried out by Wei et al. in which they investigated whether or not acid-suppression medicines increased the risk of bacterial gastroenteritis (Wei et al., 2017).

3. Classification based on investigator orientation: Experimental vs. quasi-experimental vs. observational designs

a. Experimental design—In experimental design (also known as interventional design), the investigator performs an intervention and evaluates cause and effect relationships.
Case examples: Investigators conducted a study about the newer versus older antihypertensive agents in African hypertensive patients (NOAAH) trial (nct01030458) to compare the efficacy of single-pill combinations of newer versus older antihypertensive agents (i.e., a single-pill combination of newer drugs, not involving a diuretic, with a combination of older drugs including a diuretic) (Odili et al., 2012). In a crossover design, a group of investigators evaluated the effect of spironolactone on nonresolving central serous chorioretinopathy (Bousquet et al., 2015).
b. Quasi-experimental design—The quasi-experimental design is very similar to the true experimental design described above and it involves an intervention. The design has been employed when randomization is inappropriate or impossible, especially when implementing complex interventions.
Case examples: Prashanth et al. aimed to understand if (and how) a package of interventions targeting primary health centers and community participation platforms affect utilization and access to generic medicines for people with noncommunicable diseases using quasi-experimental design approach (Prashanth et al., 2016).
c. Observational design—It involves only observation of natural phenomena and does not involve investigator intervention. Typically, this study design investigates associations and not causation. Examples include cohort study and case–control study. These studies can explore an association between a pharmacologic agent and a disease of interest. Case examples: Please see previous examples of these.

4. Classification based on question orientation: Quantitative vs. qualitative vs. mixed method designs

a. Quantitative design—This is based on measurement of quantity and it is applicable to phenomenon that can be quantified (i.e., expressed in terms of numbers).
Case examples: Please see experimental studies, and case–control and cohort study designs.
b. Qualitative design—Qualitative research is concerned with qualitative phenomenon (i.e., a phenomenon relating to or involving quality).
Case examples: Investigators in Canada explored the lived experiences of youth who are prescribed antipsychotics by conducting interpretative phenomenology study (Murphy et al., 2015).

c. Mixed method designs—Mixed method design brings together qualitative and quantitative methodologies within a single study to answer or understand a research problem (Hadi et al., 2013).
Case examples: Shiyanbola et al. combined focus group discussion with a survey tool to investigate patients' perceived value and use of quality measures in evaluating and choosing community pharmacies (Shiyanbola and Mort, 2015).

5. Classification of pharmacoepidemiologic study designs
Below is a brief description of traditional and novel pharmacoepidemiologic study designs. Several examples of pharmacoepidemiologic study designs are provided above. Some descriptive studies including case reports, case series, and ecological studies will not be described in this chapter.

a. Case–control studies—In this design, patients (those who develop the disease or outcome of interest) are identified and control patients (those who do not develop the disease or outcome of interest) are sampled at random from the original cohort that gives rise to the cases (Etminan and Samii, 2004; Newman et al., 2013). The distribution of exposure to certain risk factors between the cases and the controls is then explored, and an odds ratio (OR) is calculated.
b. Cohort studies—This can be described as a study in which a group of exposed subjects and a group of unexposed subjects are followed over time and the incidence of the disease or outcome of interest in the exposed group is compared with that in the unexposed group (Etminan and Samii, 2004; Hulley et al., 2013).
c. Case-crossover studies—The case-crossover may be considered comparable to a crossover randomized controlled trial in which the patients act as their own control (Etminan and Samii, 2004). Pattern of exposure among the cases is compared between event time and control time. The between-patient confounding that occurs in a classic case-control study is circumvented in this design. Tubiana et al. evaluated the role of antibiotic prophylaxis and assessed the relation between invasive dental procedures and oral streptococcal infective endocarditis, using a nationwide population-based cohort and a case-crossover study design (Tubiana et al., 2017).
d. Case–time control studies—This design is an extension of the case-crossover design, but includes a control group (Etminan and Samii, 2004). A group of researchers assessed medication-related hospitalization. They used the case–time control study design to investigate the associations between 12 high risk medication categories (e.g., antidiabetic agents, diuretics, benzodiazepine hypnotics) and unplanned hospitalizations (Lin et al., 2017).
e. Nested case–control studies—In this design, a cohort of individuals is followed during certain time periods until a certain outcome is reached and the analysis is conducted as a case–control study in which cases are matched to only a sample of control subjects (Etminan, 2004). de Jong et al. examined the association between interferon-β (IFN-β) and potential adverse events using population-based health administrative data in Canada (De Jong et al., 2017).
f. Cross-sectional studies—In this type of study, the investigator measures the outcome of interest and the exposures among the study participants at the same time (Hulley et al., 2013; Setia, 2016b). It provides a snapshot of a situation for a particular period.

Quantitative Research Designs in Pharmacy Practice

A wide range of quantitative methods are commonly applied in pharmacy practice research. These methods are widely used in published pharmacy practice literature to explore appropriateness of medicines use, appropriateness and quality of prescribing, and medication safety, through analyzing existing datasets, direct observation, or self-report (Green and Norris, 2015). Pharmacy practice research questions also seek to determine the knowledge, behaviors, attitudes, and practices of pharmacists, other healthcare providers, patients, policy-makers, regulators, and the general public. Quantitative methods are also used in evaluating the effect of new pharmacy services and interventions to improve medicines use. These practice research projects provide valuable insights about how medicines are used, and how to maximize their benefits and minimize their harmful effects. In the context of this chapter, quantitative study designs will be broadly classified into three: (1) observational, (2) experimental and quasi experimental, and (3) other designs.

Observational Study Designs

Pharmacoepidemiology is a "relatively new science that explores drug efficacy or toxicity using large observational study designs" (Etminan, 2004; Etminan and Samii, 2004). These study designs explore drug use studies that usually cannot be answered using randomized controlled trials or other experimental designs. In several instances, experimental study designs may not be suitable or feasible; in such circumstances, observational study designs are applied (Cummings et al., 2013). As the name implies, observational studies involve merely observing the subjects in a noncontrolled setting, without investigator intervention or manipulating other aspects of the study. Therefore, observational studies are nonexperimental. The observation of the variables of interest can be prospective, retrospective, or current depending on the type of the observational study.

In pharmacoepidemiology and other areas of pharmacy practice, researchers are often interested in measuring the relationships between exposure to a drug and its efficacy, toxicity, or other outcomes of interest using observational study designs. It is worthwhile to note that observational study designs investigate association, but, in most cases, not causation. Here, we provide descriptions of some commonly used study designs in pharmacoepidemiology and pharmacy practice research in general.

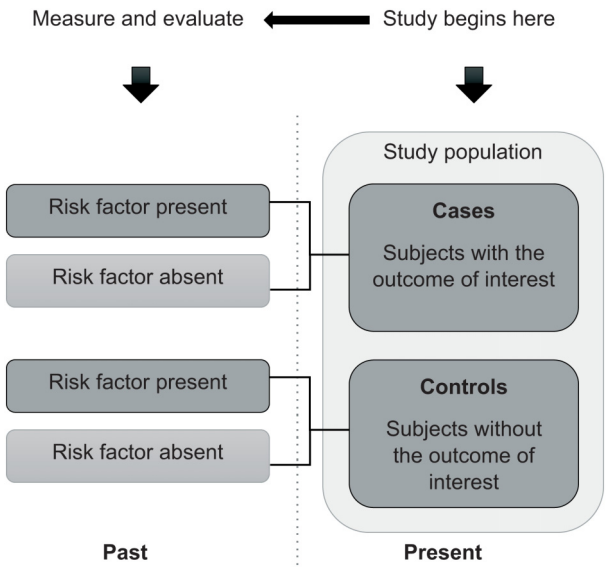

Figure 1 Case–control study design.

Case–Control Studies

Case–control study design is used to determine association between risk factors or exposures and outcomes. It is a useful design to study exposures in rare diseases or diseases that take long time to develop (Newman et al., 2013). It investigates exposures in individuals with and those without the outcome of interest. Nevertheless, case–control studies can help to identify harmful or beneficial exposures. Furthermore, the outcome of interest can be undesirable (e.g., mortality) or desirable (e.g., microbiological cure). As the name suggests, in a case–control study design, there are two groups of subjects: (1) cases (individuals with the outcome of interest) and (2) controls (individuals without the outcome of interest) (Newman et al., 2013). Cases are randomly selected based on prespecified eligibility criteria from a population of interest. Appropriate representative controls for the cases selected are then identified. The researchers then retrospectively investigate possible exposures to the risk factor. **Fig. 1** represents a schematic diagram of a case–control study.

Case–control studies are relatively inexpensive, less time-consuming to conduct, allow investigation of several possible exposures or associations, and are suitable for rare diseases. Selection of the control group is a critical component of case–control studies. Case–control studies have several drawbacks: confounding must be controlled, subject to recall, observation, and selection biases.

OR is the measure of association used for the analysis of case–control studies. This is defined as the odds of exposure to a factor in those with a condition or disease compared with those who do not have the condition or disease.

Cohort Studies

Similar to case–control studies, cohort studies determine an association between exposures/factors and development of an outcome of interest. As previously described, a cohort study is a study in which a group of exposed subjects and a group of unexposed subjects are followed over time to measure and compare the rate of a disease or an outcome of interest in both groups (Etminan and Samii, 2004; Hulley et al., 2013). A cohort study can be prospective (most common) or retrospective. While a case–control study begins with patients with and those without the outcome of interest (e.g., diseased and nondiseased patients), a cohort study begins with exposed and unexposed patients (e.g., patients with and those without certain risk factor) (Hulley et al., 2013; Setia, 2016a). In a cohort study, both the exposed and the unexposed subjects are members of a larger cohort in which subjects may enter and exit the cohort at different periods in time (Etminan and Samii, 2004; Hulley et al., 2013).

Typically, a cohort study should have a defined time zero, which is defined as the time of entry into the cohort (Etminan and Samii, 2004). The cohort (a group of exposed and unexposed subjects, who are free of the outcome at time zero) is followed for a certain period until the outcome of interest occurs. In addition, information or data related to all potential confounders or covariates should also be collected as failure to account for these can bias the results and over- or underestimates the risk estimate. There are two types of cohort studies: retrospective cohort and prospective cohort studies.

Retrospective cohort study, also known as historical cohort study, begins and ends in the present, while looking backward to collect information about exposure that occurred in the past (**Fig. 2**). Historical cohort studies are relatively less time-consuming and less expensive than prospective cohort studies (Etminan and Samii, 2004; Hulley et al., 2013; Setia, 2016a). In addition, there is no loss to follow-up and researchers can investigate issues not amenable to intervention study designs. However, these studies are only as good as the data available, the investigator has limited control of confounding variables, and it is prone to recall bias.

On the other hand, prospective cohort study, also known as longitudinal cohort study, begins in the present and progresses forward, collecting data from enrolled subjects whose outcomes fall in the future (Etminan and Samii, 2004; Hulley et al., 2013;

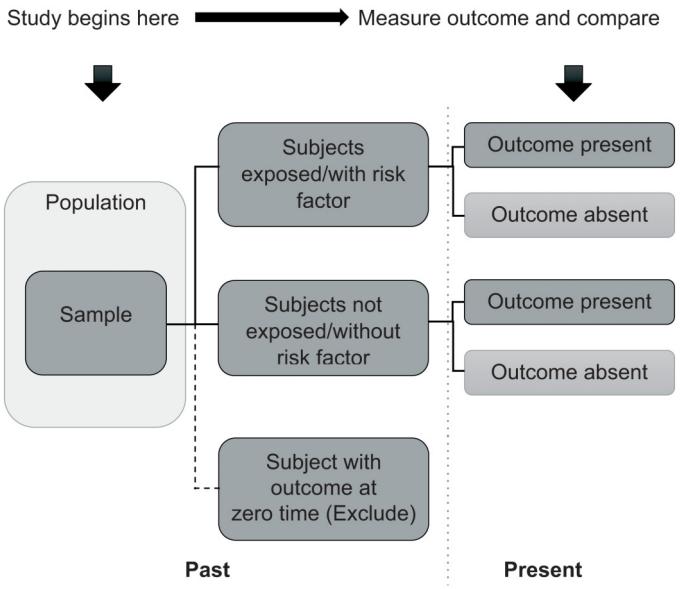

Figure 2 Retrospective (historical) cohort study design.

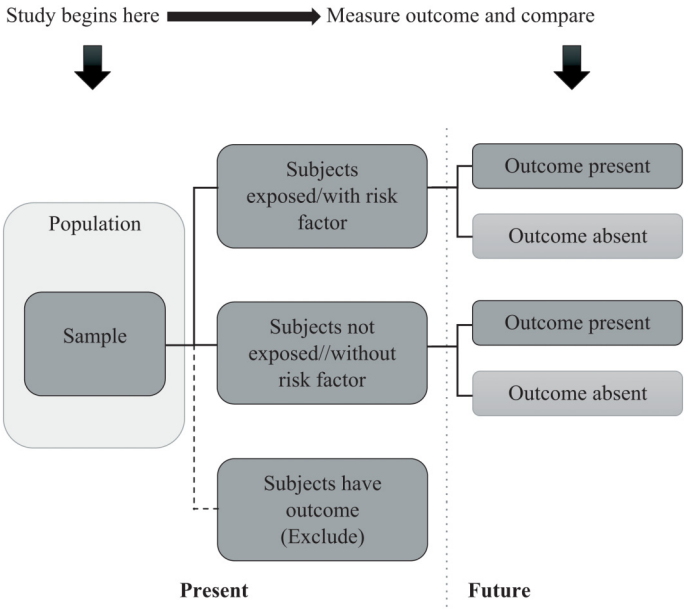

Figure 3 Prospective (longitudinal) cohort study design.

Setia, 2016a) (**Fig. 3**). Prospective cohort studies are easier to plan for data collection, have low recall bias, and the researcher has a better control of confounding factors. On the other hand, it is difficult to study rare conditions; they are more prone to selection bias, more time-consuming, expensive, and loss of subjects to follow-up is common.

Relative risk (RR) is the measure of association used for the analysis of a cohort study. This is defined as the risk of an event or development of an event relative to exposure (i.e., the risk of subjects developing a condition when exposed to a risk factor compared with subjects who have not been exposed to the risk factor).

Case-Crossover Studies

This is a relatively new design in the field of epidemiology in which the patients act as their own controls (Maclure, 1991). In this design, there is a case and a control element both of which come from the same subject. In other words, each case serves as its own control. It can be considered equivalent to a crossover RCT with a washout period (Etminan and Samii, 2004). Pattern of exposure to the risk factor is compared between the event time and the control time (Etminan and Samii, 2004). Case-crossover study design is useful to investigate triggers within an individual. For instance, it is applicable when studying a transient exposure or risk factor.

However, determination of the period of the control and case components is a crucial and challenging aspect of a case-crossover study design. Since the patients serve as their own controls, the interindividual variability that is inherent in classic case–control studies is eliminated. This is important in studies involving progressive disease states in which disease severity may differ between patients such as multiple sclerosis. OR is estimated using techniques such as Mantel–Haenszel statistics and logistic regression.

Cross-Sectional Studies

Cross-sectional studies also known as prevalence studies identify the prevalence or characteristics of a condition in a group of individuals. This design provides a snapshot of the prevalence or the characteristics of the study subjects in a single time point. The study investigator measures the outcomes and the exposures in the study subjects simultaneously (Etminan and Samii, 2004; Hulley et al., 2013; Setia, 2016b). Hence, cross-sectional studies do not follow up patients to observe outcomes or exposures of interest. Data are often collected through surveys. Cross-sectional design cannot provide cause and effect relationships between certain exposures and outcomes of interest.

Experimental and Quasi-Experimental Study Designs

In a typical experimental study design, the investigator assigns subjects to the intervention and control/comparison groups in an effort to determine the effects of the intervention (Cummings et al., 2013). Since the investigator has the opportunity to control various aspects of the experiment, this allows the researcher to determine the causal link between exposure to the intervention and outcome of interest. The researcher either randomly or conveniently assigns the subjects to an experimental group and a control group. When the investigator performs randomization, the study is considered a true experiment (see Fig. 4). On the other hand, if subjects are assigned into groups without randomization, the study is considered a quasi-experiment (refer to Fig. 5). As with experimental designs, quasi-experimental designs also attempt to demonstrate a causal link between the intervention and the outcome of interest. Due to the challenges of conducting a true experimental design, the quasi-experimental study designs have been consistently used in pharmacist intervention research.

RCTs are considered the gold standard of experimental study designs in pharmacy practice and evidence-based research (Cummings et al., 2013). The investigator randomly assigns a representative sample of the study population into an experimental group and a control group (Fig. 4). Randomization in RCT is to minimize confounding and selection bias; it enables attainment of similar experimental and control groups, thereby isolating the effect of the intervention. The experimental group receives the treatment or intervention (e.g., a new drug or pharmaceutical care for treatment of a certain disease), while the control group receives a placebo treatment, no treatment, or usual care treatment depending on the objective of the study (Cummings et al., 2013). These groups are then followed prospectively over time to observe the outcomes of interest that are hypothesized to be affected by the treatment or intervention. The result of the study is considered to have high internal validity if significant changes on the outcome variable occur in the experimental group, but not the control group. The investigator can infer that the treatment or intervention is the most probable cause of the changes observed in the intervention group. The unit of randomization in RCTs is usually the patient, but can sometimes be clusters to circumvent the drawbacks of contamination.

RCTs are very challenging to undertake and pharmacy practice researchers should ensure design of robust experiments, while considering all essential elements and adhering to best practices. For instance, to determine the impact of a cognitive pharmaceutical service, the selection of a representative sample of the population is a prime consideration in an RCT. Moreover, RCTs are expensive, labor-intensive, and highly prone to attrition bias or loss to follow-up.

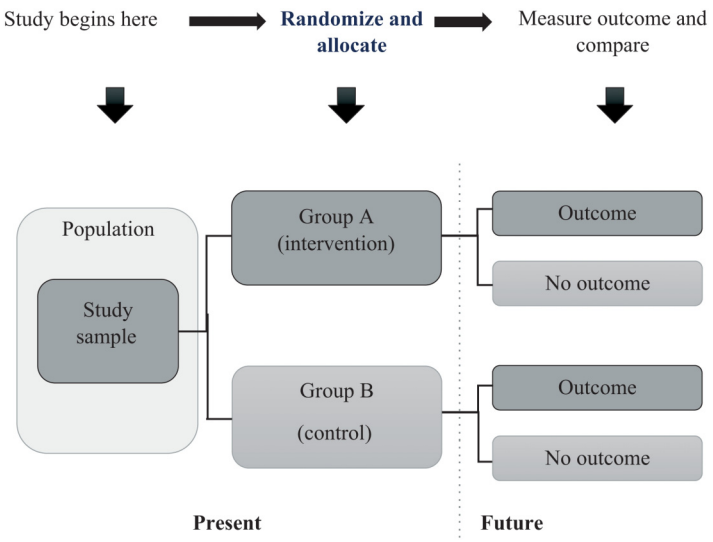

Figure 4 True experimental study design.

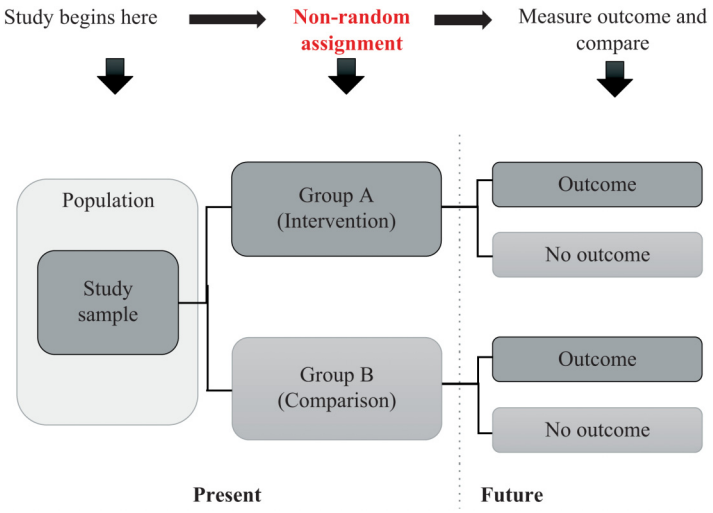

Figure 5 Quasi experimental study design.

In pharmacy practice research, it is often difficult to comply with the stringent requirements of true experimental designs such as RCTs, due to logistic reasons and/or ethical considerations (Grady et al., 2013; Krass, 2016). Whenever true experimental models are not feasible to be applied in pharmacy practice research, the researcher should endeavor to use a more robust quasi-experimental design. For instance, when randomization is not feasible, the researcher can choose from a range of quasi-experimental designs that are non-randomized and often noncontrolled (Grady et al., 2013; Krass, 2016). Quasi-experimental studies used in pharmacy literature may be classified into five major categories: (1) quasi-experimental design without control groups (i.e., one group pre–posttest design); (2) quasi-experimental design that use control groups with no pretest; (3) quasi-experimental design that use control groups and pretests (i.e., nonequivalent control group design with dependent pretests and posttests) (see **Fig. 5**); (4) interrupted time series and; (5) stepped wedge designs (Brown and Lilford, 2006; Grady et al., 2013; Harris et al., 2006).

The one group pretest posttest design and the nonequivalent control group design (**Fig. 5**) are the most commonly applied quasi-experimental designs in practice-based research literature. These designs have been commonly used to evaluate the effect of pharmacist interventions in medications management in general and specific disease states management. The lack of randomization and/or the lack of control group is a major weakness and a threat to internal validity in quasi-experimental designs (Grady et al., 2013). The observed changes could be due to some effects other than the treatment.

Other Quantitative Study Designs

In addition to the common observational, experimental, and quasi-experimental designs described above, there are other designs that are used in pharmacy. These research methods include, but are not limited to, simulated client technique, discrete choice experiments, and Delphi techniques. These methods, which are considered relatively new to pharmacy, are now commonly used in pharmacy practice research. In this chapter, we briefly describe these methods and their application in pharmacy. However, a more detailed description of their components and the nitty gritty of their application in pharmacy practice are available elsewhere within this textbook.

Simulated Client Method

The use of simulated client or simulated patient (mystery shopper) method to assess practices or behaviors in pharmacy practice has received much attention in recent times (Watson et al., 2004, 2006). "A simulated patient is an individual who is trained to visit a pharmacy (or drug store) to enact a scenario that tests a specific behavior of the pharmacist or pharmacy staff" (Watson et al., 2006). A review by Watson et al. demonstrated the versatility and applicability of this method to pharmacy practice research in both developing and developed countries (Watson et al., 2006). The investigators also identified some important characteristics that should be taken into consideration in designing studies that use this technique.

This method can be used to assess wide range of cognitive pharmacy services including counseling and advice provision, treatment of minor ailments, provision of nonprescription medicines, and public health pharmacy, among other things. This method can be a robust and rigorous method of assessing pharmacy practice if used appropriately (Watson et al., 2006; Xu et al., 2012). More recent developments have documented that the simulated patient methods have been used to provide formative feedback in addition to assessing practice behavior of pharmacists and their staff (Xu et al., 2012).

In a case example, a group of investigators evaluated Qatari pharmacists' prescribing, labeling, dispensing, and counseling practices in response to acute community-acquired gastroenteritis (Ibrahim et al., 2016). In another example, the investigators documented the state of insomnia management at community pharmacies in Pakistan (Hussain et al., 2013).

Discrete Choice Experiments

Evidence in healthcare suggests that understanding consumers' preferences can help policy-makers to design services to match their views and preferences (Ryan, 2004). Traditionally, studies to understand patients' and consumers' preferences for pharmaceutical services used opinion or satisfaction survey instruments. Nevertheless, such satisfaction surveys lack the ability to identify the drivers of satisfaction or the relative importance of the different characteristics of the service (Vass et al., 2016). Discrete choice experiments are a novel survey-based method in pharmacy that are predicated on economic theories that allow systematic quantification of preferences to help identify which attributes of a good or service consumers like, the relative value of each attribute, and the balance between the different attributes (Naik Panvelkar et al., 2010; Ryan, 2004; Vass et al., 2016). In-depth description of this method and its essential elements are described in another chapter in the Encyclopedia.

Qualitative Research Designs in Pharmacy Practice

Qualitative research methodology is applied to investigate a problem that has unmeasurable variables, to get a comprehensive understanding of the topic, through discussing it with the involved individuals, and to recognize the natural context in which the investigated issue takes place (Creswell, 2013). The use of qualitative research methodology is becoming increasingly common across diverse health-related disciplines, including pharmacy practice. This is because of its ability to describe social processes and behaviors associated with patients or healthcare professionals, which strengthen the research impact (McLaughlin et al., 2016). Therefore, pharmacy researchers and practitioners need to be better oriented to qualitative research methods (Behar-Horenstein et al., 2018).

In the following section, interpretative frameworks and philosophical orientations, methodologies, data collection and analysis methods, approaches to ensure rigor, and ethical considerations in qualitative research are briefly discussed (Cohen et al., 2013; Creswell, 2013).

Interpretative Framework and Philosophical Assumptions of Qualitative Research

Interpretative Frameworks

Interpretative frameworks are the conceptual structures for comprehension, which form researcher's reasoning and views of truth and knowledge (Babbie, 2015). Different scholars have categorized qualitative research paradigms or interpretative frameworks differently. The following are examples of interpretative framework categories that are used in health science research based on the categorization of Creswell (2013): (1) social constructivism (interpretivism) framework; (2) post-positivism framework; (3) transformative, feminist, critical frameworks and disabilities theories; (4) postmodern frameworks; (5) pragmatism frameworks.

Philosophical Assumptions

Philosophical assumptions are theories and perspectives about ontology, epistemology, axiology, and methodology, which underpin the interpretative frameworks selected by qualitative researchers (Cohen et al., 2013). As with interpretative framework, there are numerous means to categorize the philosophical assumptions that are folded within interpretative framework. The following are explanations of philosophical assumptions based on the categorization of Creswell (2013):

1. Ontological assumptions, which define the nature of reality
2. Epistemological assumptions, which clarify means for knowing reality
3. Axiological assumptions, which explain the role and influence of researcher values
4. Methodological assumptions, which identify approaches to inquiry

It is important that a qualitative researcher understands how interpretative frameworks (e.g., social constructivism, post-positivism, and pragmatic interpretative frameworks) are differentiated because of their underpinning philosophical assumptions (i.e., ontological, epistemological, axiological, and methodological assumptions).

Approaches to Inquiry (Methodology)

It is important that qualitative researchers understand the differences between the characteristics of the five qualitative approaches to inquiry, in order to select an approach to inquiry and attain methodological congruence (Creswell, 2013). The five approaches to qualitative research inquiry are:

a. Narrative research: Describes participants' written and spoken stories about their experiences with a phenomenon being investigated, while considering the chronological connection of the phenomenon's series of events (Anderson and Kirkpatrick, 2016; Creswell, 2013; Czarniawska, 2004).
b. Phenomenological research: Describes the essence of participants' common experiences of a phenomenon, so that the description is a general essence rather than an individual experience (Creswell, 2013; Giorgi, 1997; Moustakas, 1994).

c. Grounded theory research: Aims to generate a theory grounded in participants' data that conceptually explain a social phenomenon, which could involve social processes, or actions or interactions (Creswell, 2013; Strauss and Corbin, 1990; Woods et al., 2016).
d. Ethnographic research: Involves describing the shared patterns of values, behaviors, and beliefs of culture-sharing participants (Creswell, 2013; Harris, 1968; Rosenfeld et al., 2017).
e. Case study research: Provides an in-depth examination of a real-life contemporary phenomenon that researchers cannot change over time, to illustrate the significance of another general topic (Baker, 2011; Creswell, 2013; de León-Castañeda et al., 2018; Mukhalalati, 2016; Yin, 2014).

Data Collection and Analysis Methods in Qualitative Research

1. Data collection methods
   Data collection tools in qualitative research can be categorized into the following fundamental categories (Creswell, 2013):
   a. Observation
   b. Documents
   c. Individual semi-structured interviews
   d. Focus groups (FGs)
   e. Audio-visual materials
   f. Emails chat rooms, weblogs, social media, and instant messaging.
2. Common elements and steps in conducting individual interviews and focus groups
   a. Topic guides: Topic guides guide the discussions in focus groups and individual interviews, and contain open-ended questions and probes, to enable the researcher to understand the complete picture, based on participant views and experiences. They are developed based on the literature review, aim and objectives, research questions, and propositions (Kleiber, 2004).
   b. Audio recording of FGs and interviews: Audio recording of discussions that take place in interviews and FGs is essential for managing and analyzing data, and for increasing the accuracy of data collection and analysis, and ultimately enhancing the dependability and credibility of the research (Rosenthal, 2016; Tuckett, 2005).
   c. Transcription of FGs and interviews recording: Verbatim transcription refers to the word-for-word conversion of oral words from an audio-recorded format into a scripted text format. Transcribing data is considered as the first data reduction step because it generates texts that can be examined and rechecked (Miles et al., 2014; Grossoehme, 2014).
3. Data analysis
   Data analysis comprises several fundamental steps, including reading the transcribed text, arranging data, coding data deductively based on prefigured themes or inductively to produce emergent themes, and then summarizing the codes into themes, and finally presenting the analyzed data as results (Cohen et al., 2013; Crabtree and Miller, 1999; Pope et al., 2000).
   The most commonly used data analysis methods in health science research are:
   a. Thematic analysis
      Thematic analysis is characterized by identifying, analyzing, and reporting themes that are available in the data (Braun and Clarke, 2006; Castleberry and Nolen, 2018).
   b. Content analysis
      Content analysis comprises systematic coding followed by quantification of the analyzed data in a logical and unbiased way (Berelson, 1952; Vaismoradi et al., 2013).
   c. Discourse analysis
      Discourse analysis emphasizes the core format and the structure of texts to examine the assumptions and concealed aspirations behind discourses (Brown and Yule, 1983; Gee, 2004).

Quality Perspectives in Qualitative Research

Qualitative research validation involves ensuring the rigor of the utilized data collection, management, and analysis methods, by utilizing approaches to ensure the quality. In pharmacy practice research, Hadi and Closs (2016a, 2016b) argued that quality in qualitative research topic has not been discussed widely in the literature, and therefore Hadi and Closs (2016a, 2016b) suggested using several trustworthiness criteria to ensure the rigor of qualitative study. The trustworthiness criteria for ensuring quality in qualitative research (Lincoln and Guba, 1985) are:

1. The trustworthiness criteria
   a. Credibility
      This criterion aims to ensure that the results are true and increases the possibility that the conclusions are credible (Cohen and Crabtree, 2008).

b. Dependability
This criterion aims to indicate that the research results are repeatable and consistent, in order to support the conclusions of the research (Cohen and Crabtree, 2008).
c. Confirmability
This criterion aims to confirm the neutrality in interpretation by ensuring that the perspectives of participants, not the bias of researchers, influence the results (Krefting, 1991).
d. Transferability
This criterion involves identifying the contexts to which the study results can be generalized, and indicating if the study conclusions can be applied in similar setting (Yin, 2014).

2. Reflexivity in qualitative research
Reflexivity implies revealing and evaluating the effect and biases that researchers can possibly bring to research process, by explaining the researcher's opinion, feelings, and experience with the phenomenon in question, and explaining the influence of this experience on research methods, findings, and write-ups (Creswell, 2013; Krefting, 1991; Lincoln and Guba, 1985).

Ethical Considerations

Obtaining an ethical approval from the Institutional Review Board (IRB) is required before conducting the qualitative research (Creswell, 2013). The key ethical issues that need to be considered are:

a. Informed consent and participant information leaflet
Informed consent refers to the decision taken by a competent individual to voluntarily participate in a research, after adequately understanding the research. Participant information leaflet is usually distributed to participants before they consent to participate in the research to clarify them the voluntary nature of research participation, the aim and objectives of the research, the rights of the respondents and the potential risks and harms, the data collection, management and storage conditions, and the right of participants to withdraw from the research (Jefford and Moore, 2008).
b. Anonymity and confidentiality
The anonymity is usually ensured by not disclosing names of participants and by utilizing a code system to identify them during data collection, management, analysis, and in the writing up of the research. The confidentiality of participants and data is ensured by using a code system to identify participants, and by storing all data in a locked cabinet and a password-protected computer for a specified period of time (Creswell, 2013).
c. Power relations in qualitative research settings
Power imbalance is caused by the fact that participants have the experience about the investigated phenomenon, and researchers need to obtain information about these experiences. The power imbalance is usually associated with interaction between the researcher and participants during recruitment stage, and during data collection, analysis, interpretation, and validation stages. Hence, researchers should take suitable measures at each stage to decrease the influence of possible power imbalance, and should enhance trust with participants (Karnieli-Miller et al., 2009; Yardley, 2000).

Mixed Methods in Pharmacy Practice Research

Research studies in pharmacy practice usually utilize single-method research designs. However, often these report numerous limitations and may not adequately answer the research question. Therefore, the combination of more than one research method to answer certain research questions has become increasingly common in pharmacy practice research (Ryan et al., 2015). Mixed methods research design is now a popular and widely used research paradigm in pharmacy practice research fields (Hadi et al., 2013, 2014; Hadi and Closs, 2016a, 2016b; Ryan et al., 2015). Mixed methods research allows the expansion of the scope of research to offset the weaknesses of using either quantitative or qualitative approach alone (Creswell et al., 2004; Hadi et al., 2013; Hadi and Closs, 2016a, 2016b; Pluye and Hong, 2014). Typically, qualitative and quantitative data are collected concurrently or sequentially in order to increase the validity and the comprehensiveness of the study findings (Creswell et al., 2004; Hadi et al., 2013; Hadi and Closs, 2016a, 2016b; Pluye and Hong, 2014; Ryan et al., 2015). The mixed method approach provides an expanded understanding of phenomenon under investigation through the comparison between qualitative and quantitative data (Hadi et al., 2013; Hadi and Closs, 2016a, 2016b; Pluye and Hong, 2014).

This section provides an overview and application of mixed method research in pharmacy practice. However, considerations in selecting, designing, and analyzing mixed methods research studies as well as the various typologies of mixed methods research are discussed elsewhere. Johnson et al. (2007) proposed the following definition for mixed methods research: "The type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purpose of breadth and depth of understanding and corroboration."

Mixed methods design allows the viewpoints of participants to be reflected, enables methodological flexibility, and promotes multidisciplinary teamwork (Ryan et al., 2015). Furthermore, the approach allows a more holistic understanding of the research

question. However, its major limitations include: need for wide range of research expertise across the research team members, highly labor-intensive, and the complexity of data integration.

Scholars believe that it is challenging to provide researchers with a step-by-step guide on how to undertake a mixed methods study and that this is driven by the specific research question (Ryan et al., 2015). Nevertheless, the investigator should precisely determine the type of qualitative and quantitative methods to be employed, the order of data collection to be undertaken, the data collection instruments to be used, and the method of data analysis (Ryan et al., 2015). This approach encompasses a synthesis of findings from both quantitative and qualitative components, which is achieved through integration of the findings from each approach (Hadi et al., 2013; Hadi and Closs, 2016a, 2016b; Pluye and Hong, 2014).

Different models or typologies for mixed methods research have been described in the literature. The most common typologies used in pharmacy practice and health services research include: concurrent or convergent parallel design, exploratory sequential design, explanatory sequential design, and the embedded design (Hadi et al., 2013; Pluye and Hong, 2014). Scholars believe that there are several factors to consider when selecting the typology or model of mixed methods research to use. These factors include: the order of qualitative and quantitative data collection (concurrent vs. sequential); priority of data (i.e., which type of data has priority between quantitative and qualitative data); purpose of integration of the data (e.g., triangulation); and number of data strands (Hadi et al., 2013; Pluye and Hong, 2014). In mixed methods research, integration of qualitative and quantitative findings is critical, and this research approach does not simply involve the collection of these data (Ryan et al., 2015).

Summary and Take-Home Messages

- In the era of evidence-based practice, it is not sufficient to propose new pharmacy services or roles without evidence of their benefit.
- New pharmacy services and new roles must be proven to be feasible, acceptable, beneficial, and cost-effective.
- Practice-based research provides such evidence and can inform policy, confirm the value of the new service, and change practice.
- Various study designs, including, but not limited to experimental, quasi-experimental, observational, qualitative, and mixed-methods designs, have been used in pharmacy practice research.
- Pharmacy practice researchers need to be competent in the selection, design, application, and interpretation of these methodological and analytical approaches.
- The choice of any study design in pharmacy practice research is driven by the expertise of the investigator, type of research question or hypothesis, data availability, time orientation, ethical issues, and availability of funding.

Conclusion

There is a great demand for innovation and quality in pharmacy practice. These can be achieved partly through robust and well-designed pharmacy practice research. Pharmacy students, practitioners, educators, and policy-makers are exposed to a variety of research designs and methods. We need to have the best evidence (e.g., in policy, regulation, practice) for making decisions about the optimal research design that ensures delivering an ultimate pharmacy practice and a quality patient care.

Glossary

Pharmacy practice research The Canadian Pharmacists Association defines pharmacy practice research as a component of health services research that focuses on the assessment and evaluation of pharmacy practice (Koshman and Blais, 2011).
Quantitative research Is simply defined as "a research in which things are counted." These things might be people, medicines, opinions, behaviors, etc. "While qualitative research is very useful for describing phenomena in depth (particularly motivations, feelings, understandings), quantitative research can tell us how common and widespread the phenomena are" (Green and Norris, 2015).
Qualitative research Qualitative research within the health sciences has developed as a means to gather an in-depth understanding of human behavior, as well as to find the underlying reasons, attitudes, and motivations that govern such behavior (Kaae and Traulsen, 2015).
Mixed methods research A mixed methods research typically involves both the components of qualitative and quantitative research approaches embedded within a single study or research program for the broad purpose of breadth and depth of understanding and corroboration (Creswell et al., 2004; Johnson et al., 2007; Tashakkori and Creswell, 2007).
Observational studies Observational studies involve merely observing the study subjects in a noncontrolled setting, without investigator intervention or manipulating other aspects of the study in order to determine an association between an exposure and an outcome of interest.

Experimental studies In experimental design (also known as interventional design), the investigator performs an intervention and evaluates cause and effect relationships between exposure to the intervention and an outcome of interest (Cummings et al., 2013). Subjects are typically randomly assigned into experimental and control groups.

Quasi-experimental studies Quasi-experimental designs are studies that aim to evaluate interventions, but that do not use randomization and at times noncontrolled (Harris et al., 2006; Krass, 2016). Similar to true experimental studies, quasi-experiments aim to determine causality between an intervention and an outcome of interest.

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Quantitative Methods in Pharmacy Practice Research

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Background

Research methods are specific procedures, techniques, and strategies that can be employed to analyze and interpret data (Merriam, 2002; Bodgan and Biklen, 2007). The three research methods, that is, quantitative, qualitative, and mixed methods serve to a different set of epistemological and ontological perspectives (Morrison, 2000; Creswell and Creswell, 2017). The selection of a particular research method is based on its capability to provide answers to a specific research problem (Polit and Beck, 2008; LoBiondo-Wood et al., 2013). In quantitative research methods, a researcher designs a research framework, analyzes, and quantifies the relationship between the variables (Polit and Beck, 2004; Creswell and Clark, 2007).

Pharmacy and Research Methods

Pharmacy profession has experienced a significant progress in terms of health-care delivery. To play the role effectively, a pharmacist has to be well equipped with the knowledge and skills to evaluate quality and outcome of treatment; however, this can only be done by considering both qualitative and quantitative research techniques (Azhar et al., 2009).

But looking into the long history of quantitative methods, researchers, especially the pharmacists, are more familiar with the quantitative research than the qualitative research (Smith, 2010b). Quantitative research deals with the findings that can be observed and quantified by involving subject of interests. This also includes people and events to establish a relationship between variables by applying statistical techniques (Leedy, 1993; Couchman and Dawson, 1995).

In this paper, we will elaborate various quantitative methods that can be employed in pharmacy practice research.

Types of Quantitative Research Methods

Quantitative research methods employed in pharmacy practice include nonexperimental research and experimental research methods (Austin and Sutton, 2018) (**Fig. 1**).

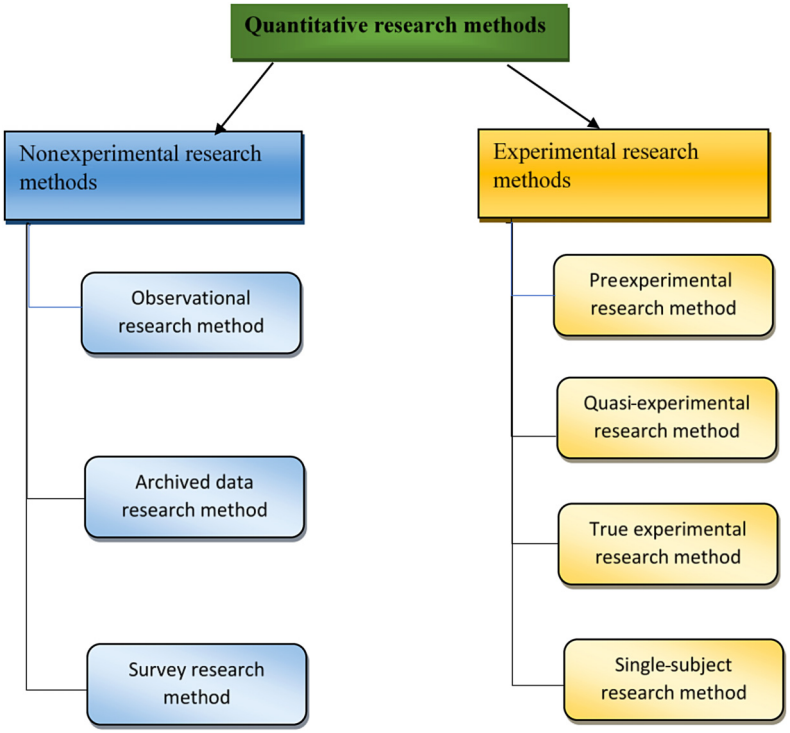

Figure 1 Quantitative research methods.

Nonexperimental Research Methods

Nonexperimental research or descriptive research method involves methodology that measures the variables in their true form without changing the study variables (Belli, 2009).

It is meant to describe a single or multivariables and a possible link between them. In this research method, researchers collect data to generate a hypothesis rather than other methods where a hypothesis is first generated and then tested. Nonexperimental research or descriptive research method selects subjects on the basis of the characteristics that meet the criteria to be included in a research study, for example, knowledge, attitudes, or health status (Dulock, 1993).

Nonexperimental research methods can be classified into the following three main categories (**Fig. 1**):

1. Observational research method
2. Archived data research method
3. Survey research method

Observational Research Method

In observational research method, a researcher observes subjects as samples and collects data for a certain period of time, but this is done without interacting with the environment they are living or working in; neither the researcher initiates any situation nor does the researcher manipulate any behavior (Smith, 1998; Austin and Sutton, 2018). In some cases, a researcher directly observes behaviors, attitude, practices, and events instead of depending upon the information provided by the participants, known as nonparticipant observation.

The researcher then analyzes the information to get numeric frequencies to establish a relationship between the observed data.

Sometimes, a researcher may visit a community pharmacy and act as a patient, observing and recording information for further analysis (Green and Norris, 2015). Madden et al. (1997) named these subjects as surrogate patients, mystery shoppers, or undercover care-seekers. In this scenario, the researcher directly observes and interprets findings, and relates and applies these to pharmacy practice setting.

Observational research method in pharmacy practice research also relies on the reported behavior and attitudes of people involved in a particular study setting (Green and Norris, 2015). Observational research methods are based on either nonparticipant observation or participant observation. However, for quantitative studies, we rely more on nonparticipant observation method where the researcher selects the site of the study and then designs a data collection tool. This method is used to explore, for instance,

services at a particular pharmacy by vising it to observe patient experience or visiting an outpatient clinic without involving the patients or healthcare providers. This technique may help in finding out more about experiences in a healthcare setting (Green et al., 2013; Austin and Sutton, 2018).

Limitations of Observational Research Method

In observational research, there is a little or no involvement from the participants, and things happen naturally in a flow, making the study more reliable.

Availability of resources can be a limitation in observation methods, as the researcher or an observer needs to travel and be present at the site of data collection. In this context, the study population and the study site could be an area of concern, especially in the settings when there are limited resources. The identity of study participants should be kept confidential in observational research, because otherwise, it may raise serious concern for the validity of the observational study (Smith, 1998).

Archived Data Research Method

Another nonexperimental method to collect data is by analyzing previously available datasets. This enables the researchers to analyze and interpret relationship between the variables of interest. Analysis of dataset is a popular method to look for possible research answers related to the use of medicines, medication safety, and rational prescribing (Green and Norris, 2015).

The following categories are described later.

Collecting Data from Administrative Datasets

Administrative datasets include information on prescribing or funding (Green and Norris, 2015). These can be available in the form of surveys, health insurance claims, electronic financial transactions for health insurance claims, computer-based patient records (CPRs), and disease registries (Lohr and Donaldson, 1994). Datasets also help in the prediction of trends. Sushmita et al. (2015) used machine learning algorithms to predict the cost of health care from data based on the public surveys and found a significant relationship between these variables.

Some administrative databases may have data on prescription medicine use, but normally they do not have data for nonprescription or over-the-counter medicines, as this happened in the case of over-the-counter sale of statins in the United Kingdom (Stewart et al., 2007).

In Canada medicines are funded on the basis of State policy; Ontario is the only state where elderly patients are fully covered by this scheme. Thus, most medicine use data and research outputs from Ontario are related to elderly population (Foster et al., 2013; Piszczek et al., 2014). This shows that the results based on a particular dataset or only on prescription medicine use may be biased, and thus it will be difficult to generalize the findings (Green and Norris, 2015).

Secondary Analysis of Primary Data

The already available data can be reanalyzed as some datasets may remain underanalyzed. Systematic reviews and meta-analysis are some examples of reanalysis of published and unpublished data, and this may help in finding the trends over rational medicine prescribing and medicine use (Green and Norris, 2015).

Survey Research Method

Survey research methods are widely used in health services research, and they employ standardized questionnaires to systematically collect data about a certain population regarding their attitudes, behaviors, and practices (Austin and Sutton, 2018). Survey research helps to describe the characteristics of a specific population and to present their opinion, attitudes, and practices (Creswell, 2005).

In pharmacy practice, these can be related to the assessment of beliefs, knowledge, attitudes, and experiences about medicine use, adherence, or other health-related topics both from patients and practitioners perspective (Green and Norris, 2015). To assess the perceptions of the general practitioners on access to medicines issues in New Zealand, Babar et al. (2015) conducted a questionnaire-based survey. The findings suggested that the GPs have the opinion that the medicines are sufficiently available to treat the conditions they saw in their daily practice. However, the majority of the GPs felt that New Zealand is slower to fund new medicines (Babar et al., 2015). Surveys are also used to assess services at the community pharmacies as shown in a survey-based study in Jordan (El-Dahiyat et al., 2019).

Survey is an excellent tool for the measurement of a wide-ranging population datasets, including traits, preferences, beliefs, and other information (Jones et al., 2013). This method is convenient and cost-effective as compared to experimental research or the case study research method (Mertler, 2016).

There are two main types of surveys: cross-sectional and longitudinal surveys.

A cross-sectional survey gives the evaluation of similar characteristics and differences among several samples of a population, and this is done at one point in time (Christensen et al., 2014c). Longitudinal survey involves the consideration of a single population during different times. This requires the administration of surveys at several points in time describing change, stability, or trends over a specified period of time (Dulock, 1993; Christensen et al., 2014c).

Method of Data Collection for Surveys

The use of questionnaire in data collection is a very useful tool. However, the results from the questionnaires can only be valid if they are constructed precisely and are consistent and clear. The method is cheap and quick, but the risk of bias cannot be ruled out in this method (Mathers et al., 2007; Austin and Sutton, 2018).

In postal surveys, the questionnaires are sent in hard copy to the targeted individuals requesting them to return the mail before a specified date. The process can be expensive, but the researcher gains access to a wider range of population. However, this also has some disadvantages, including the lack of encouragement in the absence of a face-to-face interaction resulting in a lower response rate (Christensen et al., 2014c; Austin and Sutton, 2018).

Telephone surveys are more expensive as they require individual administration to the participants. In these surveys, each survey question needs to be read by the researcher or the other supporting staff, requiring more time and resources (Christensen et al., 2014c; Austin and Sutton, 2018).

The technological advancement has led to the development of electronic surveys that are time- and cost-efficient (Mertler, 2002). Such surveys are delivered to the potential participants by sending them email messages or a link to the survey web page (Christensen et al., 2014c; Austin and Sutton, 2018).

Mentioned hereunder are the links for several websites that can be helpful in developing these surveys:

Kwik Surveys (www.kwiksurveys.com) (Kwik Surveys, 2019)
Question Pro (www.questionpro.com) (Question Pro, 2019)
So Go Survey (www.sogosurvey.com) (So Go Survey, 2019)
SurveyMonkey (www.surveymonkey.com) (Survey Monkey, 2019)

The limitations of this method include: filling the online survey, inactive email address of the participants, and failure to deliver email to multiple participants (Carbonaro and Bainbridge, 2000; Mertler, 2002).

Bias in Survey

There are several factors that contribute to bias in a survey methodology. The types of biases that can have an impact on the outcomes of the survey are discussed below (Bhattacherjee, 2012).

Sampling bias

Sampling bias is rampant in telephone surveys, where the respondents are selected and contacted from a random sample of publicly available telephone numbers. This systematically excludes people who do not have a mobile phone, landline numbers, or are unable to take the call when the survey is conducted. This also leads to disproportionate representation in the survey sample of—respondents with listed phone numbers; people who stay at home; elderly, disabled, or unemployed. Similarly, young people and students have more chances to be contacted through online surveys as they use technology and Internet more than other groups of population, thus systematically excluding people with no access to Internet.

In questionnaire surveys, there is a tendency to exclude uneducated and children as they are unable to read and write. Such bias in sampling compromises the generalizability of the results (Bhattacherjee, 2012).

Recall bias

Willingness to respond to a survey question is influenced by memory and motivation of the respondents as many survey questions draw from the past experiences (Green and Norris, 2015). It means that if a respondent cannot recall the information, the response would not be accurate. The problem of recall bias can be overcome by asking the respondents about the incidents rather than asking them about their emotions or behaviors (Bhattacherjee, 2012).

Social desirability bias

This bias arises when the respondents are asked about their views on negative opinions about their surroundings, thus making them uncomfortable to answer in a truthful manner. Many participants try to avoid responding to negative opinions or a question regarding their workplace, family, or friends.

In such situation, they usually try to spin the truth with not-so-true response as, otherwise, it may disturb their social desirability (Green and Norris, 2015).

These biases in a survey disturb the validity of the survey outcomes. The problem can be tackled by opting for an in-depth interview, as this can identify inconsistency in the answers (Bhattacherjee, 2012).

Experimental Research Methods

In experimental research methods, the researcher establishes different situations or treatments as variables and studies their effects on the participants (Hopkins, 2008). Researcher can control and manipulate variables and can study the cause and effect relationship for each variable (Christensen et al., 2014b). These are also known as intervention-based studies as they involve more than just observing the phenomenon (Hopkins, 2008).

The general requirements for the experimental research studies are as follows:

- A randomly selected or a randomly assigned group of participants to be included in a comparison group (which can either be an experimental group or a control group) except quasi-experimental design where the randomization of sample is not possible.
- An independent variable (a treatment, a cause, or an experiment variable) applied to the experimental group.
- A dependent variable commonly known as criterion variable (also known as posttest or effect variable) is identically measured in all groups in a study (Mertler, 2016).

Random selection of the study population and random assignment of these individuals to both experimental and control group are mandatory requirements for an experimental research method. This ultimately helps to maintain the equivalence between two groups, and also helps to control the factors that may interfere with the results of the study (Smith, 2010b).

Experimental research methods can be further categorized into the following four categories (Mertler, 2016) (**Fig. 1**):

1. Pre-experimental research method
2. Quasi-experimental research method
3. True experimental research method
4. Single-subject research method

Experimental methods can also be categorized into two main groups: single variable design and factorial design. Single variable design involves manipulation of one independent variable, whereas factorial design is comprised of two or more variables, in which at least one independent variable is manipulated (Mertler, 2016).

Pre-experimental Research Method

The method is called one-shot case study, and it is used to get the preliminary data regarding a problem. Preexperimental research method involves the inclusion of a single group of population that undergoes treatment and is also posttested. This research method does not control extraneous or unrelated variables; hence, it is not a preferred choice for a study research (Christensen et al., 2014b).

There is another type of preexperimental research method that is posttest only, that is, no pretest is done before exposure of treatment. Another method is pretest–posttest design, which is similar to the single group posttest design, but prior to the exposure of treatment, a pretest is done (Gay et al., 2009; Smith, 2010b). Pretest and posttest scores are evaluated to see if there is any change in the response. In this case, the researcher will be able to find out the difference in the response and its possible explanation (Smith, 2010b; Leedy and Ormrod, 2013).

Limitations

The method does not have any control over unrelated variables, hence making researcher unable to conclude definitive cause and effect relationship between variables (Leedy and Ormrod, 2013; Christensen et al., 2014b).

Quasi-experimental Research Method

Quasi-experimental research methods are considered as the closest form of true experiments, but they do not involve the random selection of the participants, and this ultimately weakens the ability to control extraneous factors (Christensen et al., 2014a). However, like other experimental research methods, quasi-experimental research seeks a causal relationship between an intervention and its outcome, and ultimately they provide further rationale for more exploratory trial involving robust research system (Krass, 2016).

Thus, in pharmacy practice, quasi-experimental method helps in the assessment of an intervention over a certain period of time. In a study at the University of Michigan Medical Center, it was observed that the medication-related discrepancies were resolved by the involvement of pharmacist in a hospital discharge program (Walker et al., 2009). Another pharmacist-led intervention study in six hospitals in Hawaii showed a significant reduction in the cost of hospitalization of elderly patients (Pellegrin et al., 2017).

Quasi-experimental research is a preferred choice in the cases where it is not feasible to randomize participants to a treatment or intervention group due to logistical or ethical reasons (Krass, 2016).

Limitations

The design is very useful in cases where random assignments of participants are not possible (Christensen et al., 2014a). However, the design lacks the random assignment of participants to the treatment groups. This ultimately results in an increased risk of bias in the study (Thompson and Panacek, 2006).

True Experimental Research Method

The method involves the random selection of participants to the assigned treatment conditions (Gay et al., 2009). In such design, participants are randomly assigned to the control and experimental group, and the study design is commonly known as randomized controlled trial. Such research design is a preferred choice in pharmacy practice research, and it helps in evaluating the impact of new health-care service or intervention (Smith, 2010b).

In control group, no active treatment is given or sometimes a standard value is used that does not affect the value of the independent variable. But, in an experimental group or a treatment group, participants receive a treatment or an intervention that can alter the value of an independent variable resulting in an impact or an effect (Christensen et al., 2014b). The involvement of at least one comparison group is an important feature in this study design (Mertler, 2016).

In a research method, where the participants are not aware of the identity of treatment or intervention is known as single blind controlled trial. In a double blind controlled trial, both researchers and participants have no information regarding who is receiving a treatment or an intervention (Hopkins, 2008; Christensen et al., 2014b). The randomization of participants helps to control the risk factors, which may emerge as a threat to the validity of data (Fraenkel et al., 2011).

Limitations

The major strength of a truly experimental research method is its ability to clearly draw a cause and effect relationship in a study. However, true experimental methods require stringent requirements to not risk the validity of the data (Mertler, 2016).

Single-Subject Research Method

Most of the experimental studies require group of participants, whereas in single-subject research design, the studies can be conducted on an individual case basis (Smith, 2010a). Single-subject research design is preferably used to study the time course, effect of a treatment, or an intervention on a single patient, and is mostly employed in primary care research-based studies (Janosky, 2005).

In the single-subject case studies, the outcome from dependent variables is measured and recorded for individual participants during different times and at different levels of intervention (Lobo et al., 2017). The performance of a subject is evaluated both in a nontreatment and treatment phase (Gay et al., 2009). The nontreatment phase can be regarded as phase A, while the treatment phase can be marked as phase B (Janosky, 2005). There are various types of single-subject design, one of which is called the A-B design. In single-subject research, initial measurement of variables (A) is taken, and then a treatment (B) is given to the subject and a change is observed to see the treatment effect (Janosky, 2005).

Another design is reverse design or commonly known as A-B-A (measurement-treatment-measurement). This design is comprised of baseline measurements (first phase) followed by treatment (second phase) and finally the removal or withdrawal of treatment (third phase). However, it is required that the researcher should accurately measure the behavior change before and after applying the treatment. This can be repeated many times (Hopkins, 2008). On the removal of the treatment, if condition reverses, it means that the treatment has some positive effect on the subject (Price et al., 2015). A study by Freeman et al. (2010) employed an A-B-A research method to determine the core stability training in eight patients with multiple sclerosis. The researcher maintained the baseline level for 4 weeks, followed by 8 weeks of intervention then was a withdrawal after 4 weeks resulting into patient's improved walking (Freeman et al., 2010).

Limitations

A major limitation of single-subject research method is that some interventions cannot be withdrawn or reversed (Mertler, 2016; Lobo et al., 2017). Also, this research design lacks the generalizability in terms of its outcome and is only focused to study the effectiveness of treatment on a single participant. This is effective to measure an impact and study behavior modifications in one single individual. However, a possibility of an alternative explanation for a certain behavior in an individual cannot be ruled out (Janosky, 2005; Mertler, 2016).

Validation of a Research Method

Validity of a research method refers to the value, truth, and originality one can place on the study findings. Validity of research is the degree to which one can say that the research outcomes are accurate and generalizable. Factors affecting internal and external validity should be controlled; otherwise, it may jeopardize the reliability of results and the conclusion of the study (Green and Norris, 2015; Mertler, 2016).

In order to measure the external validity of the quantitative research methods, it is important that the accurate data from the appropriate subjects must be collected in the right setting. The specifications of a target population must be clearly described, and the selected subjects must represent the population under study (Smith, 2010a; Austin and Sutton, 2018). The instruments used (equipment, questionnaires, or interviews that measure physiological or psychosocial variables) should be standardized. Before employing newly developed instruments into a research study, the same should be pilot tested (Dulock, 1993).

Conclusion

There are many different quantitative approaches, which give the freedom to the researcher to choose the appropriate methodology. However, it is important to understand that every design has it's own set of limitation, and this is vital to consider when choosing a research method in the pharmacy practice research.

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Qualitative Methods in Pharmacy Practice Research

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Introduction

Until recently, much of the health and pharmacy practice research undertaken focused on what were considered good rigorous practices, based on the measurement and collection of numerical data that would be able to quantify phenomena or test hypotheses (Smith, 2002). This was the result of the widespread acceptance of the scientific method as the cornerstone of science and the way by which reality could be appropriately researched (Crotty, 2003). The scientific method was built on the belief that measurement was at the center of discovery, and that the designing and execution of the right experiments or observations would lead to the advancement of knowledge (Popper, 1959/2002). This view of what would constitute good research has been increasingly challenged in recent times due to its limitations in arriving at understanding of many aspects of healthcare and the provision of services. This would be the case in studies involving human participants, who could be patients, professionals, students, educators, or other stakeholders, which need to deal with the subjectivity which is associated with human behavior (Bowling, 2014). As a result of this, it is now accepted that the world and society may not operate according to general laws, and therefore measurement may not always be possible, with the testing of hypotheses or the quantifying of variables being unable to provide complete answers to certain research questions (Robson and McCartan, 2015).

Qualitative research has presented itself as a practical solution to this problem, providing a whole new range of approaches to data analysis and methodologies for data collection that can enable the investigation of issues that could not be explored in such depth before (Patton, 2015). It has particularly succeeded on studying the perceptions of those involved in healthcare, also looking at experiences and the way that individuals and groups communicate and relate to the world, being also very useful in educational research (Austin and Sutton, 2018). This shift from focusing in measurement and prediction, to exploration and understanding can be considered to constitute a paradigm shift, affecting the way science is understood, with this no longer seen as objective and invariable (Kuhn, 1970). This is a very important point to consider for those engaging in qualitative research, which need to embrace that they will be managing more than one possible interpretation of reality, and questions which may be answered in more than one way (Denzin and Lincoln, 2017).

A range of research traditions within the qualitative paradigm have been proposed to exist in order to guide those navigating through all the possibilities that these approaches and methodologies can offer (Poth and Creswell, 2013). These have been named and categorized by authors in different ways, and can appear at times artificial and confusing (Tesh, 1990). In the following sections, key aspects to consider when undertaking and understanding this type of work have been presented without focusing on these

research traditions. This is with the purpose of avoiding confusion and helping investigators and practitioners gain the knowledge they would need to undertake, report, and critique these studies. For this reason, building on accepted terminology and classifications, this chapter would aim to prepare for *real world research* (Robson and McCartan, 2015), and for solving relevant problems in a way which is methodologically sound. On these lines it must be noted that it will focus on using qualitative data in ways which are consistent with the principles of qualitative research. Some of the approaches can be thought to be part of the quantitative rather than the qualitative paradigm, or sit in between, and they have been covered in this chapter as the results that they can arrive to can be very useful in qualitative pharmacy practice studies. It must be remembered that qualitative data is something different than nominal data; qualitative data involves information provided through the use of language on a phenomenon, while nominal data can be a value or variable which is expressed in words (Denzin and Lincoln, 2017).

There are many options to choose from when using qualitative methods in pharmacy practice research (Austin and Sutton, 2018). It is advisable to read this chapter in its entirety before using its content to inform any choices, as the subtle differences in these approaches and methodologies can sometimes only become apparent when comparing one another. The degree of interpretation and depth of analysis required by a specific study can be particularly difficult to judge by individuals with more limited experience in this field. It is therefore encouraged that familiarity with the whole qualitative paradigm is achieved before engaging in data collection and analysis, as this will ensure that rigorous practices continue to guide researchers in this area. For this purpose, understanding the different approaches to finding meanings in the data is essential, and should be achieved prior to making decisions with regard to how this data should be collected and handled.

Choosing an Appropriate Qualitative Method

The most important aspect of qualitative research and managing qualitative data is the central role which language plays to convey messages and provide meanings, which are shared by human participants, and after analysis will lead to answers to the research questions under investigation (Smith et al., 2009). The approach selected to finding meanings will therefore determine the results which will be obtained, and it is useful to consider analysis prior to making decisions about how the data will be collected (Silverman, 2016). For example, if further understanding was required on how patients make sense of being diagnosed with a terminal illness, meanings sought would be of greater depth than those involved in finding out what service users thought of having to pay car park charges when visiting a hospital. The following sections outline what aspects of the different approaches to finding meanings in the data need to be considered before choosing one based on the depth of analysis, degree of interpretation required, and the main implications of using these.

The first consideration to make when engaging on finding meanings in qualitative data would be whether descriptive or latent meanings are sought (Smith et al., 2009). This is the fundamental distinction between finding meanings by analyzing concepts and finding meanings by analyzing themes. A concept would represent an idea which is defined and described by the terminology used to relate to it, having a near literal meaning. In contrast, a theme would relate to a latent meaning found in the data after a process of interpretation, where language does not explicitly present an idea (Braun and Clarke, 2008). For example, when researching community pharmacists' role satisfaction, it could be possible to come across the following a statement from a participant in a group discussion: "Oh, yes, I like admin work." This data could include the concept "admin work," as it is explicitly quoted, and also the theme "dislike of admin work," depending on what was meant by the participant when making this statement.

The following sections explain this in more detail, providing an overview of the different approaches for finding meanings by analyzing concepts and themes, defining what these approaches are, when they would be most useful, and providing examples to illustrate how they can be applied.

Finding Meanings by Analyzing Concepts

As it has been explained before, approaches to finding meanings by analyzing concepts are not based on interpretation (Smith et al., 2009). However, it would be very difficult to argue that they do not involve some degree of subjectivity (Robson and McCartan, 2015). They aim to arrive at categorizations where there is no overlap, and in some cases, there is even a degree of quantifying taking place. When investigators aim to find meanings by analyzing concepts, the purpose is to arrive at results that could be accepted as some definitive answer to the research question (Hsiu-Fang and Shannon, 2005).

These approaches do not entirely belong within the qualitative paradigm, and are included in this chapter because they rely on qualitative data (Poth and Creswell, 2013). For some of these there are prescriptive ways of undertaking analysis, with others embedding a number of different practices (Poth and Creswell, 2013). Analyzing concepts enables researchers in pharmacy practice to ascertain, and sometimes quantify, key meanings, which is often done to inform policy and to make judgments with regard to health interventions (Smith, 2002). They can be very useful in providing specific answers to general problems, where there are larger amounts of data and limited depth in the analysis is required (Robson and McCartan, 2015).

When finding meanings by analyzing concepts, the process can be deductive or inductive, by which specific meaning are searched for in the data, or in contrast, emerge from it and are not anticipated (Silverman, 2016). For example, in a deductive approach to investigating factors that influence the choice of community pharmacy, the data may be searched for the presence of specific concepts which have been chosen prior to starting analysis (often by reviewing the literature or because these have been judged as important). These could be convenience, waiting times, services offered, and friendliness of the staff, with the analysis

focusing on whether these are present in the data and what importance participants attributed to them. In contrast, in an inductive approach, the process would involve to look for factors which emerge from the data, without any preconceptions on what these would be (Ritchie et al., 2013). As such, it could emerge that availability of parking spaces, allowing to pre-order prescriptions on-line or having a members of staff which speak additional languages are the factors present in a specific dataset. In this way, finding meanings by analyzing concepts would be useful to check interpretations, to some extent quantify and explain phenomena, and sometimes proposing hypothesis or theories for further testing (Austin and Sutton, 2018). While the more limited degree of interpretation that they require and the set steps prescribed for some of them may make them appear as more accessible and easier to use (Hsiu-Fang and Shannon, 2005), they require an amount of skills and experience which can be as large as those needed to effectively find meanings in the data by analyzing themes. They should therefore only be chosen when they would be best suited to answer the research question under investigation.

Content Analysis

Content analysis would be the most basic way of manipulating qualitative data, and is often concerned with how frequently a concept, or single unit of meaning (which could include more than one word), is present in the data. In content analysis, concepts are identified, categorized, and often counted (Hsiu-Fang and Shannon, 2005). For example, "teamwork" would be a concept often sought when undertaking analysis of job applications in order to identify, for the purpose of recruitment, what could suitable candidates for a role which involves working with others. Content analysis can be undertaken in any way which ensures that concepts are identified and grouped consistently under pertinent categories (Ritchie and Spencer, 1994). As per the example given, it can provide quicker answers to specific questions, but it is of limited used within pharmacy practice research, as there are other approaches which can deal with the greater complexities which are often present in this type of work (Smith, 2002). Sometimes authors have used the term content analysis to refer to thematic analysis (Braun and Clarke, 2008), and care must be exercised when accessing the literature, as both are very different approaches, which may be suitable in very different situations.

Framework Analysis

Framework analysis is a defined approach to finding meanings by analyzing concepts, which is carried out following set steps proposed by the authors (Ritchie and Spencer, 1994). In this approach, meanings are sought in order to construct a framework which provides an overall description of a phenomenon, dealing with a greater degree of complexity than content analysis, while looking at key concepts present in the data and how they relate to each other (Ritchie et al., 2013). For example, framework analysis could be very useful to study barriers and drivers affecting the success of a childhood obesity intervention implemented across a number of schools. Using framework analysis, concepts within the dataset can be indexed, and presented in a simple but effective model (Ritchie and Spencer, 1994). While it may not enable to investigate aspects in great deal of detail, or including additional meanings to those which are in the majority, it can be useful when answers are needed to specific questions within large datasets. Framework analysis is successfully used in policy making and larger scale studies involving qualitative data (Gale et al., 2013).

Delphi Technique

The Delphi technique involves a process by which the views of a group of individuals on a specific subject are gathered with the purpose of establishing what issues are important and determine a hierarchy of how these would relate to each other (Keeney and McKenna, 2010). This is done following steps which aim to arrive at consensus among the individuals in the group on the degree of importance of these different issues. It is a structured approach to arrive at which concepts are more pertinent to the research question under investigation. By arriving at those which are more representative, it would be expected that predictions could be made (Salkin, 2010). Delphi technique often involves a face-to-face data collection event where there are two rounds of questions, for which answers are provided, with these being ordered by the group and a hierarchy arrived at. All suggestions are then passed unedited and unattributed to all group members, who are asked to re-rank suggestions, drawing up a priority list from members' rankings (Skulmoski et al., 2007).

The Delphi technique can be useful when agreement is sought from a group of informants or experts on an aspect for which there is little or no evidence, there would be a variety of factors to consider, and it is necessary to narrow these down to those which would be most important (Skulmoski et al., 2007). For example, in order to identify which would be the attributes which define professionalism in practicing pharmacists in order to inform the development of a suitable education and training initiative, this could be a useful approach.

Grounded Theory

Grounded theory is a well-defined and prescriptive approach to finding meanings in qualitative data where a theory is constructed at the end of the process (Poth and Creswell, 2013). Grounded theory can be useful in large datasets when the purpose is to arrive at a model which would aim to describe and explain relationships within the phenomenon under investigation (Bowling, 2014). This approach could sit well within the quantitative paradigm if it were not based on the analysis of qualitative data. It follows a set of defined steps with the purpose of standardizing the analysis and avoiding the need for interpretation. The two main approaches to undertaking grounded theory (Glaser and Strauss, 1967; Strauss and Corbin, 1997) are covered in a different chapter of this book.

Finding Meanings by Analyzing Themes

In contrast to those included in the previous sections, approaches for finding meanings by analyzing themes are based on varying degrees of interpretation (Braun and Clarke, 2008). Their way of manipulating data leads to categories that overlap, and no quantifying takes place, nor becomes necessary. In these, interpretation is aimed for and put at the center of analysis (Smith et al., 2009). These approaches enable qualitative data to be fully understood and analyzed following the fundamental principles which guide the qualitative paradigm. When finding meanings by analyzing themes, there is no single prescribed way of how analysis should happen, with authors making suggesting rather than proposing set methodologies or steps (Robson and McCartan, 2015). Analyzing themes enables researchers in pharmacy practice to ascertain, sometimes unveil, but never quantify, meanings within the data which can often be hidden. These are used to understand how individuals perceive service provision or a certain aspect of reality (Smith, 2002). They can be very powerful in providing insights and answers to research questions which involve personal views and accounts, experiences, and how these are felt by those being researched (Crotty, 2003).

Approaches to finding meanings by analyzing themes are language centered, but they are also concerned with the context in which the language frames meanings (Polgar and Thomas, 2013). They see this as a tool for communication, not merely for the transmission of information, and these approaches are built on the assumption that how things are talked about matters, in addition to what it is said (Smith et al., 2009). Researchers must be careful therefore when using these approaches to avoiding fragmenting the phenomena being study, and ensure that there is clarity with regard to how themes have been developed to ensure transparency and rigor of the practices followed. When finding meanings by analyzing themes, the approach should always be inductive, by which themes emerge from the data, rather than investigators looking for the presence or frequencies of certain themes (Patton, 2015). In this way, these approaches would be useful for studies which aim to build interpretations, explain phenomena, and sometimes propose hypothesis for further testing (Smith, 2012).

Thematic Analysis

Thematic analysis would be a versatile approach to finding meanings in qualitative data for pharmacy practice and health research in general (Bowling, 2014). This is due to its flexibility, lack of assumptions on what constitutes knowledge, and its ability to provide ways to find meanings which allow a degree of interpretation that can be adapted to the nature of the research question and the aims of the study. It focuses on finding patterns of commonality, which are not always obvious in the data, and for which clear practical ways have been proposed (Braun and Clarke, 2008). Thematic analysis is undertaken by facilitating that themes emerge from the data, rather than being imposed by looking for specific concepts. In order for this to happen, research questions are left deliberately loose, and a process of induction and iteration, by which researchers go through a dataset many times, is used until meanings are found (Patton, 2015).

Thematic analysis would be best suited for real life problems which require an investigation which does not need to be entirely focused at the outset, is able to deal with complexities and individuality on how a situation is perceived, while aiming to gather common themes that can illustrate key aspects of a phenomenon (Braun and Clarke, 2008). For example, it can be very useful at assessing views on services or educational interventions, where there is limited knowledge about what are the perceptions of the relevant stakeholders.

Discourse Analysis

Discourse analysis is concerned with looking at the ways that things are talked about. It aims to reveal socio-psychological aspects that intentionally or accidentally are hidden in language (Robson and McCartan, 2015). It is similar to thematic analysis, but can be considered to have added layers of interpretation. This is because discourse analysis builds on the assumption that individuals talk about things choosing certain language which on itself frames reality and would add to the meaning of the message that it gives. It aims to reveal characteristics beyond looking at a text structure and meaning (Hodges et al., 2008).

Discourse analysis can be useful to gather meanings on aspects where the choice of language is as important as the choice of content, and when there are potential relationships of power between stakeholders and non-explicit agendas guiding communication (Ritchie et al., 2013). For example, it could be useful to study the nature of discussions between pharmacists and patients about their non-adherence to prescribed medication.

Interpretive Phenomenological Analysis

Interpretive phenomenological analysis (IPA) is a very in-depth approach to finding meanings by analyzing themes, where data analysis is centered on aspects of a *lived experience*. It has been relatively recently introduced in the social sciences (Smith et al., 2009), and is being used in patient-centered healthcare research due to its powerful ways of helping to understand how an individual perceive and make sense of health and care. IPA studies involve a very close examination of the accounts of a small number of participants. This is so in order to obtain the richest meanings in the data through a thorough and complex analysis. More advanced IPA study designs may include participants which provide different perspectives of the same lived experience as a result of belonging to different groups (for example, patients and people who care for these) or they may follow these for some length of time (Brocki and Wearden, 2006).

IPA requires an insightful and skillful interpretation through a process of reflection, where researchers must make sense of how participants make sense of the lived experience under research in a process of double hermeneutic analysis (Smith, Flowers and Larkin, 2009). It would therefore be suitable for studies for which very little is known, which need to deal with the complex aspects of

interpreting human nature and human experience (Silverman, 2016). For example, it would be very useful in order to understand the experience of caring for a terminally ill patient at home, or processes such as how transgender patients' experiences in their journey through care.

Collecting Qualitative Data and Reporting Results

The previous section has described how to find meanings in qualitative data in order to provide answers to research questions which are relevant to pharmacy practice. It is necessary to understand how analysis is going to take place within an investigation in order to make decisions about how to collect and manage the data (King and Horrocks, 2010). This section provides guidance on how to do so, covering sampling and recruitment, and including specific aspects to consider with regard to ethical issues and reporting results in these types of studies.

While some of the approaches for finding meanings would be incompatible with some of the methods for gathering data, for example, Delphi technique would be incompatible with reflective diaries, when the practicalities enable the collection of the data needed to be done by a specific method, investigators can decide how to pair the approach to analysis with the method for data collection (Polgar and Thomas, 2013). There will be occasions where data can be obtained using more than one method, but in others there may be one which is more adequate to arrive at meanings of type sought (Austin and Sutton, 2018). The aim at all times should be to obtain data which is of the most possible quality, as any compromises made here will have an impact on the study; analyzing data which has not been collected well is much more difficult to do, as its focus can easily deviate from what was the original research question set for investigation (Bowling, 2014).

Sampling and Recruitment of Participants

Sampling of participants in qualitative research is different than that in other types of enquiry, as it allows the intentional selection of specific individuals by virtue of the investigators deciding that they present a specific characteristic or characteristics which makes their inclusion in the study adequate. This is generally done through purposive sampling, where the sample frame includes potential participants which are chosen for a reason, rather than these being selected at random (Patton, 2015). For example, in a study looking at the transition into higher education of pharmacy students which have undertaken their previous education in a country other than where they register to complete their pharmacy degree, the selection of students within a course at random would not be appropriate. Those individuals which are suitable can be identified as having the characteristics sought after and subsequently invited to take part in the study. In those occasions where the characteristic which is sought in individuals to be included in the study is rare, or there is no sampling frame available, snowball sampling can be of used (Salkin, 2010). In this, potential participants and those taking part in the investigation are asked to identify further participants, which can subsequently be invited. The use of purposive or snowball sampling should not be seen as a limitation of the study, as if this is done well, it will increase richness in the data being collected and lead to more meaningful and complete results (Denzin and Lincoln, 2017).

In terms of recruitment for studies which involve the collection of qualitative data, this is often driven by the practicalities of sampling participants. It could be the case that the entirety of a group available with the specific feature or involvement in the phenomenon under research is invited, for example, having being subject to an intervention or experience an innovative service or educational program (Smith, 2002). When there are potentially large numbers of individuals for which this may be the case, accessing previous literature can be very useful to identify how purposive sampling could better take place (Austin and Sutton, 2018). Alternatively, additional practicalities for accessing participants can be used to inform recruitment strategies, always remembering that gathering quality data rather than convenience should be guiding sampling and recruitment. It must be noted that, particularly in approaches to finding meanings by analyzing concepts, sometimes sampling and recruitment of participants is not necessary, as there may be suitable secondary data already available for analysis (Ando et al., 2014).

Gathering and Preparing Qualitative Data

As in any investigation, the process of gathering and preparing data is central to qualitative research. However, unlike in other designs, in this case data collection is often an iterative process which is informed by data analysis, with results obtained feeding into how further data collection is undertaken (Braun and Clarke, 2008). This process can be flexible and allows to aim for investigating issues which may have not been anticipated but rather emerge from the data. As a result of this, piloting data collection tools is not undertaken in the same way as it would be if following a quantitative design, as it is possible to refocus how the data is collected as part of the process of gathering it (Ando et al., 2014). For example, when researching patients' health choices within individuals of a certain ethnicity, there may be a specific aspect which features as more important to some participants, which is in tension with which the literature shows to be the case for other groups, and therefore worth investigating. Once this is identified, subsequent participants can be asked widely about their choices, but also more specifically about this emerging theme. When sampling and recruiting participants to a study, it is important to consider any ethical issues that can be encountered, as there may be instances where sensitive or confidential information is involved in an investigation, or data which relates to patients and their care (Wingfield and Badcott, 2007). Ethical issues are covered in a further section of this chapter, where their implications and how to avoid key issues are explained.

Generally, qualitative research data in pharmacy practice will be obtained from documents, observations, or discussions, by being written, observed, or shared (Smith, 2002). Irrespectively of how this data is gathered, it will generally be presented or prepared as a written text which will subsequently be analyzed, either by finding concepts or themes which are present. This is not to say that data could not be accessed in other prepared formats, such as audio-recordings or pictures, which although much less common, may suit certain investigations (Austin and Sutton, 2018). The following sections will outline key practical considerations when gathering and preparing qualitative data depending on how this is obtained, in order to ensure that key aspects are not overlooked.

Collecting Data Which Is Observed

The collection of data which is observed, or participant observation, is a method widely used in other disciplines, such as psychology, in order to research behavior (Patton, 2015). In pharmacy practice it can be useful to explore how processes are undertaken and in which ways these could become more efficient, to identify learning needs and to investigate aspects of service provision which are overlooked by those involved with it. Participant observation can encounter challenges in ensuring that it is carried out with the consent of all of those which would be involved and in a way that is still able to capture real practices and behaviors, not influenced by the presence of the investigators (DeWalt, 2001). This method has great potential of growth within pharmacy practice, although currently it still encounters barriers as a result of the need to deal with issues of confidentiality, rigor of the observation and any bias introduced by the presence of the investigators (Bryman, 2015).

Data which is observed is generally collected through field notes, data collection forms or audit tools aiming to capture the aspects of reality that are being investigated (Polgar and Thomas, 2013). In any case, researchers need to be vigilant to identify conducts and trends relevant to the research question. Unlike the gathering of data by other means, participant observation often relies on collecting data in a process as it happens in real time, with no opportunity to go back to the phenomenon to check or expand on incomplete information. There may be situations where it could be possible to video-record the process which is being investigated, although when this is the case, the potential for more complete data which can be revisited at a later data may be over outweighed by the introduction of additional bias as a result of participants changing their behavior due to not only being observed, but also recorded (DeWalt, 2001).

Participant observation can be very useful in educational research, when the aim is to look at how students learn or apply some learning (Austin and Sutton, 2018). For example, it would be a good choice in order to collect data to look at inter-professional working involving students of different disciplines, and how they relate to each other when undertaking practical work.

Collecting Data Which Is Written

As mentioned earlier in this section, most of the qualitative research undertaken in pharmacy practice leads to a dataset which is converted into a written text (Smith, 2002). This section will cover the collection of data which is originated in a written format, rather than gathered in a different way to then be prepared as a written text. Written texts of any type can be subject to qualitative data analysis, and what types of texts may be suitable, if at all, to answer a research question will depend on what the question is and what meanings are sought in the data (Bryman, 2015). As explained in the previous sections, the information that could be found in written texts could be explicit, and often documents are used in this way to find meanings by analyzing concepts (Hsiu-Fang and Shannon, 2005). In some cases, investigators may be looking for information within the data of certain texts which is not explicit, in which case it would be useful to look for meanings by analyzing themes (Ryan and Bernard, 2003). For example, discourse analysis could be undertaken on written information provided to the general public on a certain aspect of healthcare, looking at how language constructs aim to influence healthcare behaviors as part of the promotion of public health.

There are two types of texts which can be particularly useful in health research: documents and reflective journals (Bowling, 2014). Documents which can be subject to analysis would include written processes, policies, lay literature, and medical documents. Reflective diaries offer an additional and powerful tool for collecting data which is written, and unlike documents constructed for a different purpose, reflective diaries are often designed and set up for gathering data to describe a specific experience (Robson and McCartan, 2015). They can be very useful to enable participants to develop a view on a particular aspect over time, or make sense of a change of identity, and they can be paper based or undertaken on-line. Reflective diaries require participants to be able to articulate their thoughts and reflections in writing, and are well suited for educational research (Polgar and Thomas, 2013).

Collecting Data Which Is Shared

The collection of data which is shared by participants can be considered the most common way of gathering qualitative data for pharmacy practice research. This is the case as this enables a focused investigation, where researchers remain in some control over participants' contributions, while allowing the necessary flexibility to follow ideas which were not anticipated but are relevant to the research question (Austin and Sutton, 2018). There are two main ways of collecting data which is shared by participants: one-to-one and group interviews, with the latter also being called focus groups (Bloor et al., 2000).

One-to-one interviews are very popular in qualitative research in general, as they would suit most investigations to some extent, the practicalities involved in carrying these out being less than those involved in other ways of collecting data, and they also perceived as being less intrusive than other methods such as participant observation (King and Horrocks, 2010). They enable the gathering of relevant data in great deal of depth, considering individualities and issues which are important for the specific participant from which the data is gathered (Robson and McCartan, 2015). In pharmacy practice research, one-to-one interviews

will generally be semi-structured, following an interview guide with set open questions which may also include scenarios or pictures to facilitate discussion (Smith, 2002). This interview schedule is designed to be used flexibly, and the questions that it contains often become more focused as the interview progresses in order to gather more general thoughts first, to then narrow these down to those aspects which are more closely related to the investigation (Austin and Sutton, 2018). In some cases, one-to-one interviews can go into more depth looking at life stories and including un-structured descriptions and accounts of life events (Smith et al., 2009). These are less used within pharmacy practice research, although they can lead to very powerful interpretations of specific aspects that can be presented as case studies. One-to-one interviews as always better carried out face-to-face, and this way of communication would almost inevitably lead to richer data. However, it would sometimes be adequate or necessary to undertake one-to-one interviews by telephone or video-conference, in which case practical aspects such as privacy and ensuring matters discussed are sufficiently covered should be considered to minimize any potential impact of the lack of face-to-face contact (Robson and McCartan, 2015).

Group interviews, or focus groups, are another way of collecting data which is shared by participants and are increasingly popular in pharmacy practice and healthcare research (Barbour, 2018). Group interviews generally involve 6–8 participants discussing a topic following an interview schedule with the direction of a moderator. While they do not provide the opportunity to arrive at the depth of exploration that one-to-one interviews may do, they allow for issues to be discussed as a group, and the different perspectives of the different people to be explored and developed (Polgar and Thomas, 2013). Group interviews can include individuals with similar or different backgrounds and a variety of stakeholders that can be similarly or differently affected by the issue under investigation, depending on the focus of the study. They can be very useful in research questions that look at processes or services which involve different stakeholders, and discussions where a range of perspectives can be beneficial (Smith, 2002). As many services and educational experiences are provided in this way, the use of group discussions would be very suitable to research these, as they would enable inclusion of different types of individuals that would be affected by the experience or phenomenon being researched. While group discussions are generally guided by a semi-structured interview schedule, they can also be based around the discussion of scenarios in the same way as one-to-one interviews (Krueger and Casey, 2014).

Both in the case of one-to-one and group interviews, the content of these discussions is generally audio recorded with permission from the participants (King and Horrocks, 2010). These recordings are transcribed verbatim to arrive at a written account which contains the narrative produced on the discussion. The process of transcribing the content of one-to-one or group interviews is very time consuming, but facilitates data analysis enormously as it enables easy access to the entirety of the dataset, assisting in the complex process of finding meanings (Barbour, 2018).

Ethical Issues

Qualitative research in pharmacy practice will inevitable involve human participants or data which relates to some aspect of human behavior. Even in situations where there are no specific individuals associated with information or data, for example, in some forms of documentary analysis, how the research may impact on research participants, researchers and society, is very important (Wiles, 2012). The two key aspects to consider to ensure that qualitative research is undertaken ethically mirror those involved in professional practice. These are confidentiality and consent (Wingfield and Badcott, 2007), which are very closely linked to each other. They are particularly relevant as this type of research can easily involve sensitive issues, vulnerable participants, and data which have been shared under certain assumptions (Austin and Sutton, 2018).

Qualitative research data is generally anonymized very early on in the analysis, if it included any participants' details, and while information can sometimes be held that can lead to linking specific meanings to a named person, this is not normally accessed and can be easily kept secure (King and Horrocks, 2010). Research participants may have agreed for the data they have provided and the information that enable linking it to individuals to be kept for a lengthy period of time, and even to be re-analyzed or contrasted with data from future studies (Wiles, 2012). However, there are two specific circumstances where care must be exercised. Firstly, when reporting this data, as while specific meanings may not be attributed to individual participants, it would be impossible to ensure that, due to its context or other details provided, a participant could not ultimately be identified (Smith, 2002). Another instance which can compromise anonymity is the collection of data through group discussions, where despite that it could be requested that all the participants keep the contents of any discussion private, there is no way to warrantee that this will be the case (Bowling, 2014).

An additional consideration would particularly apply to approaches for finding meanings by analyzing themes. In the more interpretive forms of this, there could be very powerful processes where individuals are making sense of reality, with meanings emerging during the research process which were not anticipated by investigators or participants (Smith et al., 2009). While constructing and sharing these meanings, participants may become aware of interpretations of their own reality which they did not have before (Crotty, 2003). This may mean that, for example, that an interview on a topic which could present itself as being relatively safe to discuss, can bring up unanticipated and sensitive issues. At the same time, investigators may find that very personal views and experiences are shared with them, which could have an effect on how they relate to the person being researched. It is therefore important that participants and investigators understand completely what is involved in a study, have time to reflect and understand this information, and in the case of those being researched, feel that they can withdraw participation at any time (Wiles, 2012). Provided that all the aspects described here with regard to confidentiality are adequately explained to participants, consent needs to extend as well to ensure that they understand practicalities, who is undertaking the study, how is funded, and ensuring that participants do not feel pressured to take part (Salkin, 2010).

Reporting and Writing up Results

Qualitative research in pharmacy practice can be undertaken for a variety of purposes, and while its design and results will have to be reported, this may be done differently depending on the nature of the research question, the approach to analysis and the type of data collected in the project (Silverman, 2016). Studies that aim to find meanings by analyzing concepts may follow prescriptive ways for presenting results provided by the authors, or arrive at a specific output at the end of the research process such as a framework or a theory (Glaser and Strauss, 1967; Ritchie and Spencer, 1994). Those where meanings are found by analyzing themes often combine results and discussion, to construct a narrative which tells a story and describes, explains and illustrates with relevant quotes from the participants, the given interpretation of the phenomenon under research (Smith, 2002). This section would focus on the reporting of these types of studies.

In the more interpretive types of research, where meanings are found by analyzing themes, difficulties can be encountered in constructing the narrative which will present the results and in making judgments with regard to how the story that this narrative provides should be told (Patton, 2015); researchers may unnecessarily be trying to arrive at a final interpretation, when this is conceptually unnecessary (Smith et al., 2009). The narrative presenting the results, and the quotes which are chosen to illustrate these, should be driven by the research question and what it is trying to answer, rather than how frequently a theme appears in the data and other similar measures which belong to the quantitative paradigm (Braun and Clarke, 2008). In this way, it is arriving at a useful and informative story what researchers should strive to do. While quotes can be perceived to provide validity checks of the researcher interpretation, they should instead enrich and illustrate this, building on the assumption that, if the analysis has been performed well, this interpretation truly describes aspects of the phenomenon under investigation (Robson and McCartan, 2015). When providing the quotes, these can be introduced with the participant number, transcript number, or similar, so there is an element of context provided within this story.

Any report from a pharmacy practice study involving qualitative data, as with any type of research, should contain an overview of previous literature (Smith, 2002). This will include not only that which is relevant to provide an introduction to what is being investigated, but also some background which relates to how this was researched and the characteristics of what was studied that led to the use of the selected approach to finding meanings and method for gathering data (Ritchie et al., 2013). For example, in a study looking at organizational factors affecting pharmacists' role satisfaction within a big pharmacy chain, previous literature would show that the phenomenon can be complex enough to need meanings to be sought by analyzing themes. The fact that pharmacists often work in isolation from each other, staff members work under their supervision and most organizational factors are under the control of their line managers need to be provided as a context to show that the investigation would better involve one-to-one rather than group interviews. After providing a clear account of what previous literature exists on the subject and any relevant context that informs the reader of background to the methods selected, the methodology followed to undertake the study will have to be reported with great deal of clarity, to demonstrate that this has been rigorous and the gathering, preparation, and analysis of the data are robust and trustworthy (Robson and McCartan, 2015). While in some types of studies it would not be appropriate to claim that there is a unique interpretation of what is being researched, it is always necessary to be transparent on how the given interpretation has been arrived at (Braun and Clarke, 2008). Otherwise the research runs the risk of being considered under-developed and with limited credibility on the results that it has arrived at. Particular attention will have to be paid to report how the meanings have been found, and if a tradition has been followed, whether any modifications to the way that is described by the authors has taken place, referencing these appropriately (Robson and McCartan, 2015).

Writing up a study involving qualitative research data can be a much lengthier process than initially anticipated, as further refining of the results arrived at can take place as part of the writing process. Researchers involved in reporting these type of studies are encouraged to start writing up results at the nearest opportunity, as this can take as long as the very time consuming process of finding meanings in the data (Salkin, 2010).

Final Considerations and Steps to Go Further

Investigators have been concerned with obtaining knowledge and what is its nature since research began to shape the way that we find out more about the world (Bowling, 2014). As explained at the beginning of this chapter, in the scientific method, which underpins quantitative research, knowledge can be considered to be factual, unique, and accessible (Popper, 1959/2002). In contrast, the qualitative paradigm is built on the assumption that knowledge is socially constructed, and only real as beliefs in individuals, with a changing nature and no longer valid by the time is identified (Patton, 2015). These two paradigms do not have to be in tension, nor the approaches described here or the traditions defined by other authors (Poth and Creswell, 2013). Researchers need to make methodological choices that suit the investigations they are undertaking and to be responsive to what it is being researched. A pluralistic approach, where barriers are limited and enquiry is led by the need to provide practical solutions to real world problems, rather than underlying assumptions about the world and knowledge could be favored (Frost et al., 2010). More experienced researchers can even go further to undertake dual analysis, looking at the same data from different perspectives, finding meanings by analyzing concepts, themes or both in different ways in order to maximize what it can tell about what it is investigated (Ryan and Bernard, 2003). The webpages included in the list of relevant websites at the end of this chapter provide more in-depth explanations, examples, and aspects to reflect on which can guide researchers wanting to further their expertise on this field. For this purpose, it can also be useful to revisit previous sections of this chapter that can

provide additional useful information on a second read, once further development of understanding of these approaches and techniques has taken place.

In the same way that early generations of researchers pushed the boundaries of accepted practices by using innovative techniques (Paley and Lilford, 2011), those starting to look at questions for which no easy methodological choices exist should continue to make this field to evolve. In this respect, some terms such as data saturation, triangulation, and mixed-methods are in decreased use, as a result of further understanding of what these methodologies are about (Teddlie and Tashakkori, 2008). Research in pharmacy practice should be guided by the needs of patients, practitioners, and service provision, and change to ensure it is able to provide answers to questions to better meet these needs.

Glossary

Analysis: Process by which research data is manipulated in order to present it in a way that makes the results more accessible to the reader.
Concept: A unit of meaning which contains an idea which is defined and described by the terminology used to relate to it, having a near literal meaning.
Data saturation: The arrival at a point in the research process where the collection of additional qualitative data to answer a specific research question is thought to no longer arrive at finding additional meanings.
Deduction: Process by which pre-specified meanings are sought in research data.
Epistemology: The branch of philosophy which studies the nature of knowledge.
Framework: An ordered presentation of results which has some structure. It aims to provide some explanation of a phenomenon but is less developed than a theory.
Hermeneutics: Method for understanding aspects of a phenomenon based on interpreting how these are perceived by individuals who relate to them closely, generally by having experienced them.
Induction: Process by which meanings emerge from research data, without being pre-specified or anticipated.
Iteration: The recurrent process of looking at meanings to frame understanding of a phenomenon, which will then determine the way by which further meanings continue to be sought.
Meanings: In the context of this chapter, meanings are concepts and themes, both of which are understood as aspects of a phenomenon.
Nominal data: Data which relates to properties, which can provide a measure of an attribute without including any numerical values.
Paradigm: A model, which could be based on beliefs about the world and what is knowledge, which underpins explanations about reality, and how this can be studied.
Phenomenon: An occurrence that can be observed and researched. This is often what a research question in qualitative research aims to describe.
Phenomenology: The philosophical study of the structures of experience and consciousness.
Philosophy: The study of the fundamental problems concerning existence, knowledge, values, reason, mind, and language.
Research tradition: An accepted overarching and distinct set of assumptions about the world and knowledge, and how this would be best understood and researched.
Scientific method: An approach to investigation based on measurement and the collection of data to test pre-formulated hypotheses and build theories.
Theme: An idea which has been extracted from a latent meaning found in data after a process of interpretation, and which has not been explicitly shared by research participants.
Theory: An ordered and structured presentation of results which aims to explain phenomena. A theory would be further developed than a framework.
Triangulation: The use of one or more methods of data collection with the purpose of corroborating or arriving to a more complete description of a phenomenon.

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Meta-Synthesis of Qualitative Research in Pharmacy Practice

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Introduction

Qualitative research in health care is a relatively new phenomenon and has gained a lot of attention in the past two decades (Shuval et al., 2011). It intends to synthesize views, experiences, behaviors, and opinions of a wide variety of pharmacy-oriented stakeholders, which may include pharmacists, patients, and other health-care providers (Tonna and Edwards, 2013). It provides a valuable snapshot on why people do what they do and focuses on extracting underlying reasons, factors, and attitudes in doing so (Austin and Sutton, 2014; Yin, 2016). A variety of methods to conduct a qualitative study in pharmacy practice have been adopted such as interviews, focus group discussions, participant observations, contextual inquiry, and document analysis (Kaae and Traulsen, 2015; Tonna and Edwards, 2013). The study sample is chosen in such a way as to bring out distinctive experiences and opinions, which may or may not include a general pattern or theme (Yin, 2016). The syntheses of a number of qualitative studies generate new evidence-based knowledge for potential use in pharmacy practice and health-related policy formation (Tong et al., 2012).

What Is Meta-Synthesis of Qualitative Research?

Much like a systematic review, a systematic approach to identify, sum up, and synthesise novel knowledge from multiple qualitative studies on a chosen topic of interest is called meta-synthesis (Barnett-Page and Thomas, 2009). According to Walsh and Down, it is a process that assembles findings from a collection of different yet interconnected qualitative studies with an "interpretive, rather than aggregating, intent" (Walsh and Downe, 2005) and as Margarete Sandelowski describes, "are more than the sum of parts, in that they offer novel interpretations of findings" (Thorne et al., 2004). The process uses a systematic style to infer readily accessible and understandable themes from studies about the topic of inquiry, to enable knowledge development (Barnett-Page and Thomas, 2009; Thorne et al., 2004).

The process of meta-synthesis goes one step ahead of systematic literature review and traditional narrative review (Britten et al., 2002). It involves translation and comparison of interpretations gathered from the selected studies into one another to synthesise new knowledge and possibly to introduce "conceptual innovation." This conceptual development through systematic charting of the concepts extracted from the available data distinguishes meta-synthesis from other methods of literature review (Britten et al., 2002). It enhances the power of available qualitative data by generating theories that can be further explored and investigated (Britten et al., 2002; Sandelowski, 2007). However, the analysis and interpretations, otherwise known as third-order interpretations, depends mainly on the "judgment and insights of the reviewers" (Noblit and Hare, 1988; Thomas and Harden, 2008). Hence, an interdisciplinary team can further improve the quality of a meta-synthesis (Lachal et al., 2017).

Several scholars have illustrated the process of meta-synthesis. Thorne explains meta-synthesis as a process that,

> "demands exploitation of variations and complexities within the data set toward an integrative conclusion that extends beyond the scope of what would have been achievable within the temporal, spatial, or epistemological confines of individual studies or programs of research" (Thorne, 2008).

Barroso explains it as a method that "refers to both an interpretive product and the analytic processes, by which the findings of studies are aggregated, integrated, summarized, or otherwise put together" (Julie et al., 2003). Meta-synthesis is an umbrella term and has been used interchangeably with meta-ethnography and qualitative meta-analysis many times (Finfgeld, 2003).

A classic explanation of meta-synthesis by Schreiber states,

> "it is the bringing together and breaking down of findings, examining them, discovering the essential features, and, in some way, combining phenomena into a transformed whole" (Schreiber et al., 1997).

Types of Meta-Synthesis

There is no definite rule to perform meta-synthesis. It can be done in a number of different ways, and each technique has a name as proposed by Schreiber (Schreiber et al., 1997) and explained by Finfgeld (Finfgeld, 2003). These approaches overlap in many instances and can go hand in hand (Finfgeld-Connett, 2010). A brief description of the types of meta-synthesis is as follows:

1. Theory building, for example, grounded formal theory or meta-study
2. Theory explication
3. Descriptive meta-synthesis or meta-summary
4. Meta-ethnography

Theory building is the approach of meta-synthesis that involves building either a formal theory using "Grounded formal theory" or creating a new theoretical interpretation using "meta-study" method based on findings found from the qualitative studies included in the process (Finfgeld, 2003). Theory explication reconceptualizes an original concept. It involves a deconstruction, followed by a reconstruction and finally synthesis of the findings around a single concept. In descriptive meta-synthesis, original findings are evaluated comprehensively (Finfgeld, 2003).

Meta-Synthesis of Qualitative Research in Pharmacy Practice

The aim of meta-synthesis in pharmacy practice qualitative research is to combine, understand, and synthesize findings from the present pool of empirical qualitative studies around a phenomenon and then to generate a comprehensive understanding of that phenomenon (Sandelowski, 2007). It has been applied expansively in health-related research and has branched out into the field of pharmacy practice. A well-executed qualitative pharmacy practice meta-synthesis has the potential to develop new knowledge and understandings. This also has the capability to help make evidence-informed policy decisions and value-added clinical choices (Finfgeld-Connett, 2010; Mohammed et al., 2016b).

The approach of meta-synthesis is in its infancy in pharmacy practice qualitative research and here are a few examples of qualitative meta-synthesis.

Examples of Meta-Synthesis in Pharmacy Practice

Illustrated examples of meta-synthesis in pharmacy practice research (2005 till 2018)

Categories	*Examples*	*Synthesis*
Pharmacy services	Qualitative meta-synthesis of barriers and facilitators that influence the implementation of community pharmacy services: perspectives of patients, nurses, and general medical practitioners (Hossain et al., 2017)	Three-stage method for thematic synthesis described by Thomas and Harden (2008)
Meaning of medications for patients	Understanding the meaning of medications for patients: The medication experience (Shoemaker and Ramalho de Oliveira, 2008)	Analytic technique, "free imaginative variation" to determine the essential, structural themes
Perceptions and experiences of taking oral medicines	Perceptions and experiences of taking oral medications for the treatment of Type 2 diabetes mellitus: a systematic review and meta-synthesis of qualitative studies (McSharry et al., 2016)	Meta-ethnography model described by Noblit and Hare (1988)
Accessibility and affordability of medicines	Trans-Pacific Partnership Agreement and Its Impact on Accessibility and Affordability of Medicines—a meta-synthesis (Yap et al., 2017)	Meta-synthesis—thematic analysis
Migraine patients' perspectives regarding migraine treatment	Meta-synthesis on migraine management (Minen et al., 2018)	Meta-synthesis—thematic analysis
Medication-related burden and patients' lived experience with medicines	Medication-related burden and patients' lived experience with medicine: a systematic review and meta-synthesis of qualitative studies (Mohammed et al., 2016a)	Meta-ethnography methods and a comparative thematic analysis
Patients' experiences and perceptions of receiving benzodiazepines and Z-drugs	A systematic review and meta-synthesis of patients' experiences and perceptions of seeking and using benzodiazepines and Z-Drugs: toward safer prescribing (Sirdifield et al., 2017)	Thematic synthesis

Step-by-Step Guide to Meta-Synthesize Qualitative Literature in Pharmacy Practice

There are a number of recommended guidelines to synthesize new and overarching knowledge from the existing qualitative studies (Lachal et al., 2017; Noblit and Hare, 1988; Tong et al., 2012; Walsh and Downe, 2005). These guidelines coincide in many respects and have differences as well; however, none are binding or all-encompassing. Based on our literature review, some of these guidelines assume an "aggregate" approach toward meta-synthesis, while most incline toward "interpretative" style. A multidisciplinary meta-synthesizing team is deemed important "to assess rigor and develop richer and more complex understandings" of the data (Lachal et al., 2017). The team can choose one author's guidelines or may combine two or more depending on the nature of their review and the intended approach.

The earliest work on meta-synthesis is done by Noblit and Hare, who recommended seven steps to perform a meta-ethnographic synthesis: *getting started:* the initial stage where the meta-synthesizers build an interest in their research topic; *deciding what is relevant to the initial interest:* the stage where relevant qualitative studies are sought and included; *reading the studies*: to read the included studies in-depth; *determining how the studies are related*: creating a list of relevant concepts and chunks from all the studies and establishing a relationship among them; *translating the studies into one another*: the stage in which all the extracted concepts and chunks are compared and contrasted; *synthesising translations*: bringing together all the concepts and chunks in one new piece; and *expressing the synthesis*: as a written paper or in the form of a video (Noblit and Hare, 1988). Later, Walsh and Down illustrated five stages of meta-synthesis, which include framing the scope of the meta-synthesis, locating relevant papers, framing the inclusion criteria, appraising the studies, and finally analyzing and synthesizing (Walsh and Downe, 2005).

Tong advanced the concept of standardizing the process of qualitative synthesis as a whole by composing the ENTREQ (The Enhancing transparency in reporting the synthesis of qualitative research) checklist, which provides an all-encompassing framework to report the key steps in qualitative syntheses (Tong et al., 2012). This 21-item checklist gives a very broad sense of planning and executing a synthesis and covers five general domains: introduction, methods and methodology, literature search and selection, appraisal, and synthesis of findings (Tong et al., 2012).

After reviewing a set of seminal academic work on meta-synthesis, the following step-by-step guide provides comprehensive information for reviewers who intend to design and conduct a meta-synthesis.

Step 1 Frame a Clear Research Question/Objective

A clear and focused research question or objective should be established before diving into the process of meta-synthesis. One rational approach to frame the research objective is to have a preliminary review of the available qualitative literature. Therefore, a preliminary literature search on the topic of interest is required to ensure that enough data are available to meet the merit of a meta-synthesis. The team aiming to write a meta-synthesis should be clear about "What" and "Why" of their research objective.

In one example, the research question in a qualitative meta-synthesis was to pinpoint barriers and facilitators to implement community pharmacy services in Australia from the available literature (Hossain et al., 2017). Just like a systematic review of primary studies, they conducted a systematic search in three databases, namely, PubMed, Scopus, and Informit, to find studies that explored patients', general practitioners', and nurses', perceptions about community pharmacy services in Australia.

Step 2 Strategize the Search

The next step is to establish a strategy to systematically search for the required literature. However, there is no clear consensus on the need to follow some sort of methodical search strategy, and this is one way where a meta-synthesis differs from systematic review (Britten et al., 2002; Tong et al., 2012). Furthermore, for a meta-synthesis, there is no set requirement on the number of studies to include (Thomas and Harden, 2008). The process of data inclusion can terminate once saturation is achieved.

The search strategy includes a set of rules to find and select studies starting off by identifying the databases that are relevant to the research objective. Commonly used databases include PubMed, EMBASE, Web of Science, CINAHL, COCHRANE, SCOPUS, and ProQuest. Search terms or queries are developed based on the target topic. These search terms or queries can be developed using a number of search tools such as PICO, PICOS, and SPIDER (Alison et al., 2012; Curtin University, 2018).

PICOS and SPIDER are intended for qualitative and mixed methods evidence synthesis. Whatever search tool or concept is preferred, it results in a list of relevant key words or search terms. The PICO tool (Curtin University, 2018) is the most comprehensive one and focuses on the *Population, Intervention, Comparison and Outcomes*. It is intended for quantitative evidence synthesis but has been descrambled to suit qualitative setting as *Population, Interest and Context* (Curtin University, 2018). The PICOS tool focuses on the *Population, Intervention, Comparison, Outcomes and the Study design* of an article. The SPIDER tool, developed by Cooke et al. focuses on *Sample, Phenomenon of Interest, Design, Evaluation and Research type* (Alison et al., 2012). It narrows down the initial number of articles due to its high specificity (Methley et al., 2014). Methley recommends SPIDER for researchers achieving systematic narrative reviews of qualitative literature but finds it less effective than PICO (Methley et al., 2014). To translate the research topic more effectively into search queries, Boolean operators OR, AND, and NOT can be used with the search terms.

The search strategy may also include the following filters:

1. Original qualitative studies: Would you include only qualitative studies or mixed-methods too?
2. Language: Would you include studies published in English only?
3. Time span: What would be the time span, e.g., from 2000 to 2018, to search studies?

One way of reporting the search strategy clearly is by using the PRISMA tool. Although meant for systematic reviews and meta-analyses, it is a comprehensive tool to enhance the quality of search strategy (Moher et al., 2009).

The search strategy of a meta-synthesis on women's experiences of their pregnancy and postpartum image used PICO tool—Population (pregnan* OR postnatal OR postpartum OR prenatal OR antenatal OR *gravida* OR *parou) and Outcome (appearance OR body image OR body dissatisfaction). In addition, the researchers observed PRISMA guidelines to report their methods (Hodgkinson et al., 2014).

Step 3 Define and Refine an Inclusion Criterion

Once an initial list of studies has been finalized, the meta-synthesis panel will review all the studies to filter the ones that meet the inclusion criteria. In general, a study may be included based on the following information:

1. Relevance to the research objective
2. Relevance to the design methodology predefined by the meta-synthesis panel
3. Published in a peer-reviewed journal

At first, the screening process includes reading the titles and abstracts of all articles to evaluate if they align with the research objectives. Later, the preferred literature is refined by reading full text articles. Another recommended manual practice is to adopt the "pearl-growing" technique, which is to hand-search the reference lists and selectively choose additional research articles from the included literature (Schlosser et al., 2006). This way citations are thoroughly screened to assess their eligibility to be included in the meta-synthesis.

An optional yet valuable step is to do a quality appraisal of included studies. Most researchers have found it useful (Atkins et al., 2008; Tong et al., 2012; Uhrenfeldt et al., 2013). It could be performed by using any quality assessment tool from a plethora of options such as Critical appraisal skills program (2017), The Joanna Briggs Institute Reviewers' Manual (2015), checklist designed by Atkins et al. (2008), etc. An assessment of the quality of the selected studies can make a difference in the overall quality of the meta-synthesis. Before selecting a study for review, the reviewers can check its trustworthiness and rigor, i.e., Are the findings credible? or How valid is the data? (Sullivan and Sargeant, 2011).

Levack and his team explored the use of meta-synthesis to inform discussion on the selection of outcome measures for evaluation of services provided to adults with traumatic brain injury using several databases. They included studies comprising adult participants between 1965 and 30 June 2009. The search strategy was based on text–words and Medical Subject Headings terms intended to detect studies that talked about the key components of topic (Levack et al., 2010):

1. patients with TBI—search terms "exp Craniocerebral trauma/," "exp Cerebrovascular Trauma/," "brain injury," as a text–word, etc.,
2. study methodology of interest—search terms such as "exp Qualitative Research/," "qualitative" as a text–word, "grounded theory" as a text–word, etc., and
3. phenomena of interest, e.g., text–words concerning the concepts of experience, outcome and recovery

Step 4 Synthesize New Knowledge

This phase is the essence of a meta-synthesis. After finalizing the studies to be included, the meta-synthesis team can read the studies together with extracting relevant codes and themes. Later, all the codes and themes are organized together to look for similarities and differences and can be grouped under major themes or concepts. These themes are then further discussed and refined.

1. **Reading and analyzing to generate analytical themes**
   The reading phase is the nucleus as all the subsequent steps are dependent on this step. Effective reading might involve: R = recording, E = extracting, A = appraising, D = describing (Lachal et al., 2017). Careful reading of each study is essential to familiarize oneself with the original content and with the prominent findings across all the studies (Noblit and Hare, 1988). These findings are in the form of either interpreted data, original quotes, documents, or notes. In addition, formal details about each study, which may include study context, location, methodology and data analysis, should be recorded and presented in the final report (Lachal et al., 2017). During and after this phase, each member of the panel should start extracting codes and themes they find relevant to their research objective or theoretical framework. For the management of qualitative data, NVivo, a computer software, is a recommended tool (Mohammed et al., 2016b). Data extraction and management could be done by other ways too, for instance, using a methodological framework that entails categorizing extracted data in a tabular form or in groups or in the form of a grid (Britten et al., 2002) and then codifying that data for themes and concepts related to the topic under study (Graneheim and Lundman, 2004).

In principle, data analysis, that is, coding and/or thematizing, can be performed simultaneouly on both forms of the data, that is, informant quotes (findings/results) and authors' interpretations (dicussion). At this stage, initial extracted themes or concepts should be clustered in one place, be it NVivo or a simple Excel sheet, to have an idea about the available data. This would help in translating the studies into one another. One way of doing the analysis is using Noblit and Hare's ethnographic approach to begin with identifying the first-order constructs. These are key findings or codes identified by the reviewers from the original quotations in the studies. This should be followed by identifying the second-order constructs, which are extracted key findings or codes from the interpretations done by the authors in the discussion section of the studies (Noblit and Hare, 1988). The reviewers generate their third-order constructs, which are the final product of a meta-ethnography, based on the first- and second-order constructs (Thomas and Harden, 2008) translated across all the studies. These synthesized third-order constructs open on to the synthesis of new knowledge that might take the form of a succinct conceptual "line of argument" that goes "beyond the content of the original studies" (Thomas and Harden, 2008), and/or a new model or theory (Atkins et al., 2008; Lachal et al., 2017).

Data analysis can also be performed by following the six phases of thematic analysis described by Braun and Clarke: (1) familiarization with the data; (2) coding; (3) searching for themes; (4) reviewing themes; (5) defining and naming themes, and; (6) writing up (Braun and Clarke, 2006). In addition, Thomas and Harden describe thematic synthesis in three steps (Thomas and Harden, 2008). The first step is coding of findings of studies "line-by-line" and to group the codes based on similarities and differences between them. This step complements Noblit and Hare's recommendation to translate studies into one another, that is, themes from one study are compared with themes from another, through a repetitive comparison of similarities and differences across studies. The second step is the development of "descriptive themes" to describe the cluster of codes and/or concepts. Third, the generation of "analytical themes" where comprehensions of the reviewers are included that act to a specific review question and/or a theoretical framework. (Thomas and Harden, 2008). The analytical process in meta-synthesis works by an initial deconstruction of "what is known" and "how it is known" (Paterson et al., 2001). It includes extracting, aggregating, interpreting, and finally synthesizing the analytical themes from primary qualitative studies (Sandelowski, 2007).

Conceptually, analytical themes seem very much like third-order interpretations; however, according to Thomas and Harden, they differ based on the types of review questions. Analytical themes are constructed by comparing and contrasting the descriptive themes with a specific review question. In contrast, third-order interpretations build on the data to attend to a comprehensive or emerging review question (Thomas and Harden, 2008).

At this stage, the meta-synthesis team has developed key overall concepts or translations across studies, which are synthesized to grow into overall new interpretations or understandings (Britten et al., 2002; Noblit and Hare, 1988). The SAGE encyclopaedia of Qualitative Research Methods elaborates on this step as:

> "the meta-synthesist's task is not simply to determine a best fit, but rather to transform the data set that exists, with all of its inherent strengths and limitations, into a new conceptualization with the capacity of integrating the entire body of qualitatively derived knowledge about the phenomenon" (Given, 2008).

In one example, the reviewers adopted thematic synthesis to synthesize new insights about suicidal youths' care in the field of psychiatry. They developed their third-order interpretations to recommend a more conceptual line-of-argument or conclusion stating that "the violence of the message of a suicidal act and the fears associated with death lead to incomprehension and interfere with the capacity for empathy of both family members and professionals" (Lachal et al., 2017).

2. **Going back and forth to confirm analytical themes**

With codes, core themes as structured data sets or constructs, and analytical themes in place, clarification is done next through in-depth examination and analysis. Both Braun and Clarke and Thomas (Braun and Clarke, 2006; Thomas and Harden, 2008) emphasize that thematic analysis is an iterative process—moving back and forth between the stages is recommended as part of reconsidering original data. The analytical themes now require team work to redetermine the analysis with frequent discussions on the extracted common themes and on the emerging themes or concepts by recurrent returns to the original data.

A meta-synthesis on perceptions and experiences of taking oral medications for the treatment of Type 2 diabetes mellitus by McSharry et al. translated the included studies by identifying one paper and adding it to the first row of the translation table. Subsequent papers were added to this translation table in chronological order of publication. Later, they assessed the relationships, variances, and contradictions across studies to develop twelve overall translations. Three third-order constructs, such as (1) medication for diabetes: a necessary evil, (2) the passive patient as active experimenter, and (3) taking oral medication for Type 2 diabetes: a unique context, were established (McSharry et al., 2016).

3. **Framing the syntheses output**

After interpreting, reinterpreting, and analyzing the formulated theories and concepts across the studies, the final meta-synthesis report should generate a synthesis of new knowledge, understandings, and interpretations that go beyond a compilation of the primary studies. This new knowledge could be a new model of evidence, a critical framework, or a new theoretical insight (Tong et al., 2012). **Fig. 1** illustrates the process of meta-synthesis.

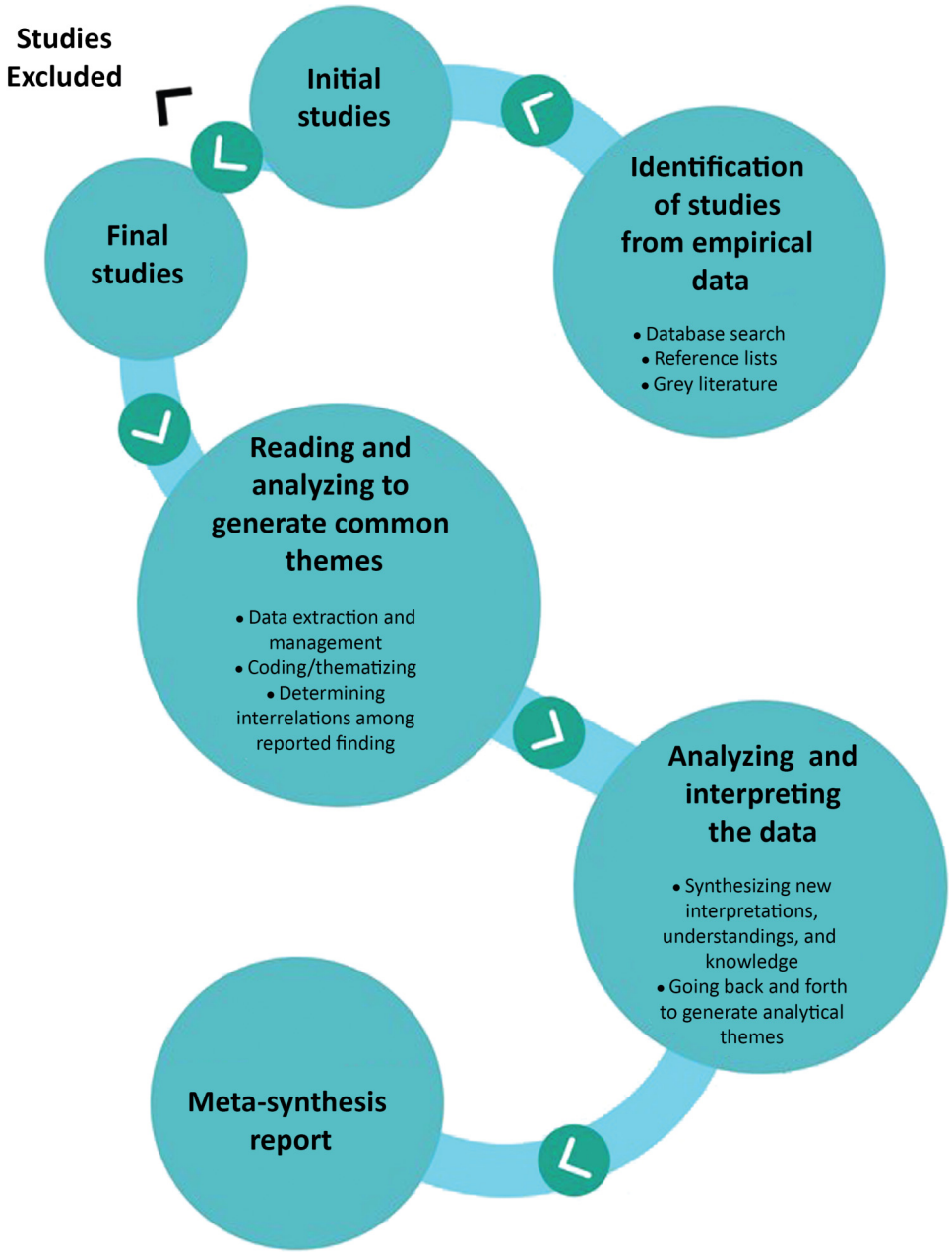

Figure 1 The step-by-step process to prepare a meta-synthesis report.

Conclusion

This chapter summarizes the key stages to conduct a meta-synthesis illustrating examples from the qualitative literature. Meta-synthesis is an important approach in qualitative research, and this aims to aggregate, interpret, and present previous findings to synthesise new knowledge for a wide range of health-related stakeholders. It is a rigorous way of fusing several qualitative findings to generate new knowledge for potential application in pharmacy and clinical practice, and to inform policy.

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Mixed Methods Research in Pharmacy Practice: Basics and Beyond

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Introduction

The role of pharmacists has become more patient oriented in the past couple of decades. Pharmacists are now involved in direct patient care and play a crucial role in ensuring safe and effective use of medicines in both community and hospital settings (Dhanani et al., 2017). In this context, pharmacy practice research is critically important to generate evidence to support and identify weaknesses, if any, for improvement of pharmacy services within health care systems (Bissell and Traulsen, 2005). Although, mixed methods is not a new methodology, it has become more popular in the last decade as it brings together strengths of both qualitative and quantitative approaches (Creswell and Plano Clark, 2018; Johnson et al., 2007; Pelto, 2015). Mixed methods research offers an alternative methodology to researchers who seek to answer complex research questions requiring both qualitative and quantitative approaches within a single study (Creswell and Plano Clark, 2018). Furthermore, it allows researcher to choose and mix methods from both qualitative and quantitative methodologies best suited to answer the research question.

In this chapter a range of topics related to mixed methods methodology have been discussed including typologies of mixed methods methodology, methods of integration of qualitative and quantitative strands within a mixed methods study, challenges in undertaking these studies, how to evaluate quality of these studies and examples of research questions that can be answered by mixed methods studies. These examples have been taken from the recent pharmacy practice literature.

What is Mixed Methods Research?

Mixed methods is often referred to as the *third methodological movement* (Teddlie and Tashakkori, 2009; Venkatesh et al., 2013). Although, mixed methods studies have both qualitative and quantitative components but how and when these strands should be combined is still a hotly debated area among methodologists (Tashakorri, 2007). Various terminologies have been used in the literature to describe mixed methods research including "integrated," "hybrid," "mixed research," "mixed methodology," "mixed methodology research," "combined," "multimethod," and "methodological triangulation" (Bryman, 2007; Driscoll et al., 2007; Johnson et al., 2007; Morse, 1991). Johnson et al. (2007) analyzed definitions of mixed methods provided by a number of "leaders" in the field. After analyzing these definitions, they defined mixed methods research as a type of research *"in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of breadth and depth of understanding and corroboration."* (p. 123).

This definition was extended with a definition of the research type:

> "A mixed methods study would involve mixing within a single study; a mixed method program would involve mixing within a program of research and the mixing might occur across a closely related set of studies" (p. 123).

Figure 1 Knowledge cycle illustrating phases in the planning of mixed methods research design in pharmacy practice.
Source: Adapted from Creswell and Plano Clark (2018).

Tashakkori and Creswell's (2007) defined mixed methods research in the first editorial of *Journal of Mixed Methods Research* as *"research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or program of inquiry"* (p. 4).

The key message from these definitions is that the mixed methods designs should be not used as a "tool" to collect two different datasets but there should be purposeful integration between qualitative and quantitative datasets to comprehensively answer the research question.

Planning of Mixed Methods Research

Several frameworks have been developed to guide on how to conduct and evaluate mixed methods research (Creswell et al., 2011; Tashakkori and Teddlie, 2010; Wisdom et al., 2012). In this chapter, we have adapted and modified framework developed by Creswell and colleagues (Creswell and Plano Clark, 2018) to illustrate the planning of a mixed methods research design (**Fig. 1**). In the first phase, the researcher would be driven by their curiosity regarding a theme or issue within the health-care setting. According to King et al. (1994), intellectual stimuli are the "purest" drive for conducting research (King et al., 1994). If the researchers decide to pursue this curiosity, they will have to formulate objectives and research questions which require a mixed methods approach. The rationale for using a mixed methods research design should always be justified and should result in more valuable and comprehensive findings than using a single method (Creswell and Plano Clark, 2018).

After formulating a strong research question/objective, a suitable methodological approach must be considered. The selection of appropriate mixed methods research study design in pharmacy practice must always be guided by the research question (Hadi et al., 2013a). There are a few questions which researchers need to ask themselves to establish if a mixed method approach is suitable for the planned study; Do the posed questions have quantitative and qualitative elements? How will the quantitative and qualitative methods be prioritized? In which sequence will they be conducted? And how and when will the integration of data take place? (Creswell and Plano Clark, 2018; Liamputtong, 2013). The sample size, data collection, data analysis must be planned for both qualitative and quantitative phases, and ethical approval should be obtained, if necessary. It is also critically important to consider and plan the integration and interpretation of the data. All these steps should be clearly and transparently reported in a manner that other researchers can replicate the methods. Authors must reflect on the findings of the study and explain how the use of mixed methods has helped to answer the original research question.

Mixed Methods Research Designs: How to Use Them?

Choosing between mixed methods designs is challenging (Creswell and Plano Clark, 2018; Leech and Onwuegbuzie, 2009). It is recommended for new researchers to familiarize themselves with established mixed methods research designs and choose a suitable

mixed methods design based on the research question (Bryman, 2007; Driscoll et al., 2007). Although, mixed methods research is a flexible methodology, it is important that the study design is justifiable and the pros and cons of all available study designs are weighed carefully (Creswell and Plano Clark, 2018).

Several typologies and classifications of mixed methods research exist in the literature (Greene et al., 1989; Leech and Onwuegbuzie, 2009; Teddlie and Tashakkori, 2009). We need to consider how each component will be integrated when the data have been collected. The following four guiding questions can help researcher to choose best mixed methods design for their research study (Creswell and Plano Clark, 2018):

- First, the researcher should decide the level of interaction between qualitative and quantitative strands. Will the qualitative and quantitative strands be kept independent or interactive?
- Secondly, the researcher must decide on the timing of data collection of both qualitative and quantitative strands. Quantitative and qualitative data can be collected sequentially or concurrently.
- Thirdly, the researcher needs to consider weighing of each component in mixed-methods design. Will the quantitative or qualitative component be given priority in answering the research question, or will they be weighed equally?
- Lastly, the researcher must decide the timing of integration of two datasets, as this can happen at different phases of the research (i.e., during data collection, data interpretation, etc.).

The four commonly used typologies used in mixed methods research are described below together with an example of their application from published pharmacy practice literature.

The Exploratory Sequential Design

In this design, the research is conducted in two sequential phases. This qualitative component is conducted first and is given more weighing in answering the research question. The quantitative component is used to generate generalizable data from the qualitative phase (Hadi et al., 2013a; Morse, 1991; Teddlie and Tashakkori, 2009; Wittenberg, 2000).

Fisher et al. (2018) conducted a mixed methods study to gain understanding of pharmacist independent prescribers' knowledge, perception and beliefs about departmental infrastructure, pharmacy and multidisciplinary team support, attitudes and behavioral determinants associated with prescribing. The study was conducted across 14 health care boards in Scotland. The qualitative data, gathered through focus groups and semistructured interviews of pharmacist independent prescribers, informed the design of a structured questionnaire (online cross-sectional survey) used to assess knowledge, perception, attitudes, and beliefs toward prescribing. Using mixed methods as methodological approach in this study allowed not only generalizable results but also provided broader insight to which organizational culture changes are required to influence prescribing.

The Explanatory Sequential Design

This design also consists of two phases. The quantitative component is conducted first and is given preference in answering the research question. In the first phase, quantitative data are collected and analyzed. In the second phase qualitative data are collected. This method is suitable when the qualitative component is needed to explain and clarify findings from the quantitative component (Hadi et al., 2013a; Morse, 1991; Teddlie and Tashakkori, 2009; Wittenberg, 2000).

Stewart et al. (2018) used an explanatory mixed methods research design to explore behavioral determinants related to error reporting among health care professionals. In the first phase behavioral determinants were identified through a cross-sectional survey. The authors reported that medication error reporting was associated with issues related to emotions and belief of consequences. Although, all health care professionals included in the sample had these issues, however, these were more common among younger health care professionals. In the second phase of the study, focus group interviews were conducted to develop an in-depth understanding of the survey findings. The data from the two components were triangulated at the completion of study to get a broader understanding of medication error reporting.

The Convergent Parallel Design

In convergent parallel design, the quantitative and qualitative components are undertaken at the same time. Each component is carried out independently but at the same time (i.e., each dataset is collected, analyzed and then findings are integrated during the interpretation phase). The study design allows to triangulate findings from the two components in order to understand the research question. For this reason, the study design is also referred to as "current triangulation," "simultaneous triangulation," and "parallel study design" (Hadi et al., 2013a; Morse, 1991; Teddlie and Tashakkori, 2009; Wittenberg, 2000).

El-Jardali et al. (2017) used a convergent parallel mixed methods research design to investigate the attitudes of community pharmacists and their practices in relation to the implementation of the generic drug substitution policy in Lebanon. The two components in the study were given equal priority. The quantitative component (self-administered questionnaires) was followed by the qualitative component (semistructured interviews). The aim of both components was to document experiences while implementing this new policy. In the quantitative phase, respondent's attitudes toward generic substitution and outcomes of the new generic drug substitution policy were measured. The semistructured interviews supplemented the quantitative findings by

expanding on the participants' experiences by exploring perceived barriers and facilitators. The data collection was carried out separately, but the findings were interpreted and reported together.

The Embedded Design

In the embedded design, one component act as a principal method and the other component is used as a "supportive method." Depending on the study objectives, both qualitative and quantitative components can act as the principal method. The data can either be collected concurrently or sequentially. The research design is suited when the researcher intends to use different methodologies for different research questions within the same study (Hadi et al., 2013a; Morse, 1991; Teddlie and Tashakkori, 2009; Wittenberg, 2000).

Hadi et al. (2013b, 2016a,b) conducted a mixed methods study to evaluate nurse pharmacist managed pain clinic. The quantitative component evaluated the impact of clinic on patient reported outcomes (e.g., pain intensity, physical functioning, and quality of life) and qualitative component explored patients' experiences of the clinic. This research design allowed the authors to answer different research question within a single study by using different methods. Quantitative method was given priority in answering the research question and the qualitative component (semistructured interviews) were used as supportive method which generated data associated with the quality and effectiveness of the service and interaction with the nurse and pharmacist.

Literature Review: Mixed Methods Studies in Pharmacy Practice

To develop a broader picture of how mixed methods research designs have been used in recent pharmacy practice literature, a scoping literature review was undertaken. We searched PubMed for studies describing or evaluating the roles of pharmacist and pharmacy interventions using mixed methods design in the past five years (1 June 2013–31 May 2018). During our search we used the keywords: "Pharmacy practice," "pharmacy," "pharmacist," "mixed methods," "pharmacy interventions," "public health pharmacy," "health system pharmacy," "health pharmacist," "medicine use," and "Health care." The search was restricted to only include full-text research articles only published in English language. Fifty-three articles were identified for full-text review. The final sample included 35 relevant articles after duplicates were removed (date of search; 8 August 2018). The included studies were conducted in UK (15)), USA (3), Qatar (2), Uganda (1), Guatemala (1), Ghana (1), Iraq (1), Australia (2), Korea (1), India (2), Lebanon (1), Thailand (1), Canada (1), Brazil (1), Netherlands (1), and Switzerland (1). This highlights that mixed methods approach has gained popularity among pharmacy practice researchers across the world. The studies were conducted in community pharmacies, primary care settings, hospitals and clinics. Mixed methods studies investigated pharmacy services, physicians' attitudes and perception, medicine use, and education and knowledge of patients.

In the literature review, all the studies were labeled as mixed methods studies, however only one-fourth of the studies described and justified the application of the mixed methods design.

There were few examples of multimethods research inappropriately labeled as mixed methods. As mixed methods has evolved over time, we believe that the mixing of quantitative and qualitative methods should only be labeled as mixed methods research. Labeling multiple methods of collecting qualitative or quantitative data only as mixed methods research design is inappropriate and should be discouraged.

The quantitative component in included studies mostly consisted of surveys. There were more variations in the use of the qualitative component which included interviews, focus groups, observations, and document analysis. Only four of the included studies described how the quality of the collected data was assessed. The description of the integration between quantitative and qualitative components was found to be very shallow in most studies. Scarce details and unclear reporting of a study does not only make it hard for the reader to understand the intend of the study but also makes it low quality research.

Approaches of Integration of Findings in Mixed Methods Research

As previously mentioned, mixed methods research does not only involve mere collection quantitative and qualitative data. Without meaningful integration, the true purpose of undertaking mixed methods study would not be fulfilled. The integration of data starts as early as at the planning stage of the research (e.g., study design and methodological approach). In the early days of mixed methods research, Jick and colleagues acknowledged the method's ability to draw on the strengths of individual qualitative and quantitative methods used in the study (Jick, 1979).

Hammersley (1996) proposed the following three methods for integration of qualitative and quantitative data: triangulation, facilitation, and complementarity. There must be a clear reflection from the beginning of the study on how one approach will be supporting the other (Venkatesh et al., 2013). The literature describes triangulation as a method to study a research question using multiple methods (Fetters et al., 2013; O'Cathain et al., 2010). The literature classifies triangulation into four categories: methodological triangulation, theory triangulation, data triangulation, and investigator triangulation (Denzin, 2009). There are limitations with regard to a step-by-step guidance on how to perform triangulation of results in health care studies (Jick, 1979; Östlund et al., 2011). Farmer and colleagues have developed a triangulation protocol which can help increase transparency in the conducted research regardless of the used typology (Farmer et al., 2006). In terms of triangulation the researcher must consider three aspects of

the research methods: First, explore the research process itself (e.g., did the applied methods answer the posed research question). Second, look for incongruity in the used method; are the findings the same or do they contradict each other? Finally, look at how the methods complement each other; which results are gained from each method (Farmer et al., 2006)? O'Cathain et al. emphasizes the importance of making an informed decision about the weighing of the used dataset (O'Cathain et al., 2010). Currently, these decisions are likely to be subjectively assessed. If there is no consensus approach on how to order triangulated datasets, these decisions are left to the researcher. Farmer et al. (2006) described that these decisions should be based on the contribution each method brings toward answering the research question (Farmer et al., 2006). One method can be used to validate the findings from the other method. Quantitative data can, for example, be used to explain findings from qualitative data (Fetters et al., 2013).

Quality in Mixed Methods Research

It is commonly agreed that health services research should be reported transparently (Creswell and Tashakkori, 2007; O'Cathain et al., 2008b; Wisdom et al., 2012). The literature reports on various methods for evaluating the quality of quantitative and qualitative methods on their own. During our review of pharmacy practice literature, we found that there is a lack of definition of the mixed methods research. There are currently several definitions of "mixed methods" (Creswell et al., 2004; Johnson et al., 2007) and it is important to justify and describe the adapted definitions, so the reader can make an informed judgment of the quality of the study.

There is a lack of consensus in the description of quality of a mixed method study. This is also being observed in other areas of health serviced research (Hadi and Closs, 2016b; O'Cathain et al., 2008b). One reason for this trend could be that there is a lack of consensus guidelines on how to evaluate mixed methods research designs. Currently there are no rules on how to evaluate mixed methods research. However, there are several mixed methods guidelines and frameworks proposed in the literature (Hadi et al., 2014a; Leech and Onwuegbuzie, 2010; NIH, 2018). The mentioned guidelines and frameworks have a common goal to improve reporting quality. The key elements in the guidelines are to: justify the used methods approach, describe the mixed methods design (priority, purpose, sequencing, and stage of integration), describe the used methods (sample size, data collection, and analysis), describe how, when, and where integration has occurred and identify limitations related to the applied research design. Adhering to these guidelines and frameworks as well as to individual standards for the quantitative and qualitative components is recommended. In terms of integration of data and how will disagreements between two components be dealt with. It is important to emphasize that it should be described how these disagreements will be resolved to allow the reader to asses quality of the study (Curry et al., 2013; O'Cathain et al., 2010).

To summaries, different disciplines uses different typologies within mixed methods research design (Tashakkori and Teddlie, 2010). There are no rigorous rules on how to validate mixed methods research designs, and hence it is up to the individual researcher to choose an appropriate method to evaluate their study design.

What are the Challenges in Using Mixed Methods Research

Mixed methods is as challenging as any other method, expertise in multiple areas is required due to the use of quantitative and qualitative methods in the same study.

Conducting mixed methods research is time consuming and expensive, hence the researcher must consider if they have the necessary time and resources to carry out mixed methods research (Ivankova et al., 2006). The researcher also needs to consider, whether one has the necessary skills to conduct mixed methods research. In the past, the tendency has been toward studies being carried out by researchers who either possess quantitative or qualitative skills. This trend has changed toward research projects being carried out in research teams utilizing the individual researcher's strengths across disciplines (Hadi et al., 2014a,b; O'Cathain et al., 2008a). A lead investigator with research experience with quantitative and qualitative methodologies can act as in an important bridge in the mixed methods research team. There is currently no standard systematic way to conduct a mixed methods study. A well-considered rationale for the approach may help ease this process (Hadi et al., 2014a). Bryman suggests that it is not easy to make sense of one's findings the mixed methods research designs may need to be reconsidered (Bryman, 2007). Lastly, there is the question of reaching a wider audience. Policymakers and practitioners need multiple forms of evidence to document and inform a research problem. Pioneers in the application of mixed methods in pharmacy practice have reported that it has been challenging to report on mixed methods without compromising on the transparency of the design due to the journals word limit of original articles (Hadi et al., 2014a,b; Wisdom et al., 2012).

Application of Mixed Methods Methodology in a Program of Inquiry

Until now, the focus of this chapter has been on the use and application of mixed methods research within a single study (fixed mixed methods designs), however, mixed methods approaches (emergent mixed methods designs) can be used within a program of enquiry. Emergent mixed methods arise to resolve quires and address issues that develop during the process of conducting research (Creswell, 2018). To illustrate this we will use an example of health services evaluation of a chronic pain service. As part of these

services the pharmacist conducted medication reviews and offered medication related advice to ensure safe and effective use of medicines. The nurse educated patients about pain, clarified misconceptions, managed treatment expectations, and promoted self-management of chronic pain. The original focus of the research at the beginning of protocol development was to evaluate a community-based nurse-pharmacist managed pain clinic using a mixed methods design (Hadi et al., 2013b, 2016a). However, during extensive literature review and the course of the study, following additional questions arose:

1. Is pharmacist-led medication review effective in the management of chronic pain in adult patients?
2. What is the magnitude and extent of the impact of chronic pain on patients' quality of life in relation to other long-term conditions?
3. What are the barriers to effective pain management encountered by patients with chronic pain in primary care?

Subsequently, a pragmatic approach was adopted to answer these questions. For the first question, a systematic review and metaanalysis was conducted to evaluate the effectiveness of pharmacist-led medication review in chronic pain management (Hadi et al., 2013b, 2014b). The metaanalysis found that patients in pharmacist-led medication review group had significant reduction in pain intensity, improvement in physical functioning and patient satisfaction compared to the control group. For the second and third questions, the qualitative interview guide was expanded and additional questions were asked to explore the impact of chronic pain on patients' lives and barriers to effective management of chronic pain in primary care, in addition to originally proposed questions aiming to explore patients' experiences of nurse-pharmacist managed pain clinic. In order to truly understand the impact of chronic pain of patients' lives, a mixed methods approach was adopted (convergent parallel design) (Hadi et al., 2018). Published data on quality of life from two different datasets, the Third Oxford and Lifestyles Survey and Welsh Health Survey, were also extracted and a secondary analysis was undertaken to allow comparison of QoL of chronic pain patients with that of the general population and patients with long-term conditions. The authors found that patients with chronic pain had significantly poorer quality of life compared to patients with other long-term conditions (Hadi et al., 2018). Qualitative themes emerged from data analysis reflected the diversity in the nature of impact of chronic pain on patients' lives. For the third question, qualitative-only approach was used and qualitative data were analyzed with an aim to develop themes based on the barriers encountered by patients with chronic pain in primary care (Hadi et al., 2017). This example demonstrates the use of emergent mixed methods design in pharmaceutical health services research. It should be noted here that the selection of choosing an appropriate method was guided by research question. Quantitative-only and qualitative-only and mixed methods approaches were used as appropriate during the program of enquiry. The emergent mixed methods design gave authors the flexibility to choose the best method to answer the research question.

Conclusion

A mixed methods approach is suitable when the use of two methods is likely to enhance our understanding enhance the knowledge in a specific research question as compared to using a monomethod approach. It is essential to choose an appropriate typology for the mixed methods research approach and this should be guided by the individual research question. Rigor in mixed methods research should be ensured by adhering to quality principles of the quantitative and qualitative components as well as mixed methods research guidelines and frameworks. Both humanist and financial resources should be carefully considered before embarking on a mixed methods study. New mixed methods researchers should choose fixed mixed methods approach and should consider collaborating with an experienced researcher early during the designing phase of the study.

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Publication Bias

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Background

The "dictionary of epidemiology" defines publication bias as "an editorial predilection for publishing particular findings, e.g., positive results, which leads to the failure of authors to submit negative findings for publication (Last et al., 2001)." The term "Publication Bias" was first defined by Begg in 1985 as studies in which the observed efficacy of the treatment is much more likely to be reported than those in which the observed efficacy is average or poor (Begg, 1985). Publication bias is the biased projection of researchers, reviewers, and editors to submit and publish studies based on usually positive findings (Dickersin, 1990). Publication

bias also occurs when the chance of getting publishing a paper depends on the outcome of the findings (Brown et al., 2017). It means that the statistically insignificant results, studies of small magnitude or findings contradicting prior theories or findings from other studies will be less likely to be published (Harrison et al., 2017; Dickersin and Min, 1993).

Publication bias can also be explained as results having statistical significance, have a likelihood to be published faster, multiple times, publishing in high impact journals and to be cited more often. In this regard, the evidence based on "non-significant results" in systematic reviews cannot be ignored and hence it is as much important as the evidence contributed by significant results (Rodrigues, 2013).

Role of Publication Bias in Evidence-Based Clinical Decision Making

Publication bias has not only influenced the education and psychology related research, but it has also greatly affected the medical literature too. The main consequence of this bias would be exaggerated claims of treatment effects or presence of risk-factors related to published work. These could be misleading in many ways including management of patients or health related policy making (Easterbrook et al., 1991). Meta-analysis and systematic review-based syntheses of published research is in high demand to support the evidence-based decision making policy. But, research with unfavorable results is less likely to be published and hence contributes to bias in the selection of the studies for meta-analyses or systematic reviews (Dickersin, 1990; Dickersin and Min, 1993; Easterbrook et al., 1991). As unpublished studies and studies are marked as grey literature and they are not easily accessible (Mueller et al., 2013). So, the effect estimates on the basis of such publications might be overestimating the effect size than what actually exists (Song et al., 2000; Easterbrook et al., 1991). It also compromises the quality of the systematic reviews and meta-analysis, which are only based on published literature (Easterbrook et al., 1991). Systematic reviews and meta-analyses are considered as the most powerful analytical tool, thus claimed to have an impact on the current and future research trends (Easterbrook et al., 1991; Crawford et al., 2010).

Easterbrook et al. performed a literature search for 1982–89 and found that two-thirds of meta-analyses are based on the studies, which were more biased prone especially more toward publication bias. The study further suggested that non-randomized trials with small sample size should be used cautiously, specifically when to be included in a systematic review or meta-analysis or otherwise (Easterbrook et al., 1991). This can be further explained as the field of medicine relies on multiple studies based on small sample size (Ioannidis, 2005). So, if the effects of a medicine are demonstrated as combination of both positive and negative outcomes, so, only the studies with positive results will be published. In this context, the researcher and practitioner will think that the medicine or a treatment is beneficial, while this is not the case in actual sense (Paulson et al., 2011). Paulson et al. evaluated abstracts submitted at the 2006 Center for International Blood and Marrow Transplant Research (CIBMTR)/American Society for Blood and Marrow Transplantation (ASBMT) "tandem" meeting. They found that only 43% of the abstracts were later published as complete papers. Another interesting finding came out from the study that the results with the positive findings were published in high impact journals, while unstated or negative studies were published in low impact factor journals (Paulson et al., 2011).

Similarly clinical trials-based medical decisions are based on the public reporting of such clinical trials (Craig et al., 2001; Hagdrup et al., 1998).

Due to the failure of an intervention, the results of a clinical trial remain unpublished especially if the intervention is found to be harmful, so chances are that considering these studies may have greater harm to the patients (Parekh-Bhurke et al., 2011). Therefore, selective publication of clinical trials and their associated outcome can mislead due to unrealistic estimation of drug effect (Kyzas et al., 2005; Whittington et al., 2004). In this regard, Turner et al. conducted a systematic review of literature on 12 antidepressants agents and compared them with the reviews from Food and Drug Administration involving 12564 patients in trials (Turner et al., 2008). They compared the trials' outcomes and effect size of the treatment from published data and the data obtained from the FDA. The published literature showed that 94% of the conducted trials were positive comparable to the 51% derived from the FDA (Turner et al., 2008). Thus, a non-representative selection of the data in a systematic review may decrease the validity and usefulness of practice and policy based on such studies, hence it is important for clinicians, health policy makers, and researchers to understand the concept of publication bias before considering such evidence (Parekh-Bhurke et al., 2011).

History of Publication Bias

The decision of what should be or what should not be published is solely a personal decision and to some extent influenced by the trends, however, science does not dictate any formal guidelines on what should be included in a publication (Dickersin, 1990). Robert Boyle was the first scientist to bring the necessary details of the experiments into the publication. This initiative of sharing research findings with peers led to a new type of reporting that described the errors and difficulties, one can encounter doing the experiment. Thus, between 1600 and 1800s, the scientific reporting not only presented the "positive" but also the "negative" results. In 1661, Boyle being concerned about the publication practices in the field of science expressed his concerns over this issue and said that the scientists are being compelled not to publish the experiments but to bring out something "big" (Dickersin, 1990).

Awareness of publication bias began in 1956 when the editor of the *Journal of Abnormal Social Psychology* indicated that negative studies were less likely to be published in his journal (Thornton and Lee, 2000). In 1959, it was found that very few negative results were reported in four psychological journals, a finding strongly suggesting publication bias (Sterling, 1959). Since 1979, the number

of references relevant to publication bias has increased (Boisen, 1979). In 1979 Rosenthal used another term "file-drawer problem" to describe the lack of publication of completed studies (Song et al., 2013).

Types

Publication bias does not only include the urge to publish positive results, but it also includes various other reasons which can be listed as different types of bias influencing the publication.

Here are different types of publication bias:

Multiple Publication Bias

Depending upon the nature and outcome of the study, studies that get chance to publish in more than one place might get more weightage for readership and more likely to be included in a meta-analysis (Egger and Smith, 1998; Higgins and Green, 2011).

Time Lag Bias

Time lag bias indicates that some studies take long time to get published especially those with the undesired or no positive outcome. Contrary to this, studies with positive results or attention drawing findings are published much faster (Hopewell et al., 2007). For example, one study assessing efficacy trials of HIV treatments concluded that the time from study enrollment to publication was significantly longer for negative trials than that for positive trials (Ioannidis, 1998).

Location Bias

It is related to the publication of research findings in journals, which are indexed in different databases and then perhaps comparing them with the outcomes of the study (Pittler et al., 2000; Vickers et al., 1998).

Citation Bias

Citation bias is based on the selection of the study that a researcher wants to cite from other studies or sources (Christensen-Szalanski and Beach, 1984).

Language Bias

The choice of publication in a particular language, ignoring those studies which are not in your native language (Egger et al., 1997).

Outcome Reporting Bias

It is based upon the publication of selective research findings depicting positive outcome of the study (Chan et al., 2004).

Confirmatory Bias

When one's beliefs and experiences are supported by some studies and they emphasize certain studies to build a support and ignore others though relevant, this type of bias is known as confirmatory bias and it is most evident in clinical research (Mahoney, 1977).

Funding Bias

Sometimes the funders may withhold the results with negative outcomes and do not disclose them to the public. It has been observed that independent studies have less significant or favorable results than the funded studies (Lexchin, 2012).

Factors Contributing Toward Publication Bias

Several factors contributing toward publication bias are described as below:

Design and Implementation of Study

The role of design or execution of single studies is a factor contributing toward publication bias as sample size and method of data reporting greatly influences the phenomenon (Thornton and Lee, 2000). Besides, the belief and expectation of the investigator also play an important role in publication bias (Angell, 1989). A small sample size lacks the power thus fails to prove the statistical

importance of an effect under study and hence fails to get published (Thornton and Lee, 2000). Contrary to this, large studies have a good chance to answer many questions as the author has to dig in the information deeply to obtain positive results even if the data is showing negative outcomes. This means that the chances to get significant results will increase with the detailed analysis of further subgroups (Angell, 1989; Thornton and Lee, 2000). Publication bias also arises if the data recording is inadequate. Although the difference between data produced and published is rare, but some researchers may tamper the data and this data tempering remains unnoticed during peer-review and even during the replication (Engler et al., 1987; Felson, 1992)

Publication Bias due to Unpublished Studies

Sometimes findings from a study do not seem to impart much for the promotion of a certain theory or a policy, for which the study was meant for. Certain results seem less interesting to be published and less appraised by the editors and reviewers. Due to these reasons, researchers find it inconvenient to publish certain research findings (Brown et al., 2017).

Publication bias may also occur when researcher has a lack of interest in publication or want to submit the research to a specific journal for the publication. For instance, if a study is based on a large sample size, researchers are keen to publish their research, regardless of the outcome of the study (Thornton and Lee, 2000).

Publication Bias due to Rejection of Journals

The *British Medical Journal* states that "negative results have never made riveting reading" (Dickersin, 1990). Some readers and editors strongly discourage negative outcome-based studies as thinking that only positive outcome studies improve the clinical practice. While negative studies are not published, however in some cases it has been found that even the studies with negative outcomes are better planned and conducted than positive outcome studies (Dickersin, 1990).

A study explored process of peer review by assigning manuscripts with positive, negative, no and mixed results to 75 journal reviewers. Reviewers gave minor revisions on studies with positive outcomes and gave major revisions and rejections to the negative studies (Mahoney, 1977).

Sponsorship

Sponsorship is another important factor which cannot be ignored while evaluating factors of publication bias. Sometimes funders decide whether a study would be published or otherwise, considering that, if a pharmaceutical product shows null effects, the manufacturers usually discourage the publication of the results (Thornton and Lee, 2000; Lexchin, 2012). A study revealed that up to 89% of studies funded by the pharmaceutical industry ended up in favoring a new therapy, while only 61% favored the therapy, if the studies are funded by other sources (Begg and Berlin, 1988).

Methods of Detecting and Correcting for Publication Bias

To address problem of publication bias, is as crucial as to promote good scientific knowledge (Brown et al., 2017). Hence, several methods have been developed to identify and minimize such bias (Song et al., 2010).

A Health Technology Assessment (HTA) report published in 2000, highlighted the issues in publication bias. The report included 193 systematic reviews published in 1996 (Song et al., 2000). It was found in the report that not only the literature search was inadequate in some reviews, but also the publication bias was not taken into account while conducting those reviews (Landis and Koch, 1977). Another shortcoming of this review was the lack of representation of the sample studies (Landis and Koch, 1977). Besides, it was found in HTA report that the issue of publication bias was largely being overlooked, as a small number of reviews actually used any methods to identify, avoid, or counter publication bias (Song et al., 2000).

To evaluate whether the practices have changed an assessment of systematic reviews published in 2006 was compared to the systematic review done in 1996. It has been observed that there has been a remarkable increase in the consideration of measures to identify and decrease publication bias in a decade (Parekh-Bhurke et al., 2011).

To detect publication bias in a systematic review or a meta-analysis, several measures have been suggested (Song et al., 2010) as below:

Unpublished Data and Publication Bias

If relevant studies are missed or are available as gray literature or in languages other than English, risk of bias is present. Hence, to overcome the issue an in-depth literature search should be done while conducting a systematic review and multiple electronic databases should be searched, as many journals are not listed in certain databases. These strategies help to avoid chances of bias (McDonald et al., 1999). An in-depth literature search related to non-bibliographical sources will also help to overcome publication bias. This include searching for conference abstracts, scientific reports from companies, reports from government and regulatory bodies, study registries, scientific data from personal research group, which are otherwise not available in standard databases (Lefebvre et al., 2009).

Graphical and Statistical Methods

To assess the publication bias different methods are used including both graphical and statistical methods. Graphical assessment includes funnel plots which were first used in the educational research (Richard et al., 1984). To detect publication bias in systematic reviews, most common methods employed were, Begg's test, Egger's test, and funnel plots. Similarly, in 1996, the Fail-N safe method was used in some reviews, however it is being much less likely to be used in recent reviews (7% vs. 1%, respectively) (Song et al., 2010).

Funnel Plot

Funnel plot is the simplest and easiest method to detect publication bias. A funnel graph is a simple graph between sample size of the component studies and summary outcome measures or effect size, assuming that all studies will assume the similar effect (Richard et al., 1984). It is plotted by taking effect size on *X* axis and variance or sample size on *Y* axis (Borenstein et al., 2009).

To do so, the point estimate from studies under consideration is plotted against the standard error or the sample size. The studies having highest precise values usually appear high on the *y* axis in a cluster fashion (Borenstein et al., 2009). Plot of studies having little or no publication bias appears more like an inverted funnel. Small studies appear arranged in a symmetrical manner on both sides of the larger studies which are located at the apex of the funnel plot (Torgerson, 2006).

However, in case of publication bias, usually one side (mostly the left side) of the funnel is missing indicating negative or null studies (Borenstein et al., 2009). On the other side, it can also be recognized as deterioration of the central part of funnel, suggesting that publications with statistically significant results are published while those without significant results are not. Therefore, it is necessary to consider the funnel plots before and during finalizing the systematic review (Torgerson, 2006).

Funnel plot asymmetry may not always reflect accurate publication bias, and there may be other factors contributing toward asymmetry, therefore, if the results from funnel plots are interpreted inappropriately, it could lead to misleading conclusions (Lau et al., 2006; Ioannidis and Trikalinos, 2007; Sterne et al., 2008). In some cases, due to small and methodologically weak studies, an irregular funnel plot appears, producing biased estimates of effect and this appear as positive. In reality, however this should appear as null or negative result otherwise (Torgerson, 2006).

Sterne et al. has listed four reasons that may possibly contribute toward an asymmetry in funnel plots. These include bias in publication, poor study design, irregularity in data, and heterogeneity (Sterne et al., 2000).

Fail-Safe N Test

To check whether a systematic review has a publication bias, one can use Fail-safe N test to detect publication bias (Rosenthal, 1979).

This test determines the number of missing studies averaging a *z* value of zero to make the combined effect size of zero (Rosenthal, 1979). This would reduce the summary effect to non-significance or would show the overall probability of Type 1 error to a stated level of significance, such as $P = 0.05$ (Rosenthal, 1978, 1979). Rosenthal (1979) suggested that to make *P*-value insignificant, it is important to know that how many missing studies would be needed to retrieve and to be added in the analysis, considering the mean effect of the missing studies as zero. In case, if only a few studies such as five or ten are required, to cancel the effect, then the true effect will be zero, while, in case if a large number of studies are needed to cancel the effect, such as 20,000 studies, hence it will be safe to assume that there is no publication bias in this case (Rosenthal, 1979). Rosenthal (1979) also identified the presumed location of missing studies as File drawer and Harris Cooper (Begg and Mazumdar, 1994) suggested that to nullify the effect, the number of missing studies to be incorporated to an analysis should be called the Fail-safe N (Begg and Mazumdar, 1994).

Fail-safe N test has certain limitations, that it does not emphasize on the substantive significance (real world relevance), rather its more oriented toward the statistical significance (Miller, 2008; Borenstein et al., 2009). For instance, it focuses on questions such as how many hidden studies should be added to make the effect statistically insignificant instead of looking into the answer that how many hidden studies are required to reduce the effect where it no more remains of substantive importance (Borenstein et al., 2009). This test relies on the *P*-values based test of significance, but with recent development in statistics, first the summary effect is calculated and then the *P*-value for this effect is computed. As the *P*-values are computed by using different approaches, testing different null hypotheses means that *P*-vales are not the same. Hence, the approach is not recommended in cases where effect size is priority (Borenstein et al., 2009).

Orwin's Fail-Safe N

Orwin (1983) developed a variant to Rosenthal's method, as the later allowed to determine that how many missing studies could bring the overall effect to a specified level, rather to bring it to a zero value (Orwin, 1983). Thus allowing the researcher to select the value with smallest effect is important as one can calculate that how many studies will be needed to bring the summary effect below the specified point (Borenstein et al., 2009). This method also helps the researcher to label the mean effect in missing studies as non-zero value and allow to compute a model for a series of other distributions and missing studies (Begg and Mazumdar, 1994).

Duval and Tweedie's Trim and Fill

The Trim and Fill method is used to estimate the number of studies missing from a meta-analysis that may result from the suppression of the most extreme results on one side of the funnel plot. The method does not validate the outcome or the overall effect but it helps in the determination of particular form of publication bias (Duval and Tweedie, 2000b, 2000a).

Trim and Fill method re-computes the effect size by removing the extremely small studies from the positive side of the funnel plot, thus making the funnel plot, more like a symmetric as of the new effect size. This trimming yield adjusts effect size, reduces the variance effect, and produces a confidence interval of too narrow value. Hence, the algorithm adds back the studies to the analysis and produces a mirror image for each, making the variance correct but no impact on point estimate (Borenstein et al., 2009; Duval and Tweedie, 2000a, 2000b).

The advantage of the above-mentioned approach is that it helps in the estimation of unbiased effect size. Besides, the computer programs based on Trim and Fill method are able to create a funnel plot comprised of both the observed and the imputed studies (to replace the missing data) (Borenstein et al., 2009). Hence, one can easily observe that how the effect size shifts when studies are added to the plot (Borenstein et al., 2009).

Limitations of this method includes that Trim and Fill method largely depends on the assumptions that why studies are missing. Also, the algorithm for detecting an asymmetry can be influenced if one or two studies are not-uniform (Borenstein et al., 2009).

Comparison of Published and Unpublished Data

Another method to detect publication bias is to compare the results from both published and unpublished studies evaluating the same research question. If a single meta-analysis includes both published and unpublished studies, the difference in results can indicate the presence and extent of publication bias.

In an example, published results of selective serotonin reuptake inhibitors showed favorable risk benefit profile for childhood depression, however the unpublished data on citalopram, paroxetine, and sertraline clearly indicate the associated risk of these medicines and their impact on children and youngsters (Whittington et al., 2004). However, the true estimates of unpublished results are difficult to predict, as to obtain data from such unpublished studies is a big challenge for the researchers (Song et al., 2013).

Analyzing Larger Studies Only

Another strategy to deal with publication bias is limiting the analysis to only larger studies (Borenstein et al., 2009). If it is assumed that the publication bias is majorly associated with smaller studies, then considering only larger studies would overcome the problem in theory. A strategy is to illustrate all possible thresholds by drawing a cumulative meta-analysis. This is developed by running one study at a time, then perhaps adding a second study, third, and so on (Borenstein et al., 2009).

Similar to this is a cumulative forest plot. In the forest plot the first row shows the effect expressed by one study, the second rows show effect based on two studies, and so on.

A potentially useful strategy is to illustrate all possible thresholds by drawing a cumulative meta-analysis (Borenstein et al., 2009). In order to examine the effect of different threshold for study size, the studies are arranged in the sequence of largest to smallest or being most precise to least precise.

Then a cumulative meta-analysis is performed with the addition of each study. If the point estimate has no effect upon the addition of smaller studies and if it has stabilized with the addition of larger studies, it can be assumed that smaller studies are not contributing toward any bias. Contrary to this if point estimate upon the addition of smaller studies shows a shift then there is a definite need to find out the reason for this shift (Borenstein et al., 2009).

Technological Aids in the Detection of Publication Bias

A number of computer-based programs are available to help in the detection of publication bias in meta-analysis. These include Comprehensive Meta Analysis (CMA), RevMan Analyses, Stata, and MetaWin (Borenstein, 2005).

Comprehensive Meta Analysis (Version 2.0)

Comprehensive Meta Analysis (CMA) is considered as the unique program for carrying out meta-analysis. The software was developed with the collaboration of experts from medicine, social sciences, and epidemiology (Meta-analysis.com, 2006). The program has an ability to execute all tests for the detection of publication bias including funnel plot, forest plot, rank correlation test, Trim and Fill, Egger's test, and other related tests (Borenstein et al., 2005). CMA accepts data in around 100 formats, the most utilized of which are number of events occurring in a single group and sample size. It can also execute the data if data input is in the format of means and standard deviations, correlations, point estimates, and confidence intervals (Borenstein, 2005).

Review Manager (Version 4.2)

Review Manager is a special software provided to researchers by the Cochrane Collaboration, meant for the reviews to be included in Cochrane library (Cochrane, 2014). The statistical procedure of the software is based on a module called RevMan Analyses, previously known as MetaView (Borenstein, 2005). RevMan will only execute data in the format of point estimate and standard error. It also accepts data in the form of number of events and sample size in each group, means and standard deviation (Borenstein, 2005).

Stata (Version 8.2)

Stata is a general software based on statistical package, which is not routinely used for meta-analysis (Stata.com, 2018). However, with some modifications in the running of this program (by using certain macros), Stata can create funnel plot, forest plot, compute

Egger's test, Trim and Fill test, rank correlation test (Sterne et al., 2009). It will accept data in the format of point estimate and standard error, point estimate and confidence interval, number of events and sample size, and means and standard deviations in each group (Borenstein, 2005).

MetaWin (Version 2.0)

MetaWin is another program for meta-analysis. It is mostly utilized in the field of ecology but due to its generalizability, it can be used in many other fields. It is capable to create funnel plot, forest plot, to compute the fail-safe N test, rank correlation, and other tests (Borenstein, 2005). MetaWin will only process the data if it is available in the format of number of events and sample size, means and standard deviation, correlations. It will also analyze the data if data is formatted as point estimate and variance (Rosenburg et al., 2000).

Tackling Publication Bias

There are many strategies which can help minimizing publication bias:

Trial Registries

If the researcher add registries in their search strategies and the results are accessible, this can help in the reduction of publication bias (Parekh-Bhurke et al., 2011). Because once the trial is registered, regardless of the outcome whether negative or positive or insignificant, the trial needs to be published (Parekh-Bhurke et al., 2011).

In 2004, an initiative was taken by the International Committee of Medical Journal Editors, which made it mandatory to register the trial and it needs to be available to the public at no cost (De Angelis et al., 2005). In 2005, the World Health Organization has initiated efforts to set International standards for clinical trial registration (Gülmezoglu et al., 2005). The British Medical Journal has also asked for trial registration and devised a modified-criteria for the registration of trials (Abbasi, 2004). These policies have resulted in the numbers of trial registration and been effective in reducing the risk of publication bias (Laine et al., 2007).

Data Availability

Sharing of the data and making it public would reduce the chances of publication bias. However, the availability of data and issues related to its privacy are challenging. A number of data repositories are available, where data can be saved with no or minimal cost. In addition to this, challenges related to data privacy and its transparency can be overcome by arranging the data in such a way that the data linking with participants cannot be possible (Brown et al., 2017).

Mandating Publication

Another approach to tackle the publication bias is to have the mandatory publication of research studies (Carroll et al., 2017). Some institution has made it mandatory to publish the research funded through them and one such initiative is Wellcome Open Research (2018). Another option is to publish in the journals, where authors can upload the paper even before the peer review, for instance F1000 research open platform, where authors upload the manuscript before the actual review of the study (F1000 Research, 2018).

Open Access Journals

Sometimes scientifically valid results remain unpublished due to limited readership, editors' decision making and due to limited space in journals. Therefore online, open access journals improve the readability and reduce publication bias. Therefore the studies which might get delay in publication due to being less attractive to the high impact print based journals can be published in online, open access journals, without wasting too much time on the process of rejection and submission (Brown et al., 2017). The electronic publishing has more advantages as compared to conventional publishing as electronic publish is not bound to follow the limits as the traditional printed journal has to do (Berlin, 1992)

Peer Review Process and Publication Bias

Peer review serves as the source to improve quality checks to published articles, but delay in publication or preference of a reviewer or even journal's choice to publish a certain study result in publication bias (Brown et al., 2017). Thus, change in the traditional review process may decrease the chance of publication bias.

Some journals have the policy that the editor of the original journal, which has originally rejected the article may suggest an alternative journal, thus decreasing time between submissions and peer-review process. Another option is "registered reports"; this is a two tier process, in which the outcome is independent of the review process (Chambers, 2013). An article is published based on the proposed hypotheses, methodology and predesigned analysis and it is published once the data is collected, interpreted and results

are finalized. Thus publication in such journals is based on the methodology and perhaps not on the outcome of the results (Brown et al., 2017).

Editorial Policy

An editorial policy can also be helpful to eliminate the publication bias (Thornton and Lee, 2000). This can be done only if the journal editors and reviewers could focus on reviewing high standards in conducting research, as well as excluding key factors influencing publication bias. They can look or may ask for the proof of registration of a trial, confirmation of randomization or any other factor that may contribute toward publication bias (Begg and Berlin, 1988; Chalmers et al., 1990).

Conclusion

The publication bias has significantly influenced the scientific research. It can be in various forms; however, it deteriorates the quality of published research thus resulting in the waste of resources and leading to poor patient health outcomes. There is a need to employ data quality assurance techniques before publishing scientific results as this may undermine the quality of evidence-based decision making in health research.

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Discrete Choice Experiment

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Introduction

Methods for eliciting people's preferences for choosing products and services have evolved over the time. Opinion polls and traditional satisfaction surveys have been the most commonly used methods. However, more rigorous methods used in marketing and psychology research started to attract considerable attention from the pharmacy practice research community.

Preferences, in general, can be either "revealed" in the choices people make in real-life situations or "stated" by the individual when asked about them in surveys. Revealed preferences are considered the most informative for understanding the real decisions made by individuals. However, there are methodological problems that hinder the feasibility of measuring revealed preferences, particularly in the context of preferences for pharmaceutical products and services that are still in development and not currently available in the market. Hence, measuring stated preferences is more widely used in this context and is generally considered an acceptable alternative (Quaife et al., 2018).

Stated preference methods, on the other hand, involve asking people to state how they would behave, or what they would prefer, based on a hypothetical scenario (Louviere et al., 2000). Several methods exist for assessing stated preferences. These can be classified into either choice-based; where individuals are asked to make choices between alternatives with different attributes (i.e., characteristics), or nonchoice-based methods; where only one option is given and the respondent is asked to rate her/his preference for this option (Carson and Louviere, 2011). **Fig. 1** provides a taxonomy of stated preference elicitation techniques.

Choice-based methods are, generally, preferred for eliciting stated preferences as these can give more granular information regarding the trade-offs that people are willing to make between different attributes of a product or service (e.g., people may be willing to accept higher risk in return for improved outcomes and/or reduced costs). They also reflect real-life situations, where people are faced by choices and trade-offs to make in their everyday life. The most widely used of these choice-based methods is the conjoint analysis, best-worst scaling, and discrete choice experiments (DCEs) (Elliott and Payne, 2005). In this chapter, we discuss DCE as a promising methodology that has many applications in pharmacy practice research.

Discrete Choice Experiment

Definition

DCE is a survey-based quantitative technique for eliciting individuals' preferences. The method involves asking individuals to choose between alternatives, where each is described by a number of attributes and their levels (Mangham et al., 2009). These attributes are the characteristics of the intervention of interest and can relate to its outcomes (e.g., the probability of conceiving for a fertility treatment) or the processes involved in delivering the intervention (e.g., waiting time for or the location of a service).

The choices are usually presented to respondents in the form of choice sets. Respondents are asked to indicate their preference between a discrete set of two (or more) alternatives; using the attributes and levels to describe these alternatives (Amaya-Amaya et al., 2008). The responses are used to determine the attributes that significantly influence individual preferences as well as their relative importance (Mangham et al., 2009).

Fig. 2 presents a hypothetical example of a choice set from a DCE illustrating its basic elements.

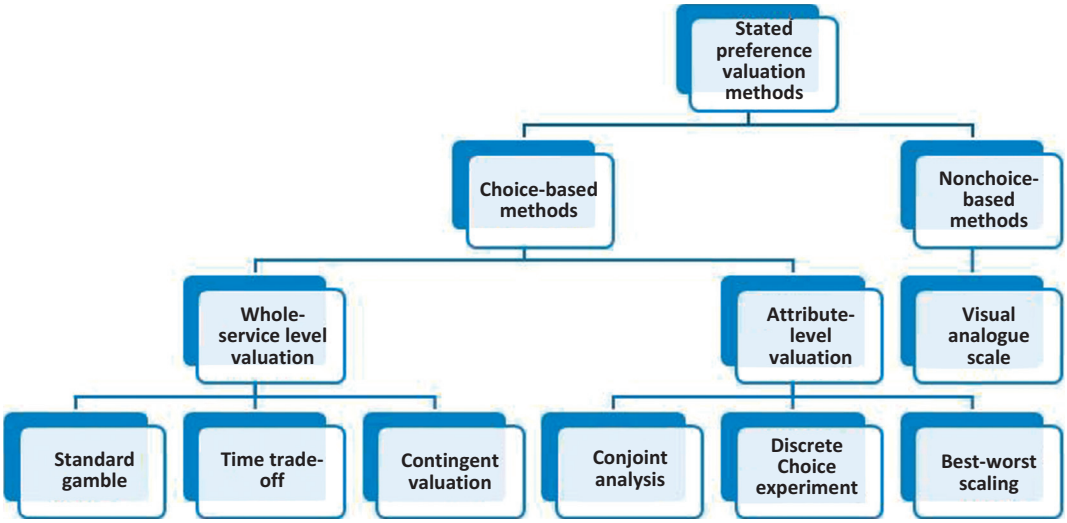

Figure 1 Stated preference valuation methods.

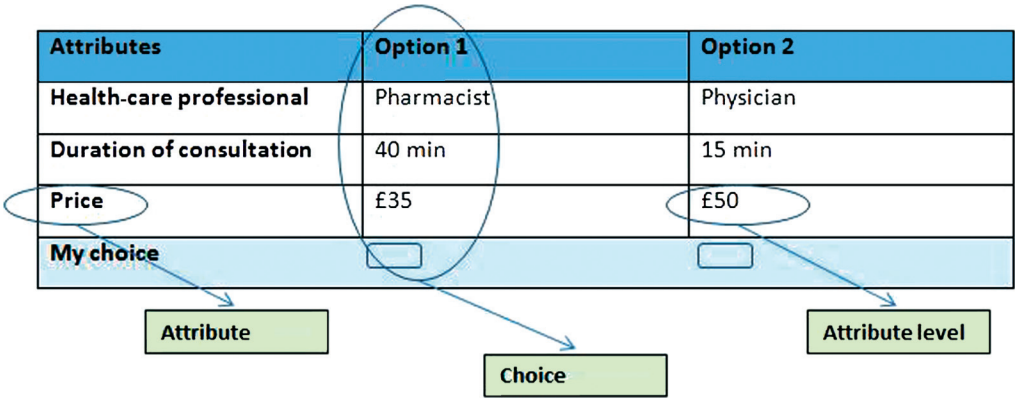

Figure 2 A hypothetical example of DCE choice set with illustration of its elements.

The DCE technique is particularly useful in the absence of revealed preference data; for example:

- if the product or service in question is still under development,
- if there is no variation in the available product or service, and
- if there is value for individuals who are not currently using the product or service in question (e.g., if the individual would have preference for a service to be available for potential use in the future).

Theoretical Foundation of Discrete Choice Experiments

DCE has its foundations in economic theories, namely, random utility theory (Hall et al., 2004b) and Lancaster's theory (Lancaster, 1966). The former is based on two main assumptions: "economic rationality" and "utility maximization." These refer to assuming that individuals make rational choices (economic rationality), and in doing so, they choose the alternative that yields the highest individual benefit (utility) for them (utility maximization). Lancaster's theory argues that utility generated for the individual by an alternative is assumed to depend on the utilities associated with its composing attributes and attribute levels (Lancaster, 1966).

As Mangham et al. (2009) explain:

If $\boldsymbol{Y_{iq}}$ is the utility of individual q for the ith alternative, then

$$Y_{iq} = X_i\beta_i + \varepsilon_{iq}$$

where

$\boldsymbol{X_i}$ is a vector of attributes for the ith alternative, $\boldsymbol{\beta_i}$ is a set of weights that establish the relative contribution of each attribute to the utility associated with the ith alternative, $\boldsymbol{\varepsilon_{iq}}$ is the residual capturing the unobserved variation in the characteristics of different options and any measurement errors.

Design and Administration of Discrete Choice Experiments

As an experimental technique, undertaking a DCE involves a number of steps. It starts with design, followed by data collection, analysis, and interpretation. The ultimate aim of the experiment is to examine the effect of the intervention's attributes at their different levels on respondents' preferences for/valuation of the intervention. Thus, the attributes are considered as the independent variables, which can take two or more values (levels) each and the preference for/valuation of the intervention as the dependent variable.

However, before embarking on undertaking a DCE, it is important to make a decision about the target population. This means deciding whose preferences should be elicited. Eliciting the preferences of current service users is usually the main aim of a DCE, but it is also important to consider the views of future users to inform service/product development. Furthermore, in health care, eliciting the views of the service providers such as doctors, nurses, and pharmacists would be important to allow comparisons with the views and preferences of the service/product users.

The following are the main steps involved in undertaking a DCE.

1. *Choosing the attributes*

   The first step in designing a DCE is the choice of the attributes that can be used to describe the product or service of interest. These attributes can be qualitative (e.g., who delivers an immunization service) or quantitative (e.g., the number of follow-up visits required) (Hensher et al., 2005; Ryan et al., 2001). Mangham et al. (2009) consider reviewing the published and gray literature, such as policy documents, to be the best starting point for identifying relevant attributes (Mangham et al., 2009). However, they argue that primary data collection might still be needed to improve the face validity of the DCE by ensuring that it reflects the study setting. This usually takes a qualitative research approach (e.g., face-to-face interviews or focus groups) and requires input from stakeholders and decision makers who will be using the results of the DCE in informing the design and/or delivery of the product/intervention.

   It is also important to ensure that there is no overlap between the attributes, which is referred to as inter-attribute correlation, as this makes it difficult to establish the effect of each attribute in isolation. The chosen attributes should also represent both the benefits and risks of the product or intervention in question in order to give a comprehensive description and ensure that the respondent is aware of both aspects when making a choice (Ryan et al., 2001). This is particularly important when a trade-off is required between benefits and harms, for example, where increased efficacy through using higher doses of a drug means more side effects. Including both risks and benefits of pharmaceutical products allows the estimation of benefit–risk assessment (BRA) models and calculating the maximum acceptable risk (MAR) that respondents are willing to take (Seston et al., 2007a).

   Including a cost attribute has an added benefit, as it allows estimating the monetary value placed by the respondents on each of the attributes included in the DCE (Morris et al., 2007). When a cost attribute is included; the willingness to pay (WTP) for a favorable change in the level of each of the other attributes can also be calculated. This is presented as the marginal rate of substitution (MRS), which is a measure of the trade-offs that the respondent (consumer, patient, or health-care professional) is willing to make, and is calculated by dividing the coefficient for this attribute by the coefficient for the cost attribute (i.e., $\beta_{\text{attribute}}/\beta_{\text{cost}}$) (Morris et al., 2007). This trade-off vs cost can, alternatively, be represented as the willingness to accept (WTA), which is the amount of money respondents believe compensates for an unfavorable change in the attribute. A drawback of including a cost attribute arises in health systems where the intervention will be free at the point of service, where the respondents may not provide credible answers (Guttmann et al., 2009). More detailed discussion of the applications of WTP calculations in pharmacoeconomic evaluations using cost–benefit analyses can be found elsewhere (Drummond et al., 1987).

   It has to be noted that it is not possible to include every single attribute or characteristic of the service/product in question in the DCE. This is why deciding the number of attributes to include in a DCE is another important aspect of its design. In practice, most DCEs will include fewer than 10 attributes so that all of them can be considered by the respondents when making their choice; with some arguing that a maximum of 7 should be considered (DeShazo and Fermo, 2002). The rationale behind this is that the more the attributes, the greater the cognitive burden of completing the DCE. So, to avoid the risk of low response rate, it is advisable to limit the number of attributes to a recommended maximum of 7–10 (DeShazo and Fermo, 2002).

2. *Assigning levels to the chosen attributes*

   The nature of the attribute, qualitative or quantitative, will dictate the nature of the levels to be used. For example, an attribute may be related to who delivers the service in question, and in this case, the levels listed will be those professionals that are likely to provide the service (e.g., for an immunization service, this could include pharmacist, nurse, or doctor). Quantitative attributes, such as the frequency of administration of a new drug and cost, will be given numerical levels.

   The chosen levels should reflect the range that the respondents might experience or expect to experience if the product or service is a new one (e.g., a new treatment being developed), so that a comprehensive description of the intervention in question is given (Lancsar and Louviere, 2008). Additionally, the chosen levels for the quantitative variables should be evenly spaced and cover a wide range to avoid respondents' not making a choice because of the similarity of the levels. This also allows more accurate estimation of the effect of these quantitative attributes (Lancsar and Louviere, 2008).

   A specific issue relating to defining levels for risk attributes (e.g., percentage probability of side effects) is the difficulty that some respondents may have in understanding probabilities. Hence, effort should be made to ensure that the descriptions are clear and communicated in a way easy to understand (Peters et al., 2006).

Similar to the number of attributes, the number of levels should be kept to a minimum to avoid cognitive overload and difficulty making choices for the respondent. Piloting can then show whether a change to the chosen attributes and levels is required (Mangham et al., 2009).

3. *Designing the choice sets*

   Each DCE consists of a number of choices made of the same number of attributes. The total possible number of choices in the experiment will be based on the total number of attributes and levels in a full factorial design. Considering a DCE that includes 5 attributes, each with 3 levels, then, the total number of possible choices is 243 (3^5). However, this is likely to result in an unmanageable number of choices to be presented to the respondents. As a general rule, it has been reported that respondents can manage between 9 and 16 pairwise choices before they get tired or bored of the experiment (Hanley et al., 2007).

   Hence, approaches have been developed to allow reducing the number of choice sets in a DCE. These include linear and nonlinear methods. The classical linear method uses fractional factorial design and orthogonal arrays to create the choice set, while nonlinear methods utilize Bayesian optimal designs.

   The linear fractional factorial design uses a principle of maintaining orthogonality. This means that each attribute independently affects the overall preference for the service and its utility. The task of reducing the number of choice sets is facilitated by the use of programs such as SPSS Statistics Software (IBM®). These can provide scenarios that describe the level to assign to each of the attributes. However, the full and fractional factorial designs may result in DCE parameters that do not fit the linear models.

   A Bayesian design, on the other hand, maximizes precision of estimated parameters for a given number of choice questions by incorporating *a priori* information about the sign and value of parameters (Reed Johnson et al., 2013). The *a priori* information can be obtained by undertaking pilot studies (Hifinger et al., 2017b). Bayesian optimal designs can be generated algorithmically by using JMP statistical software (SAS Institute Inc.).

   Creating the choice sets then follows, by combining the scenarios in sets of two or more. Two methods are usually quoted as the most commonly used approaches to undertake this task: constant comparison and random pairing (Phillips et al., 2002). In the former, one scenario is kept constant and paired against the remaining scenarios to create the choice sets. This is usually a scenario that describes the status-quo or the existing service. In the latter, the scenarios are randomly paired to create the required number of choice sets.

   Additionally, decisions concerning various presentation options, including whether and how to include the opt-out option and how to frame and depict the attribute levels should be made. The inclusion of a nonchoice option is considered to represent the real-world context. However, these nonchoice responses do not provide any information on how individuals trade-off the attribute levels presented to them. Labeling the choices, e.g., by mentioning the product name, is not generally preferred as it usually introduces selection bias and reduces respondents' attention to the attribute levels (de Bekker-Grob et al., 2010).

   Checks can be incorporated to assess internal validity by examining whether the respondents understand what is required. Two approaches are reported in the literature to do this, namely, dominance and consistency (Janssen et al., 2017). Dominance works by including a choice that includes a dominant scenario, which is better than the alternative in all attributes. If the respondent understands the task, then he/she should be choosing the dominant option. On the other hand, consistency works by repeating a choice set to check if the respondent will have consistency in his/her choice by choosing the same scenario in both instances (Janssen et al., 2017).

4. *Designing the DCE questionnaire*

   Designing the DCE questionnaire is a very important step that affects its validity and usefulness. The choice sets created form the basis of the DCE questionnaire. However, it is important to provide enough context to the task, and this is why the questionnaire usually starts by a detailed introduction to the task and what is required.

   Taking into account the level of respondents' understanding and ensuring they know what is required and how to complete the task will ensure collecting useful data. This is usually achieved by providing enough explanation and examples. Thus, it might be essential to provide the questionnaire in more than one language and more than one format (Mangham et al., 2009).

   Additionally, in populations with lower levels of literacy, the use of diagrams and pictures can be particularly useful. Another design decision that has to be made is about the order of presenting the choice sets, which can affect the choices respondents make. It is good practice to collect data on socioeconomic indicators as this allows analysis of the impact of individual characteristics on the choices made (Mangham et al., 2009).

   Sample size calculation is an important consideration at the stage of designing the DCE. Formal calculations of sample size need to take into account the heterogeneity in preferences and any planned subgroup analysis (de Bekker-Grob et al., 2015). A commonly used method for calculating sample size in DCEs is the Rule of Thumb calculation described by Orme (Orme, 1998, 2010). It has been reported that the precision of DCEs rapidly decreases at sample sizes less than 150 (Reed Johnson et al., 2013).

5. *Pretesting/piloting*

   Piloting is an essential step before the administration of the DCE. The pilot exercise should be used primarily to ensure that respondents properly understand the questions and the tasks they are asked to complete. For example, respondents can be asked to mark every question or answer category that they did not understand and provide suggestions for improvement. This is particularly relevant when working with different languages and or/cultures (Hall et al., 2004a).

   During piloting, it is also possible to check whether respondents consider the range of attributes and levels included in the DCE to be appropriate and to invite them to suggest changes to existing attributes or their levels, addition of new attributes or levels or omission of attributes or levels. This can be done in different formats, including the use of face-to-face interviews or focus groups.

It can also take the form of a ranking exercise in which the respondents are asked to rank the attributes according to their importance (Mangham et al., 2009).

If a sufficiently large sample is included in the pilot DCE, it is possible to quantitatively analyze the data to get some information about the significance of the included attributes and any interaction between them. This information is very valuable in informing the analysis of the final DCE. Additionally, the quantitative information from the analysis of pilot DCE data can be used to finalize the decisions regarding the appropriate attributes and levels that can be included in the analysis of the final DCE. Piloting also ensures that the range of socio-economic and other information requested from respondents in the final DCE are appropriate. Moreover, sample size calculations can be based on the pilot data to ensure that significant differences for each attribute can be detected (Bliemer and Rose, 2009).

6. *Administration*

Once the design of the DCE is finalized, based on the outcomes of the piloting stage, and the sampling frame is agreed; administration and data collection for the main study can be initiated. The DCE can either be self- or interviewer administered. Self-administered questionnaires can be administered by post, phone, or online, while Interviewer-administered DCEs are usually completed face-to-face or over the phone (Ryan, 2004).

Postal and online surveys may not always be feasible particularly in settings with lower levels of literacy. Additionally, they usually have low response rates. Thus, having trained interviewers administering the DCE is usually the preferred method as it can ensure that respondents will be given the required directions to facilitate completing the task. However, this is usually more costly.

Analysis and Interpretation

Analysis of DCE data is based on the use of statistical regression models, which have a categorical dependent variable that is either dichotomous or polychotomous (Hauber et al., 2016). These models include probit, logit, and multinominal logit. Panel data estimation techniques are usually required in the analysis of DCE data as respondents are asked to consider multiple choice pairs, which means independence of the error terms cannot be assumed (Hauber et al., 2016).

In DCEs where two choices without an opt-out option are presented to a respondent, either random effects logit or random effects probit are usually considered most appropriate. On the other hand, if the respondent is asked to choose from more than two options, or two options plus an opt-out, then the data can usually be analyzed using multinomial models (Hauber et al., 2016).

Generally, a positive significant coefficient, β, means that the respective attribute levels significantly increase overall preference (utility). This is usually expected for favorable attributes such as treatment efficacy. A negative significant coefficient, β, in contrast means that the respective attribute level decreases the overall preference. This is expected to be seen for attributes representing side effects or costs of services or treatments.

The analysis of DCE data also involves the quantification of the trade-offs made by the respondents. For example, in benefit–risk assessment studies of pharmaceutical products, MAR for each risk attribute is usually presented. MAR is defined as the maximum level of each risk criterion, which participants are willing to accept in order to increase 1 unit level of efficacy. It is equal to the ratios between benefit and risk coefficients (i.e., $\beta_{\text{benefit}}/\beta_{\text{risk}}$) (Vass and Payne, 2017). Similarly, as explained earlier, it is possible to calculate the WTP and the WTA in DCE studies that include a cost attribute, which represent the monetary trade-offs that participants are willing to make.(Drummond et al., 1987).

DCE is also useful in understanding the estimation of differences between subgroups and identifying the individual characteristics that have significant effect on individual preferences. This is usually done by including interaction terms into the analysis model with a priori determined variables of interest (Hauber et al., 2016).

Applications in Pharmacy Practice Research

DCE is a relatively new research method when it comes to its use in pharmacy practice research. However, its use in healthcare research in general predates its use in pharmacy research. A scoping search of the literature conducted in MEDLINE in May 2018, using the free text terms Discrete Choice Experiment* AND Pharm* to identify some examples of applications of DCE in pharmacy research, returned 61 records. Of these, 41 primary research studies, (Albada and Triemstra, 2009; Ashcroft et al., 2006; Bansback et al., 2016; Boonen et al., 2011; Boonen et al., 2009; Byun et al., 2016a; Byun et al., 2016b; Cheung et al., 2018; Cristina et al., 2002; de Vries et al., 2015; Diaby et al., 2011; Feehan et al., 2017; Gerard et al., 2012; Grindrod et al., 2010; Haac et al., 2017; Hifinger et al., 2017a; Hifinger et al., 2017b; Hong et al., 2011; Kawaguchi et al., 2014; Laba et al., 2013; Laba et al., 2012; Mantovani et al., 2005; Munger et al., 2017; Naik-Panvelkar et al., 2012a; Naik-Panvelkar et al., 2012b; Ngorsuraches et al., 2015; Ngorsuraches and Thongkeaw, 2015; Park et al., 2012; Porteous et al., 2016; Porteous et al., 2006; Rennie et al., 2012; Rockers et al., 2012; Scalone et al., 2009; Scott et al., 2007; Seston et al., 2007a, 2007b; Tinelli et al., 2009; Wang et al., 2011; Wanishayakorn et al., 2016; Wellman and Vidican, 2008; Whitty et al., 2015) and 3 systematic reviews (Katherine and Rachel, 2005; Pradnya et al., 2013; Vass et al., 2017) were considered relevant.

The identified systematic reviews (n = 3) were all focused on studies of pharmaceutical services (Katherine and Rachel, 2005; Pradnya et al., 2013; Vass et al., 2016). The primary research studies dated back to 2002, with the number published annually up to 2017 ranging from 1 to 7.

Most of the primary research studies focused on examining aspects of pharmaceutical services (n = 23), while the remainder focused on pharmaceutical products (n = 18). The studies were either conducted in a single country (n = 39) or were multinational (n = 2). The single country studies were conducted in the United Kingdom (n = 8), the United States (n = 7), the Netherlands (n = 6), Australia (n = 5), Korea (n = 3), Thailand (n = 3), Italy (n = 2), and one each in Canada, Cote d'Ivoire, Japan, New Zealand, and Uganda. Of the two multinational studies, one was conducted in the United Kingdom, Hungary, and Romania, and the second was conducted across 12 European countries.

Studies of Pharmaceutical Services

The most recent systematic review of DCEs in pharmacy has included 17 studies (Vass et al., 2016). These covered studies published up to 2012. Since then, six more studies were identified that were considered to be good examples of using DCEs to assess preferences to pharmaceutical services, taking the total to 23 studies (Albada and Triemstra, 2009; Boonen et al., 2011; Boonen et al., 2009; Cristina et al., 2002; Feehan et al., 2017; Gerard et al., 2012; Grindrod et al., 2010; Hong et al., 2011; Kawaguchi et al., 2014; Munger et al., 2017; Naik-Panvelkar et al., 2012a; Naik-Panvelkar et al., 2012b; Porteous et al., 2016; Porteous et al., 2006; Rennie et al., 2012; Rockers et al., 2012; Scalone et al., 2009; Scott et al., 2007; Seston et al., 2007b; Tinelli et al., 2009; Wang et al., 2011; Wellman and Vidican, 2008; Whitty et al., 2015).

The main interventions/services assessed in these studies included pharmacist prescribing, medicines management and other specialist services, electronic prescribing, pharmacist counseling, community pharmacy service models, community pharmacy-based services for chronic conditions, and management of minor ailments.

The sampling frames in these studies included single, mainly patients or health-care professionals, or multiple populations. The number of respondents ranged from 80 to 9252; with response rates ranging from 10% to 99%. Similar to studies of pharmaceutical products; studies that used face-to-face and online administration seemed to achieve higher response rates. In the majority of the studies, mailed survey was the method used for the administration of the DCEs, followed by online/web administration, which was used in the most recent studies.

The approaches used for choosing the attributes and levels were primarily literature reviews with expert input. Few studies reported the use of some form of formal qualitative research methods and, where used, reporting quality was generally low. The number of attributes included in the scenarios ranged from 3 to 11, with the majority including 6 or more attributes. The number of levels for each attribute ranged from 2 to 7. This is likely to be due to the complex nature of the pharmaceutical services interventions compared to pharmaceutical products, which necessitates the use of large number of attributes to allow accurate description of the intervention. The attributes were generally study specific. Examples include who delivers the service, length of consultations, waiting time, the cost or copayments, and workload.

Similar to studies of pharmaceutical products, the most commonly used DCE design was the fractional factorial design, though Bayesian approaches featured in a few studies. The analysis approach used in the majority of the studies utilized the multinomial logit model.

Studies of Pharmaceutical Products

Studies of pharmaceutical products (n = 18) focused on assessing patients' and/or health-care professionals' preferences for the characteristics of these drug products (e.g., timing, frequency, and route of administration), the benefit–risk trade-offs they make, their WTP for and adherence to these products) (Ashcroft et al., 2006; Bansback et al., 2016; Byun et al., 2016a; Byun et al., 2016b; Cheung et al., 2018; de Vries et al., 2015; Haac et al., 2017; Laba et al., 2013; Laba et al., 2012; Mantovani et al., 2005; Park et al., 2012; Seston et al., 2007a; Wanishayakorn et al., 2016; Diaby et al., 2011; Hifinger et al., 2017a; Hifinger et al., 2017b; Ngorsuraches et al., 2015; Ngorsuraches and Thongkeaw, 2015). These studies are useful in informing the development of pharmaceutical products and ensuring their acceptability to the consumer/patient and prescriber.

The pharmaceutical products covered in these studies included drugs for psoriasis, hemophilia, osteoarthritis, rheumatoid arthritis, renal cell carcinoma, breast cancer, diabetes, venous thromboembolism (VTE) prophylaxis, insomnia, and hypercholesterolemia, as well as human papilloma virus (HPV) vaccination. Two studies focused on examining the public's preferences for the characteristics of prescribed medications; in general, to assess their impact on adherence (Laba et al., 2012, 2013) while another study examined prescribers' preferences for these characteristics to assess their impact on formulary inclusion and reimbursement decisions (Diaby et al., 2011).

The sampling frames in these studies included patients, carers, consumers/general public, health-care professionals (physicians, nurses, and pharmacists). Some studies included both patients/consumers and health-care professionals to compare between the preferences of these groups (Mantovani, 2005; Park, 2012; Byun, 2016; Wanishayakorn, 2016). The number of respondents in the included studies ranged from 126 to 2663, with a response rate ranging from 10% to 100%. The majority of the DCEs were administered using postal or online surveys. Face-to-face interviews were used mainly with patients. The higher response rate appeared to be associated with face-to-face administration of the DCE.

The most common approach used for choosing the attributes and levels was using literature reviews and expert input, with only one study reporting the use of formal qualitative research methods (Wanishayakorn et al., 2016). The number of attributes included in the scenarios ranged from 4 to 8. These were primarily related to treatment efficacy, side-effect, route, and frequency of administration and cost. The cost attributes were included in 9 studies and facilitated the calculation of WTP for favorable

changes in the included attributes. The number of levels ranged from 2 to 4 and included combination of qualitative and quantitative descriptors.

The most commonly used DCE design was the fractional factorial design, although other design approaches including Bayesian design were also utilized. The analysis approach used in the majority of the studies was the multinomial conditional logit modeling.

An example of a DCE study is provided in Box 1.

Box 1

Example

Study:
Haac et al. (2017)

Title
Patient preferences for venous thromboembolism (VTE) prophylaxis after injury: a discrete choice experiment

Objective
To elicit patient preferences towards route of administration, complications, and costs of prophylaxis options for VTE after injury

Country
USA

Population
Adult orthopedic trauma patients who have survived a VTE event

DCE design:

1. *Choosing the attributes:*
   Seven attributes were chosen based on literature review, patient interviews, expert consultation, and retrospective review of patient outcomes
   The attributes are route of administration, cost, possible side effects, risk of major bleeding, risk of VTE requiring therapeutic anticoagulation for 6 months, risk of requiring reoperation, and risk of death due to pulmonary embolism (PE).
2. *Assigning levels to the chosen attributes:*
   Two attributes were qualitative: Route of administration (oral tablet, subcutaneous injection) and possible side effects (none, bruising on leg, stomach pain). Five attributes were quantitative. Risk attributes were presented as *n* per 1000.
3. *Designing the choice sets*
   Forty choice sets were developed, using Bayesian D-optimal optimal design with using JMP statistical soft-ware (SAS Institute Inc.) and randomly divided into 4 groups of 10 choice sets each. Two hypothetical medications were compared in each choice set.
4. *Designing the DCE*
   The questionnaire included questions covering the respondents' demographics including age, sex, race, type of injury, income, health insurance, and days on prophylaxis. Sample size calculation was completed using the Rule of Thumb calculation (Orme, 1998).
5. *Pretesting/piloting*
   No piloting or retesting was reported.
6. *Administration*
   The survey was self-administered face-to-face in the presence of a member of the research team. Demographic data were also collected in the survey.

Analysis:

- A multinomial logit model with effect coding was used in the analysis to calculate the marginal utility, willingness to pay (WTP), and acceptable trade-off estimates for 1% reduction in VTE complication or side effects. Preference heterogeneity based on respondent characteristics was also assessed by adding interaction terms.

Results:

- Reducing the risk of death due to PE was the most strongly preferred attribute, with a marginal utility of 4.57 ($P < 0.0001$) followed by preference for reducing the risk of VTE requiring therapeutic anticoagulation (0.25; $P < 0.0001$).
- Oral administration was also preferred (marginal utility 0.16; $P < 0.0001$); however; possible medication side effects such as stomach pain or bruising were not a significant attribute ($P > 0.1$).
- The highest WTP was for 1% absolute risk reduction in PE was $1686.9. Respondents also were willing to pay $117.45 to receive prophylaxis via the oral route.
- To change preference from oral to subcutaneous route, an absolute reduction in the risk of death due to PE of only 0.07% is required, while the absolute VTE risk reduction required for this change was 1.27%.
- Subgroup analysis assessing the heterogeneity of respondents' preferences showed that some covariates significantly affected preference for the oral route. These were being female, white, or having lower extremity injury.

Conclusion
The study demonstrated that orthopedic trauma patients preferred the oral route for VTE prophylaxis administration, when all other attributes were equal. However, reducing the risk of death due to PE was the most influential factor when making a decision about medication choice.

Summary

From this quick snapshot of the literature, it was possible to see that the use of DCE in pharmacy practice research has been growing steadily. Many topics have been suitable areas for this new research method. Studies that used DCE assessed preferences of different populations groups (patients, carers, general public, health-care professionals, and decision makers) to a range of interventions (pharmaceutical products and services) with the results directly impacting on policy making, clinical practice, and product development. This goes to show the potential for this technique to exponentially grow as a research method in pharmacy practice research over the coming years. It is important for pharmacy practice researchers to equip themselves with the knowledge of the basics and applications of this research method in order to make the best use of DCE to advance pharmacy practice and science.

Glossary

Attributes Characteristics of the intervention of interest. These could be quantitative or qualitative and are described using levels.
Best-worst scaling A survey-based method for assessing stated preferences where respondents are asked to select their most preferred and least preferred option out of a number of options.
Conjoint analysis A survey-based method used in market research that helps determine how people value different attributes of a product or service.
Discrete choice experiment A survey-based method underpinned by economic theory that allows the systematic quantification of respondents' preferences for the different characteristics (attributes) of a good or service, the balance between these different attributes and the relative value of each attribute.
Levels The values that the attributes describing a good or service can take.
Stated preferences The preferred options for individuals as stated by them when asked to choose their preferred option from a series of hypothetical scenarios.

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Quality of Qualitative Research

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Chapter Overview

This chapter focuses on, perhaps, the most debated issue among research methodologists-quality assurance of qualitative research. Unlike existing literature, which either focuses on the process-oriented approach or the output-oriented approach, this chapter provides a comprehensive review of both approaches. This chapter begins with an introduction section, which provides an overview of the issue of quality in qualitative research. The first half of the chapter focuses on process-oriented approach and various strategies/tools that can be used to ensure quality. The second half focuses on output-oriented approach and highlights advantages and disadvantages of the two most commonly used checklists developed to improve quality of reporting of qualitative research. The chapter has been divided in various subsections to improve the readability and flow.

Introduction

Like any other research methodology, quality is of critical importance in qualitative research and this is to ensure that the qualitative research is credible and dependable. The reasons that make issue of quality in qualitative research complicated are multifaceted. These include: the diversity in research methods available under the umbrella term of qualitative research methodology; multiplicity of viewpoints available in literature on the issue of "quality" and lack of clear and explicit guidance in simple language understandable to health-care researchers undertaking qualitative research, and the very nature of health-care researchers-who are fundamentally trained with "quantitative" mindset, often find it difficult to transit to "qualitative" mindset and truly embrace the philosophy of qualitative research. Furthermore, health-care researchers have "borrowed" qualitative research methods from social science disciplines, and therefore, the understanding of what constitutes a good qualitative research may vary across these disciplines.

Reynolds et al. (2011) reviewed literature debating various issues related to quality assurance of qualitative research and found two dominant, yet contrasting, approaches to quality assurance in qualitative research, process-oriented approach and

output-oriented approach. The process-oriented approach, epistemologically linked to interpretive/constructionist approach, is based on the internal set of values or principles of "best practices" inherent to qualitative research. The authors identified six principles of process-oriented approach: reflexivity in terms of researcher's epistemological position, assumptions, and practice; detailed description of decisions made, and assumptions supported; comprehensiveness of approach to research question; responsibility toward decision making throughout the research process; adherence to good ethical practices; and a methodical approach in designing and conducting the study (Reynolds et al., 2011). On the other hand, output-oriented approach is drawn from positivist or post-positivist paradigm. It advocates the use of certain techniques, often in the form checklists, and demonstrating their use is considered an indicator of quality.

In this chapter, we will discuss the issue of quality in qualitative research based on these two narratives proposed by Reynolds et al. (2011).

Process-Oriented Approach: Practices to Ensure Rigour and Trustworthiness

Given the theoretical and philosophical differences between qualitative and quantitative methodologies, applying the same quality criteria of validity and reliability across both research methodologies is unjustified. Therefore, instead of using quantitative terms such as reliability, internal validity, objectivity, and generalizability; the use of alternative qualitative equivalent terminologies such as dependability, credibility, conformability, and transferability, respectively, is advocated to describe rigor and trustworthiness in qualitative research (Lincoln and Guba, 1985; Noble and Smith, 2015).

Methodologists have developed several strategies to ensure trustworthiness of qualitative research. It is not expected that the researcher would engage with all these strategies in a single study as it will not be always either practical or possible to engage with of all them. However, it has been recommended that at least two of these strategies should be used in a particular qualitative study (Creswell, 2006). A brief description of commonly used strategies is given below.

Triangulation

Triangulation aims to reduce bias typically associated with single data source and/or method by using at least two different but related data sources, data collection methods, or researchers. It is frequently used to ensure credibility and conformability of qualitative studies (Creswell, 2006) as it helps researchers to ascertain the validity of the interpretations derived from different data sources. For example, a researcher who is interested to understand barriers to medication adherence among patients with long-term conditions may consider interviewing both patients and their health-care providers. The researcher then draws themes after analyzing and integrating data from both datasets.

Self-Description/Reflexivity

Self-description also referred as self-reflection is perhaps the most important tool not only to acknowledge but also to reduce researcher bias. Self-description allows qualitative researchers to explain their epistemological position, personal beliefs in relation to the research topic, field experiences, and previous research and/or professional training and how these things might have influenced the research findings (Hammersley and Atkinson, 1995; Long and Johnson, 2000). To recognize and disclose any personal bias, it has been suggested that the qualitative researchers should make field notes and maintain a reflective journal (Long and Johnson, 2000). Self-reflection ensures credibility and conformability of research findings.

Member Checking

Member checking, also known as respondent validation, is considered in the literature as the single most important method to ensure a study's credibility (Lincoln and Guba, 1985). Member checking involves checking of various, but not all, steps of data collection, analysis, and interpretation by the study participants from whom the data were originally collected (Long and Johnson, 2000). For example, a researcher using member checking technique may take themes emerged from the analysis of focus group interviews back to the participants of a particular focus group and discuss if the themes resonate their experiences/views. Member checking can ensure dependability and credibility of qualitative research. However, member checks should not be used as a verification strategy to judge the "truth" in data analysis. Researchers should also be very careful in accommodating respondent's views as this method can alter researcher's interpretation and may make findings descriptive.

Prolonged Engagement

Given the nature of qualitative research, establishing rapport with respondents and gaining their trust are critical to obtain in-depth information from the respondents. Prolonged engagement with respondents and community aims to do that and will help researcher to study the research topic more comprehensively (Creswell, 2006). Prolonged engagement may promote the credibility of a qualitative study. Typically used in ethnography, prolonged engagement involves spending sufficient time in the field observing different social, political, and economic constructs of a culture/society, engaging with diverse group of people, and developing

relationships with members of the culture with an aim to understand and appreciate the culture, social setting, or phenomenon of interest beyond personal preconceptions (Creswell, 2006).

Audit Trail

Audit tail involves providing detailed description of all the steps (data collection, analysis, and interpretation) and decisions made during the course of the study. This will facilitate readers to make their own personal judgments about the rigor, trustworthiness, and worth of a study (Sandelowski, 1986).

Peer Debriefing

Peer debriefing is another commonly used technique in qualitative research. In peer-debriefings, the researcher holds regular meetings with a peer throughout the research process and discusses the research methodology, data analysis, and interpretations (Lincoln and Guba, 1985). Ideally, a typical peer is someone who is not directly involved in the research and is an experienced qualitative researcher who can not only stimulate critical thinking but also can ask questions about the researcher's interpretations. Research supervisors/mentors can act as "peers" for their research students. Presenting research findings to interested groups and at conferences can also provide alternative forms of peer debriefing. Peer debriefing is also known as "analytic triangulation" (Nguyen, 2008).

Thick Description

Thick description refers to providing detailed description about settings, inclusion/exclusion criteria, sample characteristics, and data collection and analysis methods. This will enable the readers to evaluate the extent to which authors' conclusions are transferable to other external settings and different populations. Thick description is the most important tool to ensure external validity (transferability) of qualitative research (Long and Johnson, 2000). It also promotes study credibility as well.

Output-Oriented Approach: Quality of Reporting of Qualitative Research

Increasing numbers of qualitative research are being published by journals as a contribution to understanding of decisions and behaviors not only of patients but also of the health-care professionals involved in their care (Morse, 2015). The increased acceptance and publication of qualitative research is a reflection of the wide variety of qualitative methodologies and the maturity of the associated methods (Sidhu et al., 2017). In spite of this expansion, qualitative research is still viewed negatively by some journal editors as it was noted in an editors' meeting of the *British Medical* Journal. The editors argued in favor to effectively restrict publication of research aligned to the qualitative research philosophy (Greenhalgh et al., 2016; Loder et al., 2016).

Sidhu et al. (2017) argued that the current negative views about qualitative research may be overcome by ensuring that authors adhere to acceptable reporting standards. In particular, they mentioned that in addition to appropriately framing the research question in relation to existing evidence base, it is also important to make due consideration to the contribution of the research to clinical practice through the research process and the completeness and clarity of how this is being reported within the criteria imposed by relevant medical journals (Sidhu et al., 2017).

Significance of Quality of Reporting to Stakeholders

It has been highlighted that incomplete or unclear write-up reporting of qualitative research can largely contribute to rejection of papers. This, in turn, leads to the lack of dissemination of new knowledge and insights that could influence practice (Blignault and Ritchie, 2009). In addition, poorly designed studies make it difficult for users to assess the research findings and may lead to adoption and incorrect changes to health-care practice (Tong et al., 2007). It is important for authors to present clear and transparent research so that the readers can understand the process of research and how credible the findings are for adoption. Moher et al. (2014a,b) asserted that researchers have an ethical responsibility to provide a clear and accurate report of their research.

Appropriate and clear reporting of the research process and its outcome contributes to the establishment of rigor and credibility of qualitative research through demonstration of transparency (Malterud, 2001). Transparency of the research process and its findings is necessary to help stakeholders make appropriate judgments about how to identify and use the new knowledge.

Reporting Guidelines

The problem of incomplete reporting of qualitative research has led to the development of criteria, which guide authors while preparing and submitting qualitative papers. Simera et al. (2010) while writing about Enhancing the Quality and Transparency of Health Research Network (EQUATOR) described reporting guidelines as minimum set of required items (in the form of a checklist or flow diagram). These items provide advice on how to report research methods, results, and issues, which may contribute to bias in research.

The development of appropriate and relevant reporting guidelines is important for several reasons:

1. Availability of reporting guidelines enable authors to provide the necessary information required by journal editors.
2. Knowledge of established guidelines enables these to be taken account during the planning and execution of the research study.
3. Reviewers have the benefit of a uniform set of standards for comparability of submitted manuscripts.
4. There is improved appraisal of qualitative evidence synthesis due to the enhanced quality of reports available.
5. The guidelines can help peer reviewers to assess manuscripts for suitability and quality.
6. Editors can refer to existing reporting standards or develop specific guidelines, which contributes to accuracy, clarity, and transparency in the reporting of the qualitative research.
7. Meeting reporting standards will provide confidence to users of research such as health-care professionals, and it will enable them to adopt these findings into practice.
8. Stringent reporting standards provide the research community with assurance that qualitative research has appropriate scientific rigor.

Reporting Guidelines: Do They Improve Quality?

The development and promotion of reporting guidelines by editors and researchers is widely advocated. This may be a recognition that reporting guidelines are proving effective in improving the transparency and rigour in the way the design and procedures of research are communicated. A Cochrane review of the impact of the CONSORT statement indicates that the adoption of reporting guidelines contributed modestly to improvement in transparency of reporting (Turner et al., 2012). Many believe that the development and promotion of reporting guidelines for qualitative research will follow a similar pattern (The Equator Network).

Altman and Moher (2014) described a growing recognition that the adoption of reporting guidelines is effective in communication of research methods and findings. It is therefore important that researchers are encouraged to adopt reporting guidelines appropriate to their type of study as it would help improve transparency in research. In this regard, editors have an important role to play by demanding full and transparent reporting (Altman and Simera, 2010).

Concerns about the existence of checklists for reporting guidelines have been raised in that they may appear overly prescriptive thereby promoting overuse. There is a risk that without a broader understanding of the qualitative research design and data analysis, the unique contribution of qualitative research to health services research may be compromised (Barbour, 2001).

Mcleroy et al. (2016) make it clear that the primary purpose of reporting guidelines is to help readers to understand the published research by enhancing transparency. They are not intended to define how the research itself is conducted, nor are they meant to be used to evaluate the quality of the study per se. Smith et al. (2018) also states that the most appropriate reporting guidelines must be selected based on the relevant qualitative methodology guiding the study.

Common Reporting Guidelines for Qualitative Research

Guidelines for conduct and reporting of quantitative research have long existed to improve quality and allow understanding of various aspects of the respective research types. In recent years, there has been a proliferation of reporting different kinds of guidelines for qualitative research studies. However, the Consolidated Criteria for Reporting Qualitative Research (COREQ) developed by Tong et al. (2007) and Standards for Reporting Qualitative Research (SRQR) (O'Brien et al., 2014) are two key guidelines widely adopted for evaluating the quality of reporting of qualitative research. Consolidated Criteria for Reporting Qualitative Research (COREQ) is a set of reporting guidelines consisting of 30 items, which is meant to enhance comprehensiveness of reporting of interviews and focus group studies. SRQR, on the other hand, is a 21-item framework, which was developed through the input of international experts to act as standards for accurate reporting of a variety of qualitative studies.

Another widely used reporting guideline is the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) (Tong et al., 2012). The ENTREQ statement (framework) consists of 21 items grouped into five domains (Introduction, Methods and Methodology, Literature Search and Selection, Appraisal, and Synthesis of Findings). ENTREQ is useful to students and researchers on how to conduct and assess the synthesis of multiple qualitative health research studies (Tong et al., 2012). Notably, the framework has not undergone a Delphi exercise, a fundamental step in guideline development. This means that it has only fulfilled the first criterion for guideline development (Flemming et al., 2018). Users are advised to be mindful of this limitation.

There are other reporting guidelines for qualitative research studies that have been developed for specific health-care areas and other forms of interventions. The Enhancing the Quality and Transparency of Health Research (Equator) Network is an international initiative that seeks to promote accurate reporting of research through wider use of reporting guidelines thereby enhancing the value of research (*The Equator Network*). The EQUATOR website has a compilation of reporting guidelines for qualitative and other types and forms of research. In addition, it disseminates regular online newsletters highlighting new reporting guidelines and organizes workshops and courses to support the adoption and use of the resources listed on its website (Simera et al., 2010).

In addition to the above, specific guidelines have been developed by respective journals to ensure standardization of qualitative research manuscripts for peer review and publication. For example, The American Pharmaceutical Education journal (Anderson, 2010) has developed criteria to be used by authors for reporting their research. On the other hand, some journals and publications such as Biomed Central, BMJ, and Journal of Advanced Nursing advised authors to follow acceptable reporting guidelines for the respective type of study (e.g., COREQ, SRQR) as recommended by repositories such as the EQUATOR network.

Consolidated Criteria for Reporting Qualitative Research

COREQ is a 32-item checklist developed by Tong et al. (2007) for evaluating the comprehensiveness of reporting of qualitative studies. It does not purport to set standards for conducting qualitative research and it is mainly focussed on studies reporting focus groups and interviews. The development of COREQ is based on a systematic literature review and identifying items published within other tools and checklists for qualitative research studies.

Development of the COREQ Checklist

The authors searched electronic databases (CINAHL, MEDLINE), Cochrane, and Campbell protocols, including author and reviewer guidelines of major medical journals and reference lists of relevant publications for guidelines and checklists used to evaluate qualitative studies. After excluding duplicate checklists, criteria for assessing and reporting qualitative studies from each of the studies were extracted to give a comprehensive list of 72 items from 22 checklists (Tong et al., 2007). The items were grouped into three domains with duplicates removed and a descriptor was attached to each item to promote clarity (**Table 1**). Two new items: "identifying the authors who conducted the interviews or focus group" and "presence of nonparticipants" were considered relevant for reporting qualitative research by consensus and therefore included to make a final list of 32 items.

Uses and Benefits of COREQ

COREQ offers the following benefits:

1. COREQ can be used by editors and reviewers in the assessment of qualitative research manuscripts prior to publication.
2. It can be used to evaluate the validity and transferability of the findings from qualitative research reports.
3. It can be used as a form of standardization for researchers undertaking qualitative evidence synthesis and systematic reviews.
4. The popular application of COREQ as indicated by recommendations of journal editors and other members of the research community despite the absence of specific empirical validation gives an indication that it serves as a useful tool for comprehensive and accurate reporting of qualitative studies. Subsequently, there has been an increase in number of papers published in the BMJ and BioMed Central group journals by adhering to these guidelines.
5. The authors of COREQ suggest that although it was developed based on interviews and focus groups, it may still be used for other qualitative research methods.

Limitations of COREQ

1. The development of COREQ was based on interviews and focus groups, and therefore, its value may be more limited when used for other qualitative methodologies.
2. The absence of Delphi studies or consensus meetings in the development of COREQ appears to have limited its rate of adoption and acceptability.
3. The tool has not been validated to provide an empirical confirmation that it is likely to improve the quality of reporting of qualitative studies. However, the authors contend that the effect is likely to be similar to when other guidelines such as CONSORT was introduced and has subsequently been found to have improved the quality of reporting of the specific study type (Moher et al., 2001).
4. The slow development of extensions to the COREQ tool may arise from the absence of empirical validation and a lack of international consensus on uniform criteria for qualitative research.

Standards for Reporting Qualitative Research

SRQR is a 21-item checklist (**Table 2**) of clear reporting standards which is aimed at improving the transparency of all aspects of qualitative research (O'Brien et al., 2014). It was formulated through a systematic approach of rigorous synthesis of previously published guidelines followed by expert recommendations. Key elements of each item are defined and explained by the authors including providing examples from published articles (O'Brien et al., 2014).

Development of the Standards

The authors of SRQR identified previously proposed recommendations by systematically reviewing PubMed, Web of Science, and Google and by reviewing the reference list of the retrieved sources. A comprehensive list of items that were potentially important in reporting qualitative research was initially generated, which was then refined to a shorter list by identifying core concepts and combining related items.

The shorter list was then compared with the original sources to check for missing concepts and then appropriate explanatory definitions were included. The resulting prefinal list was reviewed by five experienced qualitative researchers for omitted or redundant items and to suggest improvement in clarity and relevance. Following the expert review, a final set of reporting standards was created by consolidating some items and making amendments to the wording of some labels and definitions (O'Brien et al., 2014).

Table 1 Domains and items in the COREQ list

	Details of item	*Guide questions/Descriptions*
Domain 1—research team and reflexivity		
Personal characteristics		
1.	Interviewer/Facilitator	Which author(s) conducted the interview or focus group?
2.	Credentials	What were the researcher's credentials? For example, PhD, MD.
3.	Occupation	What was their occupation at the time of the study?
4.	Gender	Was the researcher male or female?
5.	Experience and training	What experience or training did the researcher have?
Relationship with Participants		
6.	Relationship established	Was a relationship established prior to study commencement?
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? For example, personal goals, reason for doing the research.
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? For example, bias, assumptions, reasons, and interests in the research.
Domain 2—study design		
Theoretical framework		
9.	Methodological orientation and theory	What methodological orientation was stated to underpin the study? For example, grounded theory, discourse analysis, ethnography, phenomenology, content analysis.
Participant selection		
10.	Sampling	How were participants selected? For example, purposive, convenience, consecutive, snowball.
11.	Method of approach	How were participants approached? For example, face to face, telephone, mail, email.
12.	Sample size	How many participants were in the study?
13.	Nonparticipation	How many people refused to participate or dropped out? Reasons?
Setting		
14.	Setting of data collection	Where was the data collected? For example, home, clinic, workplace.
15.	Presence of nonparticipants	Was anyone else present beside the participants and researchers?
16.	Description of sample	What are the important characteristics of the sample? For example, demographic data, date.
Data collection		
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?
20.	Field notes	Were field notes made during and/or after the interview or focus group?
21.	Duration	What was the duration of the interviews or focus group?
22.	Data saturation	Was data saturation discussed?
23.	Transcripts returned	Were transcripts returned to participants for comments or corrections?
Domain 3—analysis and findings		
Data analysis		
24.	Number of data coders	How many data coders coded the data?
25.	Description of the coding tree	Did authors provide a description of the coding tree?
26.	Derivation of themes	Were themes identified in advance or derived from the data?
27.	Software	What software, if applicable, was used to manage the data?
28.	Participant checking	Did participants provide feedback on the findings?
Reporting		
29.	Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? For example, participant number.
30.	Data and findings consistent	Was there consistency between the data presented and the findings?
31.	Clarity of major themes	Were major themes clearly presented in the findings?
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?

Source: Adapted from Tong, A., Sainsbury, P., Craig, J., 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int. J. Qual. Health Care, 19 (6), 349-357.

Table 2 Standards for reporting qualitative research (SRQR)[a]

	Topic	*Item*
Title and abstract		
S1	Title	Concise description of the nature and topic of the study, identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory), or data collection methods (e.g., interview, focus group) are recommended.
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions
Introduction		
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement
S4	Purpose or research question	Purpose of the study and specific objectives or questions
Methods		
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale[b]
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/ experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability
S7	Context	Setting/site and salient contextual factors; rationale[b]
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b]
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b]
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts
S14	Data analysis	Process by which inferences, themes, etc., was identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale[b]
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b]
Results/findings		
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes) might include development of a theory or model or integration with prior research or theory
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings
Discussion		
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field
S19	Limitations	Trustworthiness and limitations of findings
Other		
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting

[a]The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

[b]The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available; the assumptions and limitations implicit in those choices; and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Source: Adapted from O'Brien, B., et al., 2014. Standards for Reporting Qualitative Research: A Synthesis of Recommendations. Acad. Med. 89 (9), 1245-1251.

Uses and Benefits of SRQR

1. The twenty one standards provide users with a framework and recommendations for comprehensive reporting of qualitative studies.
2. The standards can assist users during preparation of their manuscripts to meet requirements of editors and other reviewers for complete reporting of qualitative research.
3. Journal editors, funding organizations, and other members of the research community may find SRQR useful in relation to standardization of clarity and completeness of reporting of qualitative research studies.
4. The authors identified items with broad relevance in an attempt to cover the wide range of qualitative approaches and methodologies.
5. The framework is robust because it is based on previously published criteria, critical review by experts, and wide-ranging experience and perspectives among its authors.
6. Descriptions and examples of how the framework can be used have been supplied by the authors to enable researchers to use these standards.
7. A checklist for reporting standards such as SRQR can help advance qualitative research methodologies by enhancing transparency in the research process and its findings.

Limitations of SRQR

1. The authors of SRQR advise that it may be inappropriate to use the framework to assess the quality of research methods and findings. This follows from the deliberate avoidance of recommendations that define methodological rigour during the development of the framework.
2. The diverse range of qualitative research approaches may lead some users to be critical of the suitability of a consolidated framework for evaluating different types of qualitative studies. This could limit its usefulness among a section of the research community.

Conclusion

In conclusion, both process- and output-oriented approaches should be considered while designing, conducting, and reporting qualitative research. For novice researchers, engaging with literature of appropriate quality, getting formal training in undertaking qualitative research, and working with a senior qualitative researcher can facilitate good quality qualitative research. No single checklist is applicable to all forms of qualitative research. Checklist gives reporting so transparency in order to enable the quality of the research, but a high score intensified does not necessarily indicate high quality research, nor would getting a lower score necessarily indicate poor quality research. Engagement with reporting checklists in early stages of designing qualitative studies can help researchers ensure quality in qualitative work.

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Clinical Pharmacists as Principal Investigators in Clinical Trials

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Introduction

Clinical research is a multidisciplinary endeavor that follows a collaborative approach to promote advances in health care (VanWormer et al., 2012). The extent to which clinical trials are conducted is a reflection of the level of advancement that exists within a health care system. Clinical trials are conducted on human volunteers in a prospective manner to ascertain the effectiveness and safety of investigational products, such as drugs and devices; clinical trials data eventually serve to optimize patient care. Clinical trials are typically conducted in four phases [**Table 1**] (U.S. National Library of Medicine, 2018). Randomized controlled trials are the gold standard in the spectrum of clinical research; they ascertain the effects of interventions and possess a higher place in the hierarchy of evidence (Burns et al., 2011). Clinical trials are usually conducted by collaborative efforts of the principal investigator (PI) or investigator, subinvestigator, pharmacist, physician/dentist, research nurse, clinical research coordinator and clinical research associate or monitor. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines (ICH-GCP) defined an investigator as "a person responsible for the conduct of the clinical trial at a trial site." If a trial involves several individuals at a study site, one individual is designated as a PI and will therefore be the responsible team leader (ICH, 2016).

It is imperative for the research team to maintain the credibility of clinical trials by protecting the rights, safety and well-being of the study volunteers (ICH, 2016). After the adoption of the Kefauver Harris Amendment in 1962 by US Food and Drug Administration (US FDA), pharmaceutical sponsors are required to submit both efficacy and safety data of drugs to obtain regulatory approvals (Kay et al., 2018). This major development was a result of human tragedy that occurred due to the use of thalidomide in pregnant women, which, in turn, prompted the US FDA to amend the Federal Food, Drug, and Cosmetic Act. The American Society of Health-System Pharmacists (ASHP) highlights the role of pharmacists in the management of investigations and approving drugs in a clinical trial and/or a routine clinical care setting. Moreover, their presence in a clinical research team is crucial for executing successful research projects (ASHP, 2016; Kay et al., 2018).

The ICH-GCP, the American College of Clinical Pharmacy (ACCP), and the research guidelines issued by the ASHP uphold the participation of trained and experienced pharmacists as PIs in clinical trials. The provision of educational sessions and monitoring of investigational drugs are deemed core components of drug trials, whereas pharmacists are also best suited to perform these functions (ASHP, 2016; Kay et al., 2018).

The credit of conducting the first ever controlled clinical trial of the modern era is given to physician Dr. James Lind. This clinical trial was conducted in 1747 to ascertain the cure of scurvy (Bhatt, 2010).

Ethics in Clinical Trials

There have been several cases of unethical practices when patients' rights, safety and well-being were not taken into consideration by physicians, eventually resulting in the reporting of fatalities. For example, the Tuskegee syphilis study (1932–72), Nazi medical experiments (1939–45), and the thalidomide tragedy (1960s) are well-known historical events in clinical research. In addition, the

Table 1 Phases of clinical trials

Phase	*Objective*	*Questions*	*Typical number of subjects*
I (or first-in-man studies)	Safety	Evaluated parameters: Dose, frequency, route, pharmacokinetics and pharmacodynamics	20–100
II	Efficacy and safety	To assess efficacy and define therapeutic dose range and dosing regimen. Further information on safety, pharmacokinetics and pharmacodynamics	50–300
III	Confirmation of efficacy and safety	To assess treatment outcomes and compare investigational drug with an approved treatment or placebo	100–1000
IV	Post marketing surveillance, effectiveness of drug, and impact on quality of life	To evaluate long-term effects of drugs (efficacy, safety, and side effects) in a large number of population and explore new indications	1000

aforementioned incidents prompted the emergence of ethical principles that were included in the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki.

The ICH-GCP remains a vital document for conducting clinical trials. Several regulatory authorities, including the European Medicines Agency and the FDA, endorse the GCP as a unified document for conducting ethically and scientifically sound clinical trials. These guidelines are followed for designing, conducting, recording and reporting clinical trials involving human volunteers. The first version of the ICH harmonized guideline, E6 (R1), was released in 1996, and its amended version, E6 (R2), was recently released in November 2016 (ICH, 2016). Sponsors have a mandate to select the study investigators by assessing the statement of investigators, Form FDA 1572, which is utilized to acquire qualification and experience details. Form FDA 1572 is only required for studying investigational new drugs; this form is not employed for investigational device studies where a signed investigator agreement is collected (FDA, 2010). Investigators are permitted to initiate clinical trials (phases I–IV) after the submission of Form FDA 1572, and approval is at the discretion of the study sponsors. However, the requirement of this form is specifically for studies that are conducted under the US Investigational New Drug Application (IND); this form is also mandatory when an IND study is conducted outside the territory of the US, while foreign clinical studies are typically not conducted under an IND. Furthermore, postmarketing and observational studies are exempted from the requirement of Form FDA 1572. Investigators comply with the GCP and other requirements of regulatory authorities that are crucial for promoting the subject's safety and successful execution of clinical trials. The selection of a clinical pharmacist as a PI is subject to the inclusion of a doctor (or dentist, when appropriate) as a subinvestigator (FDA, 2010).

Health care professionals should familiarize themselves with principles and guidelines such as the ICH-GCP, the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki. These ethical considerations are of paramount importance in clinical trials to develop safe and effective medications. As of December 2017, more than 250,000 clinical studies are registered on ClinicalTrials.gov, which is recognized as the oldest and largest registry of clinical trials managed by the National Library of Medicine at the National Institutes of Health in the US Notably, 41% of the clinical studies are registered under the map of the US (U.S. National Library of Medicine, 2017).

Roles and Responsibilities of the PI in Clinical Trials

The existence of the PI is a driving force behind the successful execution of clinical trials as per the defined standards and regulations. The diligence of the PI promotes the rights, safety, and well-being of the study subjects. Likewise, investigations involving human subjects are collaborative activities, and the role of the PI as a team leader is inevitable in this regard (Baer et al., 2011; Katz et al., 2011).

PIs must perform several functions, including extensive clinical research documentation, and abide by policies and regulations after the initiation of a trial at the study site. A well-acquainted PI transfers knowledge in an effective way to the entire staff involved in clinical investigations while cultivating a proactive team mind-set and optimizing communication. Moreover, a PI ensures that clinical trial personnel are aware of their responsibilities and comply with the study protocol, hence generating high-quality clinical data. It is a prerequisite for PIs to demonstrate the training and experience required for a clinical program prior to their selection, which is crucial to perform responsibilities in a diligent manner (ICH, 2016). PIs are given adequate time by the sponsor to review the study documents such as the protocol and the investigator's brochure; the investigator's brochure is a document that contains clinical and nonclinical data on the Investigational Medicinal Product (IMP) (ICH, 2016). The following are the core responsibilities of the PI in clinical trials (ICH, 2016; Kay et al., 2018):

- Organizing GCP training

It is a common practice for the study sponsors to provide GCP training to personnel involved in clinical trials. GCP training is conducted either through the specific web portal of the trial, CDs, training sessions and/or workshops.

- Seeking IRB approval

Clinical trials are commenced at the study site after IRB approval. A PI is responsible for submitting all the required documents to the IRB. If the selected PI is a member of the IRB, then he or she will not participate in the decision process or voting. However, any information pertinent to the clinical trial can be provided by the PI to the IRB (ICH, 2016). The PI is also responsible for submitting progress reports to the IRB annually or frequently (when requested); these reports are also submitted to the study sponsor.

- Clinical trial's study file for the PI

Table 2 shows the sections and content of a PI study file provided by the sponsor for conducting a randomized, double-blind placebo-controlled trial. This table is merely used for the guidance of novice PIs and is based on previous experience in multinational clinical trials sponsored by Novartis Oncology, F. Hoffmann-La Roche AG and the London School of Hygiene and Topical Medicine. Section 8 of the ICH-GCP also discusses the essential documents that are used before, during and after the conduct of clinical trials. Data collection should follow previously established guidelines. The concept of ALCOAC (Attributable, Legible, Contemporaneous, Original, Accurate, and Complete) is followed for maintaining high standards in clinical research documentation. ALCOAC is also specified in the joined version of the ICH-GCP under the section entitled "Records and Reports" (ICH, 2016). The US FDA initially introduced the ALCOA concept, which later evolved into ALCOAC (Bargaje, 2011). There is a common saying in clinical trials, "if it wasn't documented, it wasn't done." During audits and inspections, a lack of ALCOAC

Table 2 PI study file index for clinical trials

Section	*Contents*
Inside cover	• Laminated protocol summary • Protocol • CD containing training presentations, data forms and guidance, patient and representative information sheet, consent form, adverse event form, screening log, randomization log, delegation log • Guidance for trial materials • Materials order form • Participating sites—trial website address is included for updated list
Contacts	• Contact information
Protocol	• Trial protocol version submitted to local ethics committee • Master copy of patient/representative information sheets and consent form for hospital/study site • Master copy of brief information leaflet and wall poster for the family • Protocol amendments
Training materials	• DVD training film • Trial overview • Manual of Operating procedures • Power point presentations on CD in front cover • ICH-GCP guidelines summary. website address is also provided for complete ICH-GCP guidelines • GCP training and test guidance • Further training materials on secure collaborator's intranet
Trial drug guidance and information	• Drug administration guidance • Investigator brochure • Summary of product characteristics
Consent procedure	• Consent procedure overview • Guidance for completing the consent form
Data handling	• How to complete the data entry form • How to submit data online • How to send data by upload, email and fax • Guidance on protocol violations and deviations, data discrepancies, data queries and corrections • Serious data discrepancy form sample • Protocol breach form sample
Adverse events	• Adverse events reporting guidance • How to complete AE form • Unblinding forms • AE/SAE forms—also on CD • Notification of SAE/SUSAR by trial coordinating center • Reports from PI to local ethics committee

(*Continued*)

Table 2 PI study file index for clinical trials (*cont'd*)

Section	*Contents*
Ethics	• Copy of application submitted • Correspondence with ethics committee • Ethics committee approval • Approvals of protocol amendments
Regulatory	• National regulatory approval • Approvals of protocol amendments
Other approvals and indemnity	• Indemnity • Other approvals
Agreements	• PI agreement • Other agreements
Trial monitoring	• Site visit log • Guidance on monitoring procedures • Site monitoring report sample • Consent monitoring report sample • Central monitoring report sample • Completed site monitoring reports (consent monitoring, central monitoring, site visits) • Audit and inspection reports • Close out report
Trial drugs documentation	• DAL guidance • DAL forms • Drug receipts/shipping document
Patient information sheets and consent forms	• Spare information sheets for patient and their representative—also in treatment boxes and on CD • Spare consent forms—also in treatment boxes and on CD • Alert cards and contact labels • Brief information leaflets for family • Professional legal representative log • Sample label sheet • Sample ward transfer sheet • Sample waiver label
Patient entry	• Screening log • Randomisation log • Spare entry forms—also in treatment boxes and on CD • Example letter to personal doctor • Sample transfer pack
Completed forms	• Original consent forms • Completed adverse event forms • Completed protocol breach forms
Correspondence	• Correspondence on data queries/resolutions • General correspondence, printed emails
Site responsibilities, training logs and certificates	• Delegation of responsibilities/signature log • Training logs • Site training reports • Hospital information sheet • CV template • CV of principal investigator • CVs of trial team members who have been delegated responsibilities • GCP and other training certificates
Reports	• Reports to ethics committee • Reports to regulatory authority • Final and other trial reports • Publication(s) • Log of patients who have requested the study results

DAL, Drug Accountability Log; *GCP*, Good Clinical Practice; *CD*, Compact Disk; *DVD*, Digital Optical Disk; *AE*, Adverse event; *SAE*, Serious Adverse Event; *CV*, Curriculum Vitae.

attributes in source documents is a common finding (Bargaje, 2011); PIs and other team members should follow the concept of ALCOAC during the course of a clinical trial.

- Risk Assessment Form for Investigational Medicinal Product

An IMP is defined as "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or to gain further information about the authorized form" (Directive 2001/20/EC, 2001).

The IMP Risk Assessment Form is filled out by the PI in collaboration with the clinical trials pharmacist and lead research nurse. Risk is assessed by the study sponsor, and risk level is usually categorized into three levels: (1) low, (2) medium, and (3) high. The study sponsor does not release the IMP before the receipt of this form. The purpose of the IMP Risk Assessment Form is to solicit information pertinent to the IMP storage facility, the policy of the IMP at the study site, locked cabinet/cupboard and its location, other drugs to be stored in the same cabinet/cupboard, labels (For Clinical Trial Use Only and Packs May Contain Placebo) on cabinet/cupboard, monitoring frequency of the IMP stock/drug accountability log/randomization log, and the name and role of a person responsible for monitoring the IMP stock.

- Signing/endorsing treatment box receipt

The PI is required to sign the box receipt form after receiving the shipment of the IMP and check that the packs have been received in good condition; this form is sent to the sponsor either by fax or email.

- Consenting process

Informed consent is collected by the PI from all study subjects prior to their inclusion in the clinical trial, and in particular cases, from the subject's legal representatives, depending on the nature of the population involved (ICH, 2016). The consenting process is done without coercing, and study subjects have the right to withdraw from the study at any time (ICH, 2016).

- Randomization procedures and reporting of unblinding

A PI should abide by the randomization procedures specified in the study protocol and ensure that the breaking of code follows the standard procedures. Moreover, PIs also document and inform the study sponsor regarding unbinding issues that arise either accidently or due to the occurrence of serious adverse events (ICH, 2016).

- Drug accountability log

As per the ICH-GCP, the PI is accountable for the management of the IMP at the study site. A prepopulated form is sent to the PI by the study sponsor with each drug box. The PI records the usage of all treatment packs and destroys any partly used packs or any packs that are damaged and cannot be used for randomization. The drug accountability form is sent to the sponsor either by fax or email after ensuring that all packs have been used/destroyed, or when requested.

- Delegation of trial-related duties

The PI maintains a list of all qualified research personnel that were assigned any trial-related duties by the PI. A PI also ensures that the trial team has adequate knowledge regarding their role in the clinical trial and is aware of the protocol and investigational products (ICH, 2016).

- Safety reporting

Serious adverse events/serious adverse drug reactions and unexpected adverse drug reactions are reported by the PI to the sponsor and applicable authorities (regulatory authority and ethical committee) following the reporting timelines specified in the study protocol (ICH, 2016).

- Retention of trial records

After the completion of a clinical trial, the PI/study institution is informed by the study sponsor to retain all trial-related documents for a specific time period; destroying documents is carried out after the written notification of sponsors to the PI/study institution (ICH, 2016).

Clinical Pharmacists in Clinical Research

Direct patient care is defined as "a practice which involves the pharmacist's direct observation of the patient and his/her contributions to the selection, modification, and monitoring of patient-specific drug therapy; this is often accomplished within an interprofessional team or through collaborative practice with another health care provider" (Carter, 2016). As per the ACCP, residency training and board certifications are indispensable for direct patient care. According to the ACCP, clinical pharmacists are pharmacy professionals concerned with the science and practice of rational drug therapy (ACCP, 2008). From 2003 to 2014, there was a fivefold increase in the total number of board certified clinical pharmacists in the US alone (Carter, 2016).

The action of clinical pharmacists before, during and after prescribing a drug influences the outcomes of drug therapy, thus improving patient care. The before the prescription role is pertinent to their participation in clinical trials, representation in ethical review boards and regulatory bodies, and preparation of drug therapy guidelines. The during the prescription role is related to their influence on the prescribers at the time of prescribing medications, while the after the prescription role includes medication reconciliation, patient counseling, medication compliance, and drug monitoring (Bhatt, 2014).

Clinical pharmacy professionals are uniquely qualified in therapeutics and provide comprehensive medication management to patients and health care professionals (Kaboli et al., 2006). Safety evaluation is a fundamental component of the entire drug development process, and it is crucial to monitor patient safety during clinical trials (Yao et al., 2013). There are several cases in which high-profile approved drugs were withdrawn from the market due to safety concerns. The presence of clinical pharmacists at the bedside improves the quality, safety and efficiency of care (Kaboli et al., 2006). Clinical pharmacists play an integral role in the routine care of hospitalized patients by promoting the rational use of drugs and patient safety. Previous reports found an inverse relationship between the rates of medication errors and the number of clinical pharmacists per occupied bed (Bahrani et al., 2014; Kaboli et al., 2006; Kuo et al., 2013). Clinical trials are conducted on a target population with a specific medical condition. Likewise, findings of 49 systematic reviews reported that the clinical pharmacists exerted a positive impact on the outcomes of patients with a specific disease (Rotta et al., 2015). Physicians also acknowledge the impact of clinical pharmacists on patient health outcomes (Tegegn et al., 2018).

The following are the activities of clinical pharmacists in a health care setting: assessment of current medication management, clinical review, therapeutic drug monitoring, provision of drug information to health care professionals and patients/caregivers, drug use evaluation, and conducting clinical research (ACCP, 2014). Clinical pharmacists have profoundly improved patients' outcomes by improving patients' knowledge regarding diseases, increasing patients' compliance to their prescribed therapy, and reducing the incidence of adverse events, hospitalizations and admission rates (Jacobi, 2016). Clinical pharmacists can also eliminate insecurities surrounding their profession by performing clinical interventions, participating in outreach programs, establishing professional relationships with other health care professionals and publishing scientific articles by executing clinical trials. Interventions by clinical pharmacists proved to be an effective practice to reduce treatment cost in health care and clinical research settings (ACCP, 2000b; Dalton and Byrne, 2017). Counseling the patient is one of the clinical pharmacist's interventions that tends to improve patient adherence and compliance with the treatment protocol (Martinez et al., 2017). Clinical pharmacists also assist in identifying eligible study subjects, thus increasing the research capacity and revenues of the study site (Smith et al., 2010). Pharmacists must be involved in all aspects of clinical research, from preclinical investigations to clinical studies (Koshman and Blais, 2011).

Prior to 1983, pharmacists were mostly involved in traditional pharmacy practice, and they could not obtain ample opportunities to lead drug trials for pharmaceutical companies; their roles were mainly supportive in clinical trials. In addition, research activities were confined to the university level and were common among undergraduate pharmacy students. The evolution of the pharmacy profession from the dispensing of medications to direct patient care has profoundly increased the importance of pharmacists among other health care providers. This paradigm shift also provided opportunities for clinical pharmacists in clinical research. Pharmacists are an integral part of the clinical research team, and their role is crucial for quality assurance and executing successful clinical trials (Gamboa et al., 2011; Ise et al., 2017). The process of maintaining data integrity is crucial in clinical research (ICH, 2016; Kay et al., 2018). Clinical pharmacists are required to maintain the highest standards of integrity and honesty, which is one of the core elements of their competencies put forward by the ACCP in a publication entitled "ACCP Clinical Pharmacist Competencies." Clinical pharmacists should serve as role models/leaders for other health care professionals and uphold the standards of professionalism (Saseen et al., 2017). Pharmaceutical aspects of clinical research are better managed by clinical pharmacists, thus ensuring the rights, safety and well-being of human subjects (Gamboa et al., 2011). Likewise, an increasing number of clinical trials requires the inclusion of qualified and trained clinical pharmacists (Gamboa et al., 2011). A clinical pharmacist's expertise that is pertinent to the pharmaceutical aspects of the drugs warrants them to advise patients on the correct use of investigational drugs. Consequently, clinical outcomes of the clinical trials can be improved by the presence of clinical pharmacists on a clinical research team (Kay et al., 2018; Luisetto, 2016). The Royal Pharmaceutical Society and Pharmacy Research UK (PRUK) play an important role in promoting pharmacist-initiated research studies (Crilly et al., 2017). PRUK also introduced a mentoring scheme for novice clinical researchers. The PRUK Mentoring scheme is intended for clinical pharmacy professionals who want to develop their professional capacity within clinical research and are seeking advice, guidance or support from experienced clinical pharmacy scientists (Crilly et al., 2017). The PRUK mentoring scheme provides guidance to clinical pharmacy professionals working in the UK and abroad. Time and resources are the major limitations of today's pharmacy research. The ACCP report underlined a scarcity of clinical pharmacy scientists or pharmaceutical research mentors, which has been one of the barriers for clinical pharmacists to pursue research projects (Parker et al., 2013). The other most common barrier is research funding, which remains problematic for pharmacist-initiated studies (Crilly et al., 2017; Parker et al., 2013).

The role of clinical pharmacists as PIs was first discussed in 2000 by the ACCP in a commentary article (ACCP, 2000a). Moreover, the National Institute of Health (NIH), a US government entity for the promotion of biomedical and public health research, also substantiated the role of clinically oriented pharmacists as trial investigators in a special conference on pharmacy research held from December 13–14, 2006 in Maryland, US (Figg et al., 2008). Previously, pharmaceutical companies used to show reluctance in the selection of pharmacists as PIs in clinical trials and promoted them in only pharmacokinetic studies (ACCP, 2000a). This is evident from a fivefold increase in the selection of US physicians as PIs from 1990 to 2010, particularly for industry-sponsored clinical trials.

Consequently, pharmaceutical companies retain more control of clinical trial data, which raises issues pertinent to conflict of interest and publication bias (Fisher and Kalbaugh, 2012).

A retrospective analysis revealed that a large number of pharmacists published clinical research studies in major peer-reviewed scientific journals in 1993 and 2003 (Touchette et al., 2008). The US FDA explicitly clarified their policy in 1983, 1989, and 1990, based on a query pertaining to the role of clinical pharmacists as PIs in clinical trials (ACCP, 2000a). The FDA's response document was later used as an educational tool by clinical pharmacists to educate pharmaceutical sponsors, which eventually proved to be an effective activity for acquiring PI status. Following these developments, a large number of clinical pharmacists supervised clinical trials as PIs (ACCP, 2000a). As per the ICH-GCP guidelines and Form FDA 1572, a PI should be qualified by education, training and experience; merely having a pharmacy or medical degree is not enough to serve as a PI in clinical trials (ICH, 2016). The ICH-GCP clause 4.3 explicitly states the role of physicians in the provision of medical care for trial subjects in case of any adverse events and as a decision maker in medical conditions; these guidelines do not reflect the mandatory appointment of a physician as a PI in clinical studies. The general section of Form FDA 1572 also states that the selection of a physician as a PI is not mandatory according to regulations. The US Code of Federal Regulations contains 50 titles of different sections; title 21 (21CFR 312.53), which represents "Food and Drugs," also confirms these statements regarding the eligibility of PIs. Clinical pharmacists must acquire required training, credentials and clinical experience, which are the determinants in the selection of PIs by pharmaceutical sponsors. An ideal approach is to start participating in clinical trials either as a research coordinator, clinical research associate or monitor, or subinvestigator, which will eventually pave the way for junior pharmacy professionals to acquire experience alongside an experienced clinical research professional. Mentorship and nurturing from experienced clinical researchers are also crucial for enhancing the competency of novice investigators (Ward et al., 2017). The study sponsor intends to give preference to health care professionals who demonstrate relevant experience in a population group that will be selected for the proposed clinical trial (ACCP, 2000a). There are plenty of opportunities in a health care setting or hospital where pharmaceutical companies conduct their drug trials, whereas clinical pharmacists' direct interactions with patients and physicians ease their way into the clinical research field. Consistent with this notion, an interprofessional collaboration of clinical pharmacy professionals for improving patient outcomes makes them ideal candidates for multidisciplinary clinical research. In contrast, pharmacists working in a community pharmacy setting are deprived of these opportunities due to a prerequisite of conducting drug trials in an ideal environment with basic necessities, which, in turn, facilitates the recruitment of human volunteers following the ICH-GCP guidelines.

Currently, clinical trials are being carried out under the supervision of clinical pharmacists in conjunction with a qualified physician. Likewise, there is no formal hindrance by research foundations, the pharmaceutical sector or government entities for the selection of clinically oriented pharmacists as PIs. Since the 2000 publication of the ACCP commentary regarding the role of clinical pharmacists as PIs, there has been a surge in the number of clinical trials supervised by clinical pharmacists; this surge includes both industry-sponsored and clinical pharmacist-initiated trials (Burton et al., 2010). Professionals with a PharmD degree have been successful in acquiring financial grants from different stakeholders, particularly the NIH, and executing research projects as PIs. An unwavering support from the employers of pharmacists is also a key determinant in the professional transition of novice pharmacy scientists to a veteran study investigator (Burton et al., 2010). However, clinical pharmacists in developing countries are still facing impediments to building their reputation as a PI. In the UK, 237 pharmacists were registered with the clinical trial network of the Royal Pharmaceutical Society (Malson, 2015). There are no recent statistics regarding the total number of clinical trials being carried out under the supervision of clinical pharmacists; ClinicalTrials.gov provided a hit of 523 clinical trials performed by clinical pharmacists in 2009 (Burton et al., 2010). Despite the associated prestige, the role of a clinical pharmacist as a PI has yet to be explored.

The ACCP's Position Statement for Clinical Pharmacists Working as PIs (ACCP, 2000a; ACCP, 2014)

The ACCP believes that clinical pharmacists, as PIs, are crucial for the management of successful clinical trials. Furthermore, clinical pharmacists, as PIs, play a vital role in administrative (institutional approvals and IRB logistics) and operational (physical and human resources) plans. The PI should assess the feasibility of conducting a clinical trial in his/her institution before participating in a trial. PIs are required to assess whether the study contract or investigator's agreement are acceptable to the study institution, thus avoiding issues and delays in the conduct of a clinical trial. The handling of financial contracts and the distribution of study expenses to the PI vary by institution, which needs to be figured out during the initial correspondence with the sponsors.

PIs should also determine the meeting frequency of the IRB and their requirements for conducting clinical trials; it is prudent for PIs to familiarize themselves with the review process of the IRB.

PIs are also required to locate a specific area where a clinical trial will be conducted and assess the available resources that are crucial for conducting clinical trials. PIs should also confirm a secure place for record keeping; trial documents are usually retained for a specific period of time after the completion of a clinical trial in the study institution. PIs should also determine the total number of members that will be required for clinical trials, such as coinvestigators, study coordinators and research fellows.

Recommended Education and Training for Clinical Pharmacists to Work as PIs

The dearth of clinical pharmacy scientists in universities and the industry sector prompted the ACCP to recommend necessary education and training for preparing future leaders in clinical research. Due to the establishment of a large number of pharmacy colleges, academic institutions have faced a shortage of skillful clinical research faculty for pharmacy students, whereas experienced clinical researchers are indispensable for pharmacy institutions. There is a huge demand for clinical pharmacy scientists in clinical

trials, and professionals with pharmacy backgrounds have the potential to contribute to clinical research after acquiring the necessary skills and education. Phase 1 clinical trials are conducted to assess clinical pharmacology, and other phases are designed to ascertain the efficacy and safety of investigational drugs. Pharmacists have strong knowledge on pharmacology and therapeutics, which gives them an edge to enhance the quality of clinical trials. Graduate programs in clinical pharmaceutical sciences open doors for clinical pharmacists to work with experienced PIs. Globally, a doctoral degree or PhD in clinical pharmaceutical sciences is offered by several pharmacy institutions; this degree is particularly for candidates interested in clinical research (Dowling et al., 2009). In 2009, an editorial published by the ACCP in favor of PhDs for preparing future generations of clinical pharmaceutical scientists exerted a substantial impact on the clinical research environment (Parker et al., 2013). The shortage of clinical pharmacy scientists in clinical research enterprises can also be reduced by increasing awareness among students to pursue PharmD/PhD combined degree programs. However, PharmD graduates without a PhD degree have also demonstrated their expertise in the field of clinical research, but their number is quite limited.

Clinical Research Training Programs for Clinical Pharmacists

A 2-year post-PharmD fellowship of a minimum of 3000 h is offered by the ACCP for enhancing research skills and conducting clinical trials as an independent investigator. This fellowship aids PharmD graduates in developing skills for different aspects of research, such as the formulation of a hypothesis, study design, protocol preparation, research grant writing, data collection, study management, interpretation of study results, scientific writing, and publication. It is preferred to acquire residency training or practical experience prior to the initiation of the ACCP fellowship. PharmD graduates receive clinical research education and training from experienced investigators who serve as preceptors throughout the fellowship program. The selection of preceptors is based on their qualifications, earlier experience as PIs in clinical trials, scientific publications in peer-reviewed journals and clinical research collaborations with other researchers. The participants of this fellowship are required to conduct at least one research project or participate in multiple clinical research studies, thus providing hands on experience in clinical research that is imperative to manage a study independently (ACCP, 2016).

Other Clinical Research Training Programs

The National Institute of Health (NIH) also provides funding for several research programs. The NIH Clinical Center provides clinical research training to students, residents/fellows, and mid-career professionals, thus preparing the next generation of clinical research scientists (NIH, 2017). The Office of Clinical Research Training and Medical Education at the NIH Clinical Center also provides distance learning courses, and the theme is "Core Curriculum in Clinical Research." The following three courses are provided under this theme: (1) ethical and regulatory aspects of clinical research, (2) introduction to the principles and practice of clinical research, and (3) principles of clinical research. It is the best opportunity for pharmacy students and professionals not residing in the US and those who have difficulty attending in-house programs due to professional commitments. The NIH Office of Extramural Research also offers a free web-based training course, "Protecting Human Research Participants," for health care professionals. This certification is usually requested by the Institutional Review Board or ethical committee of health care institutions before grating an approval for research projects that involve human subjects. Although not mandatory, it remains an important certification for protecting the rights, safety and well-being of human subjects. Moreover, this course consists of seven modules that take approximately 3 h to complete.

Mid-career clinical pharmacy professionals with at least 7 years of clinical research experience may join a program entitled "Sabbatical in Clinical Research Management"; participants of this program work with NIH experts. This program is not intended for novice clinical research scientists; they should consider the NIH clinical research curriculum for appropriate programs. The Clinical Research Training On-Line Course for PIs is a free web-based course that provides an ideal opportunity for clinical pharmacists and other health care professionals willing to work as a PI in clinical trials. This web-based course is mandatory for all NIH intramural PIs and is recognized as an essential standard in terms of education and training (NIH, 2017).

Clinical pharmacists should acquaint themselves with the GCP guidelines, as they also contain informative sections such as the glossary of all technical words that are used in the process of conducting clinical trials and the list of essential documents for the conduct of a clinical trial, thus serving as a strong foundation. The compliance of the PI, study sponsor and study monitor is ascertained by the evaluation of the essential documents specified in the GCP document. In addition, the validity of the clinical trial conduct and the clinical trial's data integrity also depends on the essential documents.

The core activities of clinical pharmacists in clinical trials are: (1) dispensing medications, (2) managing investigational medicinal products, (3) coordinating clinical studies, (4) providing drug information to health care professionals and patients, (5) reconciling medication, (6) representing pharmacists in a research committee to provide expertise on drug use, and (7) overseeing clinical trials as PIs or subinvestigators (Brown et al., 2017; Kay et al., 2018). Research pharmacists maintain a pharmacy file that is provided by the study sponsor for their clinical trials prior to the initiation of the subject recruitment process. **Table 3** shows the sections and content of a pharmacy file provided by the sponsor for conducting a randomized, double-blind placebo-controlled trial; the pharmacy file is managed by a clinical trial pharmacist. This table is only for the guidance of clinical pharmacists and is based on my earlier experience in multinational clinical trials. Clinical pharmacists also contribute to the development of research protocols, particularly in providing expertise for the management of drugs, which is one of the basic elements in pharmacy practice. Likewise, they also contribute to the preparation of drug information and safety tools, thus ensuring the appropriate use of investigational drugs in a clinical trial setting (Brown et al., 2017). The presence of clinical pharmacists in a trial setting is paramount for assessing protocol adherence (Shehab and Tamer, 2004). Pharmacists exert a

Table 3 Pharmacy file index for clinical trials

Section	*Contents*
General	• Safety alert • Contact information • Information for pharmacy; study drug hazard sheet • CD containing training presentations
Drug accountability	• Complete IMP management risk assessment form • Pharmacy tracking log • Drug accountability log—sample copy • QP release certificates • Drug receipts/shipping documents
Unblinding	• Unblinding guidance for pharmacies • Unblinding request form × 1
Adverse events	• Adverse events reporting guidance • SAE/SUSAR forms • Notification of SAE/SUSARs by CTU
Ethics	• Local ethics approval • National ethics approval • National regulatory approval • Approvals of protocol amendments
Trial monitoring	• Pharmacy visit signature log • Pharmacy IMP monitoring log
Correspondence	• Correspondence, emails
Protocol	• Laminated protocol summary • Protocol • Protocol amendments • Manual of operating procedures
Drug information	• Drug administration and storage guidance • Drug accountability at site—work procedure • MAIMP (packing) • MAIMP (placebo) • Summary of product characteristics • Investigator's Brochure

QP, Qualified Person; *CTU*, Clinical Trial Unit; *SAE*, Serious Adverse Event; *SUSARs*, Suspected Unexpected Serious Adverse Drug Reaction; *IMP*, Investigational Medicinal Product; *MAIMP*, Manufacturer's Authorisation for Investigational Medicinal Products.

significant impact on the quality of clinical research by improving protocol compliance due to reconciling medication, reducing the occurrence of drug-related deviations, and decreasing medication discrepancies, which eventually improve patient care in a clinical trial setting (Redic et al., 2017). Pharmacists also effectively enhance the drug-related aspects (dosage, indications, drug–drug interactions, contraindications, and adverse drug events) of clinical trials, thus strengthening the backbone of drug trials. Drug-related issues exert a significant impact on patient outcomes; clinical pharmacists are experts and are skillful in tackling the aforementioned issues (ACCP, 2000b).

The safety practices of investigational drugs have not been standardized, unlike commercially available or approved medications (Cruz and Brown, 2015). The majority of research pharmacists have consistently raised serious concerns pertinent to the safety practices of investigational drugs during the conduction of clinical trials (Brown et al., 2017). Safety concerns related to naming, labeling, packaging and storage, are also highlighted by the Institute for Safe Medication Practices (ISMP). In addition, the ISMP recommended Institutional Review Boards (IRBs) to include pharmacists for the review of all investigation drug protocols, thus mitigating safety concerns of investigational drugs (Cruz and Brown, 2015). These concerns are not new to clinical research and were also addressed in a survey during the 1980s. Cruz and Brown (2015) also addressed safety concerns of investigational drugs in the findings of a national survey; these findings were based on more than 80% of pharmacists who had safety concerns (Cruz and Brown, 2015). The ICH-GCP requires all investigators to acquire thorough knowledge regarding the investigational drugs and ensure correct use of drugs, whereas clinical pharmacists are also deemed to be the best choice to qualify for PIs owing to their pharmacy qualification and training. Moreover, investigational drugs are also managed by pharmacists during clinical trials, requiring them to ensure drug use as per the approved protocol. The management and control of investigational drugs is crucial for executing successful

clinical trials, and clinical pharmacists are deemed to be the ideal choice in a clinical research team for effectively handling these matters. Pharmacists have a vital role in the receiving, handling, safe keeping, dispensing, safe disposal, and return of investigational drugs (Brown et al., 2017). According to the Joint Commission, the safe management of investigational drugs is essential in all accredited hospitals and is solely a responsibility of a pharmacy. In addition, pharmacists place auxiliary labels containing expiry and lot number details during the dispensing of these drugs, thus ensuring safe use during clinical trials. These measures reduce medication errors and promote subject safety (Brown et al., 2017). Thirty-nine percent of prescription orders for hospitalized populations have been reported to cause medication errors (Franklin et al., 2005). Prescribing errors can be minimized by employing pharmacists to review and verify prescription orders; moreover, they can provide expertise on therapeutic drug monitoring (Brown et al., 2017; Cohen and Sanborn, 2008). Clinical trial pharmacists ensure that the transportation of an investigational drug follows all standard protocols specified in the sponsor documents and promptly notify the former in case of any divergence from this process. Therefore, the inclusion of pharmacists in clinical trials is crucial in promoting medication safety and producing high-quality data (Brown et al., 2017).

The Role of Clinical Pharmacist in Improving Adherence Issues in Clinical Trials

The act of following instructions or directions given by health care professionals or research personnel during routine clinical care and clinical trials is termed adherence (Robiner, 2005). Fear of investigational drug's side effects, polypharmacy, dose frequency, and lengthy duration of treatment eventually lead to a higher incidence of poor medication adherence, thus making it difficult to evaluate the clinical efficacy of an investigational drug. Furthermore, prevalent nonadherence in clinical trials makes it difficult to ascertain the long-term effects of drugs (Kvarnström et al., 2018). It is prudent that additional efforts be directed toward maintaining medication adherence to generate a high-quality clinical trial data. The existing literature reports subjects' poor adherence or compliance to investigational drugs during clinical trials (Martinez et al., 2017). Another study revealed a 40% decline in adherence during clinical trials over a period of 1 year (Blaschke et al., 2012). Clinical setting, drug–drug interactions, side effects, comorbidities, psychological issues, and communication problems are recognized as possible causes that lead to poor adherence (Robiner, 2005). Poor adherence profoundly affects treatment goals and increases drug resistance, thus affecting morbidity and mortality rates (Martinez et al., 2017). Moreover, it exerts a negative impact on the quality of clinical trial data and prolongs study duration, which eventually inflates trial expenditures. The research team may not obtain a satisfactory response from interventional drugs due to nonadherence; hence, statistical power is tampered. Adherence for taking long-term medications in clinical trials was found to be 59%, while it was 78% for short-term medications (Robiner, 2005). Bouwman et al. (2017) reported that 50% of patients do not adhere to the treatment protocol. Such statistics advocate for a need to enhance adherence during the conduction of clinical trials (Martinez et al., 2017). The rapport between trial participants and caregivers is correlated with adherence and retention rates (Robiner, 2005). The positive effect of the pharmacist-trial participant relationship on the medication adherence of diabetes patients was also documented (Chung et al., 2014; Jin et al., 2008). Pharmacists' expertise in drugs plays a vital role in decreasing poor adherence rates and the success of clinical trials. Consistent with this notion, pharmacists are also able to respond to drug-related queries over the course of a clinical trial in a timely manner (Martinez et al., 2017). Pharmacists keep the dispensing record of investigational drugs, which gives them an edge to scrutinize the patient's adherence to medication regimens (Kay et al., 2018). A systematic review of 38 clinical studies showed improvement in medication adherence and treatment outcomes mainly due to clinical pharmacists' interventions (Tan et al., 2014).

The Importance of Integrating Clinical Pharmacists in Clinical Trials

A randomized controlled trial in the UK found that pharmacist counseling is crucial to decreasing cardiovascular risk and medication-related issues in patients with diabetes. Participants in an intervention group showed lower levels of hemoglobin A_{1c} compared to the control group. Moreover, participants in the intervention group showed significant improvement in their quality of life (Ali et al., 2012). Likewise, a prospective randomized controlled trial in Malaysia demonstrated a decline (9.6%–8.2%) in hemoglobin $A_{1c,}$ and medication adherence in an intervention group was also significantly improved due to pharmacists' consultations (Chung et al., 2014). Failure of drugs due to the clinical trials or failure of clinical trials due to the drugs are the two important notions in an experimental setting. Pharmacists are drug information experts with specialized training in drug therapy, and their role in clinical trials is paramount. Their counseling and rapport with study subjects improves the accuracy of outcomes (Martinez et al., 2017).

A prospective, cluster randomized, controlled clinical trial in the US showed that drug therapy recommendations by clinical pharmacists resulted in a significant improvement in the control of blood pressure (Carter et al., 2009; Weber et al., 2010). Similarly, evaluations of drug regimens and the provision of recommendations to patients and physicians reduced inappropriate prescribing and safety issues (Hanlon et al., 1996).

Enhancing Medication-Related Aspects of Clinical Trials by Integrating Clinical Pharmacists

The study protocol is a mainstay for clinical trials, whereas deviation from the protocol can be managed by the principal investigator. In addition, the protocol contains all trial-related information, including the management of investigational medications (Kay

et al., 2018; Redic et al., 2017). A protocol specifies prohibited concomitant medications for the study volunteers, which prompts study personnel, particularly pharmacists, to avoid drug-related nonconformities during clinical trials; medication history is crucial in this regard (Redic et al., 2017).

Pharmacists review medication history with the study protocol requirements and identify prohibited medications. A retrospective study in the Michigan Clinical Research Unit revealed that only 20% of the investigational drugs were recorded in the electronic health records of patients, while 40% of cases lacked the correct dose. Furthermore, this study demonstrated that 21% of protocol-prohibited medications were listed in the electronic health record (Redic et al., 2017). The potential concerns regarding the accuracy of investigational drugs can be avoided by pharmacists, and their role in medication reconciliation improves the quality of clinical research (Redic et al., 2017).

Pharmaceutical Industry Considerations

Pharmacists serve in multiple industrial domains, such as research and development, manufacturing and quality assurance, drug information, patent applications and drug registration, clinical trials and postmarketing surveillance, sales and marketing/management (Thakur et al., 2016; WHO, 1994). Based on their complex and pivotal role, pharmacists are quite competent to lead clinical trials and collaborate with different stakeholders. Their apparent knowledge regarding drugs and health care provisions strengthens multifaceted collaboration with stakeholders (WHO, 1994). Pharmacists have also been involved as principal and subinvestigators in industry-sponsored clinical trials (Kay et al., 2018; Smith et al., 2010; Thakur et al., 2016).

According to the WHO report on the role of pharmacists in the health care system, the selection of pharmacists for a managerial role promotes an ethical approach within industrial settings (WHO, 1994). Qualified pharmacists as principal investigators will rigorously follow all ethical aspects of clinical trials. The WHO report explicitly mentioned that the pharmaceutical industry should not operate without pharmacists (WHO, 1994). A survey by the American Pharmacists Association demonstrated that pharmacists in a corporate environment spend most of their time handling multiple tasks, interacting with colleagues and working with teams (American Pharmacist Association, 2013).

Summary and Conclusions

Clinical research is historically linked to advances in clinical practice. The former is performed under strict guidelines and is regulated by various national and international health care bodies accordingly. The role of the principal investigator has been essential in the development of clinical trials; however, research is currently becoming more versatile by implementing multidisciplinary teams, thus enhancing the collective mind-set. In that sense, the integration of qualified clinical pharmacists as key members of multidisciplinary research teams could indeed be an asset in launching clinical trials and optimizing research team performance.

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Evidence-Based Pharmacy Practice Research in Low- and Middle-Income Countries: Issues, Challenges and Synthesis

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Pharmacy Practice in Low-Middle-Income Countries

Pharmacy expertise and services are important for achieving optimal public health. The pharmaceutical practice seeks to optimize health outcomes for patients and add value to health systems. Moreover, pharmacists can also act as advisors to physicians and nurses and contribute to policy decisions. However, in many lower-middle-income countries (LMICs), pharmacists are still underutilized (Anderson, 2002; Azhar et al., 2009). There are various pharmacy practice models in LMICs due to the obstacles that each country has experienced. Mohamed Ibrahim et al. (2016) noted that the pharmacy practices vary in the 19 countries explored, even within each country, due to lack of infrastructure and resources. In addition, differences can also be attributed to service compensation, low salaries, poor benefits, inadequate training and education, poor regulatory systems, and ineffective pharmaceutical policies. The authors further recommended a few aspects that pharmacists and pharmacy organizations need to consider to close the gaps in practice between countries to meet the Good Pharmacy Practice Guidelines (Mohamed Ibrahim et al., 2016).

The umbrella term pharmacy practice covers the various roles of the pharmacist in the health-care system, including the classic duties of pharmacists related to the provision and management of pharmaceutical supplies as well as the expanded role of the pharmacist in clinical settings. Pharmacy practice is the professional skill required of pharmacists that is needed to ensure the optimal use of medicines in society. "It includes clinical pharmacy, pharmacotherapy, social and administrative sciences, and pharmaceutical care" (Scahill et al., 2017). The pharmacy profession has undergone a transformation from "The Era of Count and Pour" to the modern concepts of '"Clinical pharmacy" and "Pharmaceutical Care" and "Managed Care" (Higby, 2005). This change has mainly been recognized with the emergence of the pharmaceutical care concept in the 1990s (American Society of Health-System Pharmacists, 1999). The new role of the pharmacist was adopted as part of "reprofessionalization" that occurred mainly in

high-income countries (Babar et al., 2013). During the last four decades, significant progress has been made in both academic and research approaches in the pharmacy profession; however, these approaches are not equally reflected in the developing world.

The low-middle-income countries (LMICs) must keep up with the latest advancements and adoption of the new roles identified through consensus by international professional organizations and health-care leaders (e.g., the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO)). Among new themes introduced in the revision of the landmark document of the Basel Statements by FIP are the collaboration of hospital pharmacists with hospital health technology assessment committees and the development of specialty practices in hospitals (International Pharmaceutical Federation (FIP), 2015a). In addition to the commitment to implement the rational use of medicine as defined by the WHO, there was the adoption of a new and comprehensive goal for the "responsible use of medicines" introduced by the FIP in 2012 (Vermeulen et al., 2016).

The new role expands the responsibility of the pharmacist to the complete drug use process and requires assurance of safe disposal and waste management of unused pharmaceuticals. The concept of a Green Pharmacy Practice has evolved, developing a need for reviewing the complete drug use process to ensure the minimization of pharmaceutical waste, as well as the environmental impact of that pharmaceutical waste, as it finds its way to water, soil, and the atmosphere (International Pharmaceutical Federation (FIP), 2015b). Safe and responsible waste practices for "antimicrobials" are important to reduce the emergence of antimicrobial resistance, a current global challenge in health care. The use of information technology, automation, and digitalization is gaining role in the regular process of medication use. Paperless electronic health records and the implementation of a merged system of medication supply, use and safety monitoring as part of the "Track and Trace System" to control the penetration of substandard and falsified medicines in the supply chain are two examples of rapid transformation in the way medicine use is going to be handled and recorded globally (Barlas, 2011; European Medicines Agency, 2011; Wirtz et al., 2017). The future of pharmacy practice research is expected to focus on the needs of the information technology-aware population; addressing social and cultural disparities and economic growth shifts; promoting multidisciplinary approach (Almarsdottir and Babar, 2016).

All of these topics are changing the image of pharmacy practice and developing new areas of pharmacy practice research. This process of change is inevitable for the developing world, and the promotion of quality research is critical to developing an informed health-care system where policies are backed by sound scientific evidence (Young et al., 2013).

The change in adopting a new and more demanding role for the pharmacist has occurred at varying levels and paces in different parts of the world. "Research, development and evaluation strategies for pharmaceutical education and workforce: A global report" by the FIP shows that there are varying degrees of progress in attaining the 13 Pharmaceutical Workforce Development Goals (PWDGs), and almost every country has made some progress in developing competency-based training frameworks, as well as increasing advanced and specialist development. The document includes case reports for 22 countries, including Argentina, Brazil, China, Costa Rica, Ghana, Kenya, Malaysia, Namibia, Paraguay, South Africa, Uganda, Zambia, and Zimbabwe, which are all LMICs (Bader and Bates, 2017). A few developing health systems, including Malaysia, Taiwan, Korea, South Korea, Singapore, and Saudi Arabia, are highlighted in the literature for their investments in the pharmacy profession workforce and systems (Babar and Scahill, 2014). Disparities in economic status between the two income groups of LMICs should be studied separately to assess their health system designs and progress in the delivery of pharmacy services (Babar and Scahill, 2014; Gray and Suleman, 2015).

The triad of practice, policy, and research acts synchronously to achieve the adoption of the new professional role of the pharmacist (Bond, 2015). Research has placed major emphasis on documenting the impact of interventions by pharmacists at different levels of clinical care settings, and this has driven policy changes in health-care systems (Bond, 2015). Research interacts with policy in four different ways: research that informs policy, research that supports a planned policy, research that confirms the appropriateness of implemented policies, and research that is aimed at understanding the processes in place (Bond, 2015).

LMICs are still in the evolution phase of the health-care system, where legal protection of the expanded role of the pharmacist within the health-care team has not yet been achieved. The acts of dispensing and prescribing are not segregated, and the availability of pharmacists in communities and institutional health-care settings are not mandatory (Babar et al., 2007). The dispensing of prescriptions by nonpharmacists and the sale of crucial medicines such as antibiotics without prescriptions are still common practices in certain LMICs (Ansari, 2017). Apart from the poor regulatory standards, compliance with existing pharmacy regulations is also not met (Hussain et al., 2012). The number of pharmacists and the quality of their academic training have been repeatedly questioned in this respect. The FIP technical document on the workforce presents a baseline to develop national action plans to develop an evidence-based workforce.

Is Pharmacy Practice Research Lacking In LMICs?

Many LMICs have failed to keep up with new trends and are not able to invest in the human resources. This deficit is also evidenced by the lack of research work in this important domain of the pharmacy profession, affecting the research quality, number, and diversity. The lack of funding, leadership, and the visionary approach to set long-term professional goals; the failure to identify and prioritize local needs; the lack of development of local solutions; the need of ownership by stakeholders, especially policymakers; and the lack of professional skills are some of the reasons that these countries have fallen behind.

There exists a wide gap between the developing and developed world with respect to evidence generation through systematic reviews and clinical trials (Alemayehu et al., 2018; Bennett et al., 2015). The literature reports several publications on the need for research capacity building in LMICs in the health sector. However, a concrete document addressing the gaps in pharmacy practice

research in LMICs is not available. Research is an essential component of pharmacy education and training. Pharmacy education and training have been outlined as one of the three impeding factors in the establishment of pharmacy practice in LMICs (Babar and Scahill, 2014). A bibliometric review on pharmacy education identified a deficiency in empirical research on pharmacy practice in Central and South America, Africa, and Eastern Europe (Babar et al., 2013).

Keeping in mind the current trends and recent advances in pharmacy practice, it is necessary for pharmacy researchers in LMICs to identify the gaps and challenges in pharmacy practice research and devise strategies to catalyze the process of change in the right direction (Mohamed Ibrahim et al., 2016).

The current chapter aims to identify the gaps in the evidence of pharmacy practice research in LMICs. The authors will explore the following questions with respect to pharmacy practice in LMICs:

1. What is the current status of pharmacy practice research in LMICs?
2. What are the individual health-care needs in LMICs and is pharmacy practice research in informing policy makers regarding ways to address these needs?
3. Is pharmacy practice research in LMICs elaborating the consequences and implications of the absence of adequate pharmacy practice?

This involves research on the current status of the pharmacy practice in LMICs, identification of the barriers and drivers, and evidence on the benefits and costs related to having a pharmacy practice in the health-care systems of an LMIC.

Broadly, research on pharmacy practice is directed toward designing new service models, measuring their quality and impact as well as identifying the implications of the absence of these services. Hence, a lack of capacity to carry out pharmacy practice research has a profound negative effect on the health-care system and the development of the professional role of the pharmacist in society. The scarce resources of LMICs demand justified investments in health services, pointing to a dire need for research in pharmacoeconomics, an area that needs to be evaluated for the presence of necessary skills in resource-limited settings. The analysis will help to identify the countries with some form of success with respect to progress in research contributions.

Historically, the research on pharmacy practice carried out in developed countries underwent phases of introspection and strong criticism to redefine its directions and produce research that was helpful in defining the role of the pharmacist. Lessons from the developed world can be used as a stepping stone by the developing world. There is a need for a multidisciplinary approach involving the expertise of other health system researchers as well as social scientists, epidemiologists, statisticians, psychologists and others, as well as the incorporation of long-term outcomes, including clinical, humanistic, and economic outcomes, to create sound evidence that can inform policy (Bond, 2015). Future pharmacy research is anticipated to include a further broadened group of potential collaborators (Almarsdottir and Babar, 2016).

The large amount of poor-quality research has become a growing problem in pharmacy practice research and is adversely affecting the image and strength of the professions' potential to inform policy and integrate with the decision-making process within the health system.

A review of systematic reviews provided a six-point recommendation for the overall improvement of systematic reviews conducted in pharmacy practice (Charrois et al., 2009). These recommendations include the coordination of a network of practice researchers, development of guidelines for reporting practice research studies, development of standardized indexing terms for identification of pharmacy practice research, registration of clinical trials of pharmacist interventions, encouragement of reporting clinically relevant outcomes and development of pharmacy research trialist collaboration for cumulative systematic reviews in chronic diseases.

Pharmacy practice research is a growing and evolving area that entails many challenges for its correct conceptualization and implementation. In this context, it is pertinent to conduct gap analysis for the evidence in pharmacy practice research regarding LMICs.

Major Health Issues of LMICs

Before determining what kind of evidence is expected for pharmacy practice in LMICs, one needs to understand the actual health-care issues of LMICs and how they differ from health concerns faced by high-income countries (HICs). Apart from sharing the historical struggle of nations in improving standards of health care, new challenges are emerging that create added complications for the developing world. These challenges include illnesses such as parasitic diseases, malaria, HIV, tuberculosis, and diarrhea that can be cheaply managed and prevented; antimicrobial resistance; natural disasters and other forms of humanitarian crises; environmental pollution; food shortages; undernutrition; increasing economic burdens; poor living conditions; and an alarming number of mental health conditions (The Health and Environment Linkages Initiative (HELI), 2018; Wiblin, 2016; worldwatch Institute)

The type of pharmacy practice needed by a region or country strongly depends on the nature of the health problems faced by their population. Communicable diseases, maternal health issues (conditions arising during pregnancy and childbirth), and nutritional deficiencies, collectively named "Group 1" conditions, account for 52% of deaths in low-income countries, whereas for high-income countries, only 7% of deaths are reported to be caused by these conditions (World Health Organization, 2018a). Likewise, 78% of global noncommunicable disease (NCD)-related deaths occur in LMICs. Heart disease and diabetes mellitus are the leading NCDs globally (World Health Organization, 2018a). Infectious diseases, including lower respiratory tract infections, HIV/AIDs,

tuberculosis, hepatitis, and malaria, are prevalent in LMICs. Global life expectancy has improved over the past decades; although, it is still low in some of the African countries (Angola, Central African Republic, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Lesotho, Mozambique, Nigeria, and Sierra Leone) (World Health Organization, 2018b). The major contribution to progress in LMICs is improved under-five mortality rates. Diarrhea, preterm birth, birth asphyxia, and lower respiratory tract infections constitute the major under-five mortality causes in LMICs (Sayem et al., 2011).

The gap in life expectancy between female children and male children differs threefold between high income countries (9 years) and LMICs (3 years). Does access to health resources and pharmacy services differ more between the two genders in LMICs? In patriarchal societies with high out-of-pocket expenses, gender disparities in access to pharmaceutical supplies and decisions regarding the purchase of medicines and bearing other health costs pose an important research question with respect to both behavioral sciences and access to medicines (Sayem et al., 2011). Marginalized communities, people with poor socioeconomic status (Barakat et al., 2018), females (Barakat et al., 2018), migrants, older and pediatric populations and, in particular, female children are particularly prone to limited access to quality health services, including pharmaceutical supplies and services. Fathelrahman et al. (2016) highlighted several critical pharmacy situations in LMICs. These and many other questions invite the exploration of medication and health facility use behaviors in communities with respect to gender and other social disparities. It is not uncommon for patients in the health-care systems of developing countries, which are often criticized for shortages and poor-quality of medicine, to consider public health facilities to be lacking in quality and to be a suboptimal option (Aziz and Hanif, 2016).

Role of Evidence in Health-Care Systems

The best evidence can be employed with confidence (Bond and Watson, 2003). Scarcity of resources and the increasing demand for services call for the justified expenditure of public and private (out-of-pocket) money in the health sector. Cost and efficacy are the two historical parameters that are together employed in the health-care decision-making process, although patient satisfaction has also been advocated as an important marker in this regard (Bond, 2015). A wider application of the process advocates the use of the term evidence-based practice (EBP) instead of evidence-based medicine, hence, applying to a range of care providers in the health-care process (Bond and Watson, 2003). The need for evidence in pharmacy practice includes evidence synthesis on the role of pharmacists and pharmacy services as well as on the choice of various systems and technologies (Vermeulen et al., 2016) involved in the medication use process. Nevertheless, evidence is also needed for developing sound human resource plans in pharmacy practice (Vermeulen et al., 2016) to meet the local needs.

Pharmacists must recognize the use of EBP as central to providing high-quality care and decreasing unwarranted poor quality in service and practice. EBP includes more than just applying the best evidence. However, the concerns and obstacles to using EBP are mostly related to finding and applying research. EBP involves the integration of the best available pharmacy-related research; the pharmacist's knowledge and skills; and the wants, needs, and values of the patients, clients, and consumers (Sackett et al. 2000).

The purpose of conducting research is to generate new knowledge or to validate existing knowledge based on a theory. Research studies involve systematic, scientific inquiry to answer specific research questions or test hypotheses using disciplined, rigorous methods. While research is about investigation, exploration, and discovery, it also requires an understanding of the philosophy of science. For research results to be considered reliable and valid, researchers must use the scientific method in orderly, sequential steps.

In general, the literature on pharmacy practice does not comment on the data with respect to the economic grouping of the countries, and very few studies have commented on the trends in practice research with respect to the economic standing of the country. The Global Survey of Hospital Pharmacy Practice conducted in 2009 discusses the hospital pharmacy practices of countries with respect to their Human Development Index (HDI) analysis (Doloresco and Vermeulen, 2009). Only a few reviewers have discussed their data directly in the context of income groups of the countries (Atif et al., 2017; Bowry et al., 2011; Doloresco and Vermeulen 2009). Initiatives for evidence synthesis in pharmacy practice targeted toward the developing world have been sparse; only a single example has been found until now (Bowry et al., 2011).

In this chapter, we have studied systematic reviews and major regional and global reports on selected themes of pharmacy practice to retrieve information on the situation in LMICs. The tabulation of these studies with income group wise contributions from countries provides an overall picture (**Table 1**). This enables the performance of a gap analysis for pharmacy practice research carried out by LMICs. The analysis is based on three discrete parameters, that is, quality, diversity, and quantity of research that are detailed as follows:

Quality

The confidence in making guidelines, judgments, and decisions in practice depends very much on the quality and strength of the research evidence (Atkins et al., 2004). Having misleading or flawed evidence is worse than having no evidence at all (Berger and Alperson, 2009). The publications discussed in this chapter can be classified into two sets: systematic reviews and reports and reviews by international organizations (FIP/WHO) (summarized in **Table 1**) with individual studies elaborated within the main text. Systematic reviews have an undoubted position in evidence synthesis and act as a tool for learning the strengths and weaknesses of the primary research (Young et al., 2013). Hence, both conducting and use of systematic reviews build the capacity of health-care decision-makers and researchers (Young et al., 2013).

Table 1 Contribution of studies in reviews according to income groups of countries

Theme (Time period)-Reference Country	*N*	*HIC*	*U-MIC*	*L-MIC*	*LIC*	*Comments/notes*
Global hospital pharmacy survey (Doloresco and Vermeulen, 2009)-USA	85	46	28		9	No. of responses grouped according to HDI index Two responses (ungraded)
InitialBasel Statement (Am J Health-Syst Pharm, 2008)-Switzerland	98					Break up not available
Revision of Basel statement (Vermeulen et al., 2016)—USA, Australia, Pakistan, S.Africa, France, the Netherlands						Limited information on participation at various levels
Global survey	62	50%	27%	13%	8%	
Internal review	9	Australia France Japan Netherlands United States	South Africa	Pakistan Ghana	Nepal	
Online forum	28					
World Café workshop	20					
Use of FIP Basel statements for assessment of hospital pharmacy services (up to Oct 2015) (Penm et al., 2016)—USA, Australia	14					
Regional or local adaptation of BS		Europe (4)	-	-	-	Quantitative (2), qualitative (2)
Monitoring of hospital pharmacy practices		-	[a]Pacific Island [a]West Pacific Region (4)	-	Uganda	Quantitative (2) Included validation of monitoring surveys (2)
Implementation of Basel Statement		Australia	China South Africa (2)	-	-	Qualitative methods
Pharmaceutical care/managed care (2004–Jan 2017)—UK, New Zealand, Pakistan	54 RCTs	21	Brazil (6) China (4) Colombia Iraq Malaysia (2) Thailand	Jordan (5) Sudan (1)	-	Related to community (7) Inpatient (n) Outpatient (n) Primary health care (n)

Community settings	7/54	7	-	-	-
Global utilization of essential medicine (1985–2015)(Atif et al., 2017) Pakistan. New Zealand, UK	60				
Prescribing indicators		Kuwait Oman Saudi Arabia UAE Andorra Russia **Serbia (3)** Sweden Samoa Tonga Namibia	Brazil **China (3)** Colombia Iran Lebanon Malaysia South Africa Peru Macedonia Guatemala	Bangladesh (2) Egypt **India (3)** Indonesia Jordan Pakistan (2) Sri Lanka Yemen Kyrgyzstan Uzbekistan Angola Myanmar Cambodia Lao PDR Cameroon (2) Ghana Kenya Morocco Nigeria (3) Swaziland Vietnam	Afghanistan Nepal Burkina Faso (2) Burundi Central African Republic Congo Eretria **Ethiopia (3)** Gambia Malawi Mali Mozambique Niger Philippines Rwanda Senegal Sudan **Tanzania (3)** Uganda Zaire[b] Zambia Zimbabwe (2) Palestine[b]
Patient care and facility-specific indicators		Kuwait SaudiArabia Sweden	China (2) Brazil Serbia	Bangladesh (2) Cambodia Egypt India (2) Indonesia Jordan Pakistan (2) Nigeria (2) Swaziland	Nepal Central African Republic Ethiopia (2) Malawi Mozambique Niger **Tanzania (3)**
Barriers in conduct of clinical trials in LMICs (1995–2015) (Alemayehu et al., 2018)—Australia	10	Eight developed countries + Saudi Arabia (2) Chile Greece Australia UAE	China (2) South Africa Africa (4)[a] Asia (5)[a]	Egypt India Cameroon	Ethiopia (2) Sub-Saharan Africa[a] Latin America[a]

(*Continued*)

Table 1 Contribution of studies in reviews according to income groups of countries (*cont.*)

Theme (Time period)-Reference Country	*N*	*HIC*	*U-MIC*	*L-MIC*	*LIC*	*Comments/notes*
Medication errors in elderly patients (Salmasi et al., 2018) (Up to November 2017)—Malaysia, Australia, Canada, Pakistan	18	16	Malaysia (1)	Indonesia (1)		3/18 studies were based on electronic aid in prescribing and automation in dispensing
Performance of community pharmacy in Asian LMICs (Miller and Goodman, 2016)—UK	91 studies					*"Intervention research in this area appears to be lacking and more research is particularly required on non-pharmacist run pharmacies and unregistered drug shops"*
Qualitative study	53	Malaysia	Thailand (5)	India (10) Vietnam (9) Indonesia (3) Philippines Mongolia Lao PDR	Bangladesh (5) Nepal (5) Yemen Arab Republic Syria	
Quantitative study	38 (11 countries)		Thailand (5)	India (7) Pakistan (2) Lao PDR	Bangladesh (3), Nepal (4), Sri Lanka (1) Yemen Arab Republic (1)	
Community pharmacy (Jan 2006–July 2016) (Melton and Lai, 2017)—USA	50				Uganda (1)	
Pharmacist led medication review in community (Jokanovic et al., 2017)—Australia						
Clinical and economic effectiveness of pharmacy services (Altowaijri et al., 2013)	53		China Thailand			Jadad score = 3 for both
(Cheema et al., 2014)	16 Qualitative studies 11 Quantitative studies		Thailand			
(Evans et al., 2011)	26/40	21 + 5 (others)				Included five other studies were not identifiable
Elderly patients (George et al., 2008)	5/8	4 + 1 other				
Pharmacist intervention for lowering CVS risk factor in diabetes (Santschi et al., 2012)—Canada, Switzerland	15	USA (7) Canada (2) Australia Spain UAE	Thailand China	India		
Pharmacist care and CVD risk factors (Santschi et al., 2011)	30					Recommend exploration of pharmacist intervention in reducing CVD risks and ways to enhance pharmacists care in different health care settings. The study from China was rated among the good quality studies.

Pharmacist-directed care Pharmacist-collaborative care	18		Thailand Brazil China			
Medication adherence (1966–2010) (Bowry et al., 2011)	RCT (5)	[a]UAE	Kazakhstan Thailand South Africa	Pakistan		Jadad sore (20-75%)
	Open cross over				Zimbabwe	Jadad score 75%
	Cohort (17)	Saudi Arabia (3) Seychelles (2)	Brazil (3) Malaysia South Africa (2)	Nigeria (2) Bangladesh India	Tanzania	
	Cross Sec (55)	Austria[a] Hungry (2)[a] Poland Saudi Arabia Slovakia[a]	Libya China (7) Brazil (4) Iraq Iran Ivory coast[b] Jamaica Libya (2) Malaysia (2) Mexico (3) South Africa (9) Turkey	Egypt (2) India (4) Jordan Pakistan (2) Trinidad and Tobago Tunisia Nigeria (5)	Ghana Sudan Zimbabwe	AHRQ tool (0-100%)
Review contributions in International Journal of Clinical Pharmacy (2010–15)	18	Australia (3) Denmark Spain (2) Italy UK Ireland (2) Qatar Portugal	Brazil (3) China (2) South. Africa			
Public health and socioeconomic impact of substandard and falsified medicinal products (World Health Organization, 2017)—Switzerland	88 countries No. of countries percentage of total samples Failure rate	13 0.4%	56 (UMIC +LMIC) 76.5% 10.5%	-	19 2.4% 10.6%	Clearly identified gaps in evidence. Higher convenient sampling Low public-sector sampling Difference in failure rate within the popularly used technique (Minilab) and gold standard (HPLC methods)

HDI, Human Developmental Index; *HIC*, high-income country; *LIC*, low-income country; *L-MIC*, lower-middle income country; *U-MIC*, upper-middle income country.
Countries written in bold had the number of studies exceeding three
[a]Continent/group of countries, individual countries not identified in the review.
[b]Not categorized in WB list of countries for income groups (The World Bank, 2018).
The World Bank , 2018. World Bank list of economies (June 2018). Available from: www.worldbank.org

Different quality assessment tools are employed for various studies, including the Jadad score for randomized controlled trials (RCTs), the Newcastle-Ottawa Quality Assessment Scale for observational studies, the Agency for Healthcare Research and Quality (AHRQ) tool for rating cross-sectional studies, and the Quality Assessment Tool for Quantitative Studies (Berger and Alperson, 2009; Health Evidence, 2013; National Collaborating Centre for Methods and Tools, 2018; National Heart Lung and Blood Institute). Systematic reviews are mostly accompanied by a quality assessment of the studies analyzed, thus, forming quality evidence. Different quality assessment methods are outlined for the evaluation of systematic reviews, among which the Jadad score for systematic reviews involving RCTs is most commonly used (Charrois et al., 2009).

Quantity

Two aspects are documented with respect to the literature discussed: The number of studies and the participating LMICs (The World Bank, 2018). Gaps in themes and initiatives regarding practice research among various LMICs are identified from these data, maintaining relevance to the individual needs of the country. In contrast to the fact that a higher proportion of the world population resides in LMICs. **Table 1** shows that the participation and input in quality research are quite low from LMICs.

In a review covering 10 publications from the period of 1995–2015 on the identification of barriers to conducting clinical trials, more than 25 different LMICs described a lack of funding as the one major cause followed by obstacles due to ethical and regulatory systems that also included untrained regulatory setups, a lack of research environment, operational barriers such as unsupportive administration, difficulty in recruiting volunteers/patients, and competing priorities such as most of the researchers having to carry out clinical roles as their primary responsibilities (Alemayehu et al., 2018).

Diversity

Thematic classification of the study areas/themes explored includes (A) hospital pharmacy, (B) community pharmacy, and (C) public health pharmacy, including pharmaceutical policy and key health-care issues with respect to LMICs. These themes are discussed below in detail, primarily with respect to the diversity in themes, relevance to the health care needs of LMICs, and critical appraisal of their quality as undertaken by the authors of the systematic reviews. **Table 1** compliments this discussion by quantifying the research evidence according to the method described under "quantity."

A. Hospital Pharmacies

Hospital pharmacies represent a major component of pharmacy services at the institutional level in health-care settings.

The Basel Statements were initially issued in 2008 (Am J Health-Syst Pharm, 2008) and were revised in 2016 by the FIP to represent the current global vision of hospital pharmacy including 65 statements (75 in the initial Basel Statements) that are categorized into six themes with a set of overarching statements (Vermeulen et al., 2016). These themes include procurement; influences on prescribing, preparation, and delivery; administration; monitoring of medicine use; and human resource training and development.

Reviews on the current global status regarding each theme were also developed as a foundation for creating statements under each theme (Cousins, 2009; Nissen, 2009; Oishi, 2009; Ombaka, 2009; Shane, 2009; Wuliji, 2009). The revision process involved a global survey using an online survey, internal review, and initial revision, an online forum and a World Café workshop. Sixty-two countries responded to the global survey, with major input provided by the Philippines, South Africa, and the United States. The percentage of responses from low-income countries was the lowest (8%). The contribution rates from the SEARO and EMRO regions were the lowest, with 3 and 6 respondents, respectively (see **Table 1**). During the internal review process, the representatives from LMICs, including Ghana, Nepal, South Africa, and Pakistan, were involved in the 2-day face-to-face meetings along with participants from the United States, the Netherlands, Australia, Japan, and France (Vermeulen et al., 2016). Insufficient participation by LMICs was observed in the international survey on the current state of hospital pharmacy practice for the formulation of initial Basel Statements. The number of respondents from the SEARO and EMRO regions was only five and seven, respectively, and only nine countries belonging to the low Human Development Index group participated in the survey (Doloresco and Vermeulen, 2009). However, 98 countries around the globe participated in the final consensus process at the Global Conference on the Future of Hospital Pharmacy Practice (Am J Health-Syst Pharm, 2008). The low participation level from the LMICs in these global initiatives represents the lack of ownership and political willingness to establish a harmonized approach to hospital pharmacy systems. Poor responses at the national level represent a failure to endorse pharmacists as an integral component of the health-care system and a lack of the leadership that is needed for involvement in global collaborative research.

The Basel Statements have also been used for the evaluation of hospital pharmacy practice as compiled in the review by Penm et al. (2016). This review categorized the research as adaptation and implementation of the Basel Statement as well as monitoring of hospital pharmacy practices on the basis of these statements (Penm et al., 2016). Only the European region took initiative to develop a tailored version of the Basel Statement suited to patient needs and relevance of hospital pharmacy practice to local needs, which are available as four individual publications. The studies comprised two quantitative studies, one documenting the process of studying the Basel Statements in the European context and reducing them to 48 statements including overarching statements and sections including selection, procurement, and distribution of medicines; production and compounding; clinical services; quality assurance and patient safety; and education and research (Batista and Preece, 2014). The new versions defined the statements for minimum requirements and the additional or advanced statements to improve and advance hospital pharmacy practice.

The other two qualitative studies from Europe involved documentation of the views of the stakeholders, including health-care professionals, and the patients on the benefits of the Basel Statements (Maskrey and Underhill, 2014). This whole rigorous exercise is important for the assimilation of the generalized version of the standards to the local settings, and other regions are encouraged to carry out similar adaptation processes (Maskrey and Underhill, 2014; Vermeulen et al., 2016). The effort has still not been replicated in any other region or countries. The LMICs need to generate a similar set of minimum standards or a stepwise approach to address the sequential adaption of the Basel Statements with clearly set priorities. Key elements or foundation points, such as the formulary-based drug utilization system, good procurement, computerized physician order entry system (CPOE), and the right to access patient records as well as the availability of information sources, can be identified as priority areas. The 2009 global survey of hospital pharmacy reported that less than 3% of the hospitals in the low HDI countries provide pharmacists with access to patient medical records, and similarly, there is less availability (33%) of medical libraries to the pharmacist (Doloresco and Vermeulen, 2009).

The largest group of studies was documented by Penm et al. for the monitoring of hospital pharmacy practice on the basis of the Basel Statements in the Pacific Islands (22 countries) and the Western Pacific Region (37 countries). Apart from these studies, three studies on the implementation of the Basel Statements from upper–middle-income countries (China and South Africa) as well as from low-income countries (Uganda) are also included in the review by Penm et al. (2016).

A qualitative study using interviews with regulatory personnel, hospital pharmacy directors, and medical experts was conducted to record the post-2012 development of hospital pharmacy systems in Madagascar (Ratsimbazafimahefa et al., 2018), a low-income country in Sub-Saharan Africa. Severe deficiencies were identified, including the heterogeneity of the health system affecting the management of pharmaceutical product inventory. The other deficiencies involved uncontrolled drug supply chains, lack of procedures for the selection of pharmaceutical products, complexities in the quantification of needs and supervision of stock management, lack of standard prescription protocols, dispensing by unqualified staff, absence of facilities for pharmaceutical preparation in hospitals, and lack of involvement of pharmacy experts in administration (Ratsimbazafimahefa et al., 2018).

Variations in the service levels across the country and within large and small hospitals have been reported in Saudi Arabia, which is a higher income country with a developing health system, in the pretext of the Basel Statements (Al Sabban et al., 2018). In short, to a certain extent, evidence related to hospital pharmacy practice from LMICs is sparse and is mainly confined to a limited number of countries and regions.

Rational Use of Medicine

A review on the global utilization of essential medicines presents the extent of rational use of medicine worldwide as documented through studies conducted using the WHO/INRUD methodology. The review covered 60 studies, out of which 10 studies were from high-income countries (Atif et al., 2017). For countries with multiple studies available, only three studies, or the studies with the maximum number of indicators were included. Only six countries had three studies included in the review, including Serbia, China, India, Ethiopia, Nigeria, and Tanzania (**Table 1**). The review reported suboptimal values in patient care and facility indicators; however, the evaluation of drug use indicators based on the World Bank Income groups showed that the lower-middle income countries had the highest average number of drugs, the number of antibiotic drugs, and the number of injectable drugs per encounter. Similarly, both the upper- and lower-middle income countries had a lower percentage of medicines prescribed from the essential medicines list. The trend of prescribing generic brands was higher for the countries with lower income.

Patient care indicators and facility indicators were documented in half of the studies ($n = 29$). Theoretically, better scores in these indicators should directly affect the values of prescribing indicators. The median values for consultation time were low in LMICs, with the lowest values in the lower-middle-income countries. The median dispensing time of $\leq$30 s for the middle-income countries is contrary to the dispensing time of high- and low-income countries of approximately 75 s. The review documented good scores for the LMICs for adequacy of labeling and patient knowledge. Upper-middle-income countries scored the lowest in the availability of key drugs among LMICs.

Evidence for the rational use of medicines in a country requires more primary data at the national and regional levels. However, it is to be recognized here that the worldwide awareness campaigns for health professionals on the rational use of medicines carried out by the WHO and INRUD have been successful in establishing the importance of the concept in health-care systems, thus inviting researchers and funding agencies to take up with this area of research. However, it is more likely that the reviewed studies cover only particular facilities and do not cover the wide geographical and socioeconomic diversity that many of the LMICs, such as China, India, Pakistan, and Bangladesh, experience. The difference in urban and rural facilities with respect to the availability of manpower and resources (especially medicines), population density, and health-care choices may reflect an entirely new set of results.

It is also worth mentioning that the overall results are better for the low-income countries than for the middle-income countries. The lower-middle income countries had the lowest scores. The funding sources of health-care systems and facilities can be further explored to answer this question.

It is also notable that foreign-funded projects in health that cover medicine supplies are mostly implemented using standard protocols to ensure the rational use of resources. Such projects are also a resource for health education of patients and capacity building of the local health professionals on the fundamental principles of safe and effective use of medicines.

Pharmaceutical Care/Managed Care

The extended role of the pharmacist in the community pharmacy and the provision of pharmaceuticals, managed care, and other cognitive roles of pharmacists are examples of clinical services provided by pharmacists in the developed world. This sharing of the clinical workload is, however, not paralleled in the LMICs despite the high population growth rates and scarcity of resources. It is theoretically a sound proposal to incorporate more health professionals to share clinical roles with physicians in LMICs. A systematic review comprising 54 randomized controlled trials (RCTs) of pharmaceutical care included 21 studies from LMICs. No studies were performed on older adults in LMICs (Babar et al., 2017). Seven out of 14 studies on diabetes included Malaysia (1), Jordan (2), Iraq (1), Brazil (2), and China (1); 8 out of 24 studies on the provision of pharmaceutical care in cardiovascular disease included Brazil (3), Jordan (2), Thailand (1), and China (2); and 1 of the two studies on depression was from Brazil. Two out of three studies related to asthma and COPD were from Sudan and China. One study from Jordan on medication management review, another study from Malaysia related to osteoporosis in women, and a study from Colombia involving epilepsy and seizures were also included in the review. The quality of the studies was mostly graded as a 3 using the Jadad score, with studies from Malaysia and Chile receiving the lowest score of 1.

Formulary and Procurement Systems

In the initial global hospital pharmacy survey by the FIP in 2009, one WHO region did not come up with even a single respondent confirming the minimum status (at least 3%) for the involvement of a pharmacist as a key focal person in the committee or procedures adopted for the selection and prescription of medications. The report does not state which WHO region did not respond. However, 77% of the respondents confirmed the role of the pharmacist in formulary development (Doloresco and Vermeulen, 2009).

Preparation and Distribution of Medicines

The review of medication preparation and distribution in hospitals identifies key interventions that help minimize medication errors and improve accuracy and efficiency in the medication use process (Oishi, 2009). These interventions include computerized physician order entry system (CPOE), pharmacy-based intravenous admixture service, unit dose drug distribution system, bar-code technology, automated medicine storage, distribution devices, and prescription filling systems. The extent to which LMICs have adopted these technologies and how cost-effective their implementation is, weighed against the high risk of medication errors and serious effects resulting therefrom must be included in the evidence reported in the literature to promote evidence-based policies and choices.

Medication Error Reporting

Older populations are more vulnerable to medication errors due to a higher prevalence of polypharmacy and the presence of comorbidities. Though the proportion of the older population (aged above 65 years.) in LMICs is far smaller than that seen in developed countries, the older populations still account for a large number of people due to the large overall population of many LMICs, for example, 8.5 million (4.3% of the total population) in Pakistan.

The results of clinical studies may or may not correspond to data in western countries. A study conducted in Pakistan reported that 64% of elderly patients in a tertiary care setting were prescribed potentially inappropriate medications (PIMS), mainly including the use of NSAIDs with antihypertensive medications and long-term NSAIDs in 90% and 75% of cases, respectively (Mazhar et al., 2018). A similar prevalence was reported for European countries (Gallagher et al., 2011), whereas a lower prevalence was observed in studies conducted in some cities of India (Pradhan S et al., 2015) and the United States (Gleason et al., 1998). However, the heterogeneity in study design and the different sociocultural settings of each country as well as the different health system designs warrant the need for indigenous data and identification of the factors contributing to the variation in the results among various populations.

Moreover, in a systematic review on medication error reporting in an aging population conducted without any language or time-period restriction, no studies were documented for Africa, Latin America, Australia, or Oceania, and only three studies were reported from Asia (Salmasi et al., 2018). Indonesia and Malaysia were the only LMIC countries included in this review, with one study each.

B. Community Pharmacies

Community pharmacies provide the pivotal pharmacy service that works at the broader interface of the public and health-care professionals (pharmacists). It has the potential to produce both professional credibility and provide health- and pharmaceutical-related care and information. In the systematic review discussed earlier in the hospital pharmacy section, 7 out of 54 RCTs were carried out in community pharmacy settings, and none of these RCTs originated from LMICs (Babar et al., 2017).

In a review of trends in pharmacy services and patient satisfaction over a decade (2006–16), the services were classified as (1) standard practice, (2) service requiring training specifically for study purpose, (3) expanded practice such as vaccination, and (4) collaborative practice services. In total, 104 studies identified on the basis of title and abstract were reviewed on the basis of the

inclusion and exclusion criteria and the availability of full text, excluding studies due to nonavailability of the full text; 50 articles were analyzed. The review did not include a quality evaluation of the studies, and out of fifty articles (Melton and Lai, 2017), only one interview-based study was from a low-income country; the study explored patient satisfaction with receiving an intramuscular contraceptive dose from trained staff at drug stores in Uganda and recorded a positive assessment (Akol et al., 2014).

A systematic review of the retail settings in Asian LMICs (Miller and Goodman, 2016) documented system inadequacies as well as determinants of poor pharmacy practice in retail pharmacies in LMICs in Asia. The reviewers identified the shift of the focus to profit incentive strategies and regulatory strengthening in comparison to the previous trend of focusing on knowledge expansion and education. The key inadequacies outlined in the review included insufficient history taking, lack of referral of patients in need of medical attention, illegal sale of prescription-only medicines without a prescription, sale of clinically inappropriate medicines and/or medicines in wrong doses, sale of incomplete courses of antibiotics, and limited provision of information and counseling. The determinants of poor practice include lack of knowledge, fewer monetary incentives for pharmacy personnel, and poor regulation. The need for intervention research is emphasized by the reviewers with a focus on the sale of medicine from medicine retail shops run without a pharmacist and unregistered drug stores.

A meta-analysis was conducted on pharmacist-led medication reviews in community pharmacy (Jokanovic et al., 2017). The meta-analysis shows that limited data were available from LMICs; most of the reviews did not provide information on the country studied or other related details. In the review on medication reviews in children, none of the studies were reported from LMICs (Costello et al., 2004). A review by Evans et al. covered interventions by community pharmacists for diabetic and cardiovascular patients with 40 studies, 20 of which were included in the meta-analysis of medication review. The meta-analysis reported the issue of an overall low quality of studies, with some improvement in the quality of studies published after 2004. The analysis provided information about the inclusion of the studies from the United Kingdom, the United States, Australia, and Canada, whereas the rest of the countries were grouped as others without mentioning details of the selected study. The majority of the primary data were from the United States (**Table 1**).

Two systematic reviews of studies on lowering cardiovascular disease risk factors were conducted by Santschi et al. (2011, 2012). One review discussed the impact of pharmacist-directed care and pharmacists in collaborative practice with physicians and other health-care professionals. The review comprised 30 studies with only three studies from LMICs, one study on pharmacist-directed care from Thailand, and two studies on collaborative practice from China and Brazil. Most of the studies were from North America. Only two studies were performed in European countries. Out of the 30 studies, 19 were identified as good quality based on the number of items with bias and the study score using the Cochrane Risk of Bias Tool. The study from China by Lee et al. (2006) was included in this category. The majority of the studies were conducted in outpatient clinics of hospitals of specialized clinics, and only a few included community pharmacies.

A qualitative study was conducted on the perceptions and attitudes of community pharmacists about extended community pharmacy services (ECPSs) in Lahore, Pakistan, documenting a positive attitude of pharmacists toward ECPSs and highlighting the need for support and facilitation in the process, mainly to overcome the lack of confidence of patients regarding advice from pharmacists and the compulsion to visit a physician even in cases in which it is not needed (Hashmi et al., 2017).

Bowry et al. (2011) conducted a systematic review for evidence synthesis regarding medication adherence for drugs used in cardiovascular diseases by including only those LMICs using the 2009 list of emerging and developing economies by the IMF (154 countries). This is one of the only initiatives for evidence synthesis aimed at LMICs. Seventy-six articles were included in the study. The pooled data from 55 cross-sectional, 16 cohort, and 5 randomized trials showed an overall adherence of 57.5%. Adherence recorded in the RCTs (42.6%) was lower than the adherence reported in observational studies (59.0%). One of the open crossover trials conducted in 1990 in Zimbabwe had a higher adherence of 97% with respect to the other four RCTs (15%–61%). A lack of family support and significant changes in symptoms were the two major predictors documented in all or the majority of the 29 studies related to the factors associated with adherence. Other significant factors included poor knowledge, negative perceptions about medications, the occurrence of side effects, and high medication costs. However, the prevalence of adherence for cardiovascular diseases was found to be suboptimal, and similar to the resource-rich countries, the difference could be in the predictors. The review did not discriminate in the clinical settings and included both inpatient- and outpatient-based studies. Adherence was highest with methods employing pill count, followed by the methods labeled as "other" methods (electronic pill bottles, e.g., medication event monitoring system, assessments by a healthcare professional, reviews of health records, and biochemical assay) and was lowest on self-reports. Quality assessment of the studies was carried out and reported as a percentage of the score on the relevant scale (Jaded, AHRQ, NOQAS); however, no studies were excluded on the basis of the quality scores. The quality scores for RCTs ranged from 40% to 75%, for cohort studies 11%–75%, and for cross-sectional studies, the quality scores were reported to be 0%–100%. The review identified the need for evidence on strategies for improving medication adherence in resource-poor settings.

C. **Public Health Pharmacy**

Access to Essential Medicines

One important determinant of the rational use of medicines is its access, primarily its affordability and availability. Access to essential medicines is advocated as one of the five key issues related to universal health coverage (Wirtz et al., 2017). A household

survey in eight counties of Kenya reported that only 57.2% of diagnosed asthma patients with a prescribed medication possessed asthma medication at home. Salbutamol was the most frequently purchased medicine for treating asthma, and approximately one-third of patients were using it orally instead of via inhalation (Barakat et al., 2018). Better therapeutic modalities, including nebulization solution and metered dose inhalers with and without steroids, are much more expensive and may often not be available in regular public supplies. Hence, poor access to medicines leads to irrational or poor choices as well as lesser control of diseases. It is not uncommon for patients to link nonavailability and poor-quality of medicine to public health facilities, as identified in the survey of hospital supplies in the teaching hospitals of Southern Punjab in Pakistan (Aziz and Hanif, 2016). This reduces the level of patient trust in the public health facilities and health system. Patients are more inclined to seek alternative medicine, spiritual therapies, and home remedies, much of which lack scientific evidence and ethical practices.

Quality of Medicine

Quality of medicine has been identified as one of the five issues regarding essential medicines that need to be addressed to achieve the goals of universal health coverage (Wirtz et al., 2017). The WHO published two landmark reports in this regard in 2017 (World Health Organization, 2017a,b).

A comprehensive literature review was carried out for the published papers, reports, and field surveys on the quality of medicine for the period of 2007–16 using defined inclusion and exclusion criteria to estimate the public health and socioeconomic impact of substandard and falsified medicines. The review covered 88 countries with more than 76% of the samples from middle-income countries, whereas low-income countries contributed only 23%. An estimated annual cost of 300 billion US$ has been calculated based on the observed (10.5%) failure rate of medicine in LMICs (World Health Organization, 2017a).

A detailed gap analysis was drawn from the review. A significant difference was identified in the failure rate of samples collected using random sampling and convenient sampling, which were 19.5% and 7.8%, respectively. The review also shows a marked gap in the sampling source from the public sector. Moreover, an under- and overrepresentation of data is expected in the review results due to the risk-based approach of sampling in most of the surveys. The samples were concentrated in certain therapeutic classes (mainly antimalarials and other antiinfectives) and specific geographical regions of the world.

These observations led to recommendations for ensuring better quality studies in the future, which included assurance of sufficient sample size with random sampling, choice of technique based on study goals such as field testing, introduction of modeling-based approach for prevalence studies, avoidance of heterogeneity of study methods, and defining of poor-quality medicines by using standardized study protocols. Other identified gaps include a lack of economic data on LMICs, including total health care spending, out-of-pocket spending, and break up of household survey data with respect to therapeutic categories. Data on actual acquisition cost (spending) for the potentially substandard and falsified medicines and the quality assured products and the necessity of funding to carry out systematic and well-planned research involving manufacturers and governments were also emphasized (Wirtz et al., 2017; World Health Organization, 2017a).

Transparency and access to public laboratory surveillance data by LMICs are rare. Access to surveillance data is also advocated in the policy advice developed by the health system researchers (Wirtz et al., 2017). The document also shared the results of two health impact models using severe childhood pneumonia and malaria in sub-Saharan Africa estimations based on a 10% prevalence figure. Up to 72,430 childhood pneumonia deaths can be accounted for by the use of poor quality medicines, which can go up to 169,271 deaths if the antibiotic has no activity at all. For malaria, the incremental deaths due to the use of substandard or falsified medicines account for approximately 2.1%–4.9% malaria deaths (World Health Organization, 2017a).

Managing Medicine Supply Chains

Managing supply chains is one of the fundamental duties attributed to the pharmacy profession. The definition of essential medicines highlights the importance of good inventory management, by emphasizing the availability of the medicinal supply at all times in suitable dosage form and strength. Ensuring the availability of medical supplies in maternal settings can have a profound effect on ensuring the safety of mothers and children during birth and better health outcomes in the postnatal period. Maternal and neonatal mortality is a major health care issue in LMICs. Countries such as Pakistan and Afghanistan have shown no or insufficient progress in these areas (Ahmed and Won, 2017). The WHO has developed a priority list for maternal and child health to aid in this respect. Prevention of stockouts is carried out through the provision of maternal and child health medicines selected on the basis of evidence, packaged as kits. The uninterrupted provision of medicinal supplies positively influenced maternal and child morbidity and mortality with negligible heterogeneity among sites in a large, stepped-wedge, cluster-randomized controlled trial carried out in Mozambique (Betrán et al., 2018). The introduction of customized disease-specific kits in the inventory management systems has also proven to be an effective approach in postdisaster and emergency situations in other LMICs (Bukhari et al., 2010). The report of the Lancet Commission on universal health coverage recommends medicine benefit packages to be introduced to ensure availability and procurement at low prices; however, evidence is needed from health technology assessment surveys to determine the effectiveness of this approach (Wirtz et al., 2017). The overall use of WHO/UN prequalification procedures is recommended for ensuring quality procurement in LMICs, and the same is being adopted by many donor agencies involved in donating medicine to LMICs (Bukhari et al., 2010; Tordrup et al., 2013; Wirtz et al., 2017).

The Need for Basic Household Data on Medicine Use

LMICs spend the least amount (less than 5%) of their gross domestic product on health, resulting in poor infrastructure and health provisions for the patient, which are insufficient in both quality and quantity. According to the World Bank reports, 50%–75% of health expenditure is funded as an out-of-pocket expense in LMICs. In a survey on asthma medication in Kenya, 55.4% of patients were found to purchase medicine from private pharmacies (Barakat et al., 2018). Alarming results are reported for a number of households in India for 2010–12 at a 10% consumption threshold of 17.9% and 11% for total out-of-pocket expenses and OOPs for medicine, respectively (Selvaraj et al., 2018).

Low Literacy and Health Education

Low health literacy leads to poor health choices, which further promulgates the high disease burden found in the LMICs. These poor choices include unhealthy lifestyles, alcohol consumption, addiction, substance abuse, lack of physical activity, lack of facilities and habits for proper sanitation, availability of clean drinking water, and unhealthy and unhygienic food. In resource-poor settings with high disease burdens and population and understaffing in the health sector, the average consultation and dispensing time have been found to be suboptimal (Atif et al., 2017). Incorporating strategies to engage pharmacists in raising health education and encouraging proper use and understanding of medication is an important tool that can prove to be more effective in resource-poor settings than in developed countries.

In the United States, the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) study group has documented that pharmacist-delivered health-literacy-sensitive interventions were particularly effective among patients with inadequate health literacy (Bell et al., 2016). A study in Saudi Arabia showed that poor understanding of medication use labels is related to poor literacy and low socioeconomic status (Alburikan et al., 2018), and similar results were recorded in a study on the inappropriate use of medicines in Pakistan (Husnain et al., 2018).

Maternal, Neonatal, and Child Health and Micronutrient Deficiency

Several interventions in the last decade have advocated effective and evidence-based use of simple pharmaceutical supplies for ensuring positive outcomes regarding maternal and child health. The WHO has formulated a priority list for Maternal and Neonatal Child Health (MNCH) in this regard. Magnesium sulfate injections (The Eclampsia Trial Collaborative, 1995) and tranexamic acid for use in the prevention and treatment of preeclampsia (Li et al., 2018; Vogel et al., 2018) and postpartum hemorrhage have been extensively researched to create sound evidence. The prevention of neural tube defects by overcoming folic acid deficiency through folic acid. Pharmacists, through their multifaceted role in the health-care system, can play a key role in the implementation of this evidence in routine clinical practice. The incorporation of the priority MNCH medicines in EMLs, formulary and standard treatment guidelines, assurance of availability and proper use of these medications, and facilitating the change in practice to promote the evidence-based use of medicines in these crucial health-care settings are necessary (Lotufo et al., 2016). The use of folic acid for the prevention of NTDs has been successfully documented using pharmacist-led action research in the developed world and can prove to be a good example for this and many other potential interventions for a parallel approach to scientific study, dissemination of knowledge, and sensitization of stakeholders to achieve required health outcomes (Norgaard and Sorenson, 2015).

Dietary supplementation is an important aspect of community pharmacy services, and pharmacy personnel share an undivided role in advising and counseling on this class of medicinal supplies (Waddington et al., 2015). A thorough knowledge of pharmacists on rational nutritional supplementation for use in iodine, vitamin D, vitamin A, calcium, and iron deficiency has the potential to minimize large scale health-related issues that evolve because of a lack of timely attention to these problems (Waddington et al., 2015).

Neonatal mortality is an important health indicator that poses a challenge to many developing nations. The neonatal mortality rates in Pakistan and Nigeria are constantly on the rise (Ahmed and Won, 2017). Promotion, knowledge, and confidence in exclusive breastfeeding, child spacing, maternal health, and nutritional status are various areas where a pharmacist can provide the community with correct advice and promote essential health education. Knowledge on the ethical marketing of breast milk alternatives and awareness among health professionals, including pharmacists and pharmacy personnel, are important, especially with respect to the fact that infant formulas and supplements are mainly sold by community pharmacies and drug sale outlets.

Many women of reproductive age from LMICs are not aware of the nutritional status needed for positive health outcomes of pregnancy (Stephenson et al., 2018). This lack of preparedness calls for action shortly before conception, psychological and personal understanding of the role of nutrition in child health and long-term societal attitudes aimed to achieve a healthy future generation by discouraging obesity, smoking, alcohol consumption, etc (Stephenson et al., 2018). Overcoming nutritional deficiencies using pharmacist-related interventions can be a helpful public health strategy. In contrast to Misuse and overuse of food supplementation can also pose risks during pregnancy by increasing risk to pregnancy-induced diabetes and hypertension as well as childhood obesity. Rational and ethical advice in retail settings can discourage such trends.

Diarrhea is an important cause of under-five mortality in LMICs. In the last decade, the WHO has introduced zinc supplementation as a recommendation for the management of acute watery diarrhea along with oral hydration solution (ORS) (World

Health Organization, 2011). A Cochrane review conducted on zinc supplementation in diarrhea supports its use in children above 6 months of age, especially in areas with a prevalence of zinc deficiency and malnutrition (Lazzerini and Wanzira, 2016). However, the availability of zinc dosage forms suited to the pediatric population and its accessibility, promotion, and awareness among health professionals, including pharmacists, needs (Oyetunde and Williams, 2018) to be assessed (Kung'u et al., 2015). To promote this intervention, bundle packages of zinc preparation and ORS are in use in many countries (Gebremedhin et al., 2016).

Preterm birth is another major contributor to neonatal mortality, and pharmaceutical issues that need to be addressed in this context include the cost and availability of pulmonary surfactants as prophylaxis and management of respiratory distress syndrome. As a high-cost biopharmaceutical, the product has limited manufacturers and involves the expertise of specialists and sophisticated facility settings for its appropriate use.

Review Contributions of LMICs in Top-Tier Pharmacy Journal(s)

The contributions of LMICs were assessed by the authors of this chapter using a review of systematic reviews published in the International Journal of Clinical Pharmacy from 2010 to 2015 (MacLure et al., 2016). Out of the 17 reviews, only six were submitted from LMICs, including three from Brazil, two from China, and one from South Africa. Two articles from Brazil were funded by the Brazilian government and the article on pharmaceutical policy from South Africa by the WHO. The topics of the reviews from Brazil included a review of the quality of systematic reviews on pharmacist health interventions (Melchiors et al., 2012), assessment of pharmacist-led patient counseling using RCTs (Okumura et al., 2014) and the effectiveness of clinical pharmacy services by reviewing systematic reviews (Rotta et al., 2015). Apart from a review on pharmacist care by Zhong et al., all other reviews clearly mentioned the review questions (Zhong et al., 2014). None of the 17 studies had a reference protocol. Two studies had defined their methodology as systematic in the title, whereas two studies did not provide a clear outline of the systematic methodology in the text despite using the word systematic in the title. One of the studies did not claim to be systematic; however, it was conducted systematically using the Cochrane collaboration recommendations. This indicates the gross situation of the quality of systematic reviews. Producing a good quality systematic review is a demanding task, and for resource-limited settings, this becomes more difficult due to lack of time, training, and resources. Evidence of team support was mentioned at all levels in all six reviews from LMICs except one in which it was only at the quality assessment level. A clear search strategy was missing in three of the reviews. All the reviews employed some form of quality assessment checklist (AMSTAR, Jadad, PRISMA, RevMan, GRADEpro, R-AMSTAR, DEPICT) except one on the pharmaceutical policies in LMICs.

The Way Forward

Promoting Quality Evidence Through Systematic Reviews

Cochrane reviews are the leading initiative with respect to evidence synthesis for use in medicine selection and use. With the goal of being self-sufficient rather than dependent, the Cochrane Collaboration has enabled people in LMICs to conduct high-quality Cochrane reviews, an example being the work of Ian Chalmer in pregnancy and childbirth (Young et al., 2013). This capacity building is aimed at developing globally competitive researchers from LMICs. This is to carry out "sensitive and intelligent" research that helps prioritize indigenous issues and creates quality evidence (Young et al., 2013).

National agencies in the developed world also conduct meta-analyses and scientific reviews to generate evidence for use in establishing and updating clinical recommendations, especially the STGs (Bond, 2015). Initiatives similar to NICE, the Scottish Medicines Consortium (SMC), the Common Drug Review for Canada (CDR), and the Pharmaceutical Benefits Advisory Committee for Australia (PBAC) need to be established in LMICs to promote the generation of locally relevant evidence in medicine and pharmacy practice.

The biggest facilitators for creating evidence to inform policy can be none other than the policy makers themselves. It is important to sensitize the policy makers in LMICs to invest the human resource as well as public and private funding for generating timely and sound evidence. The Cochrane initiative and other similar efforts also carry out advocacy for evidence-informed decision-making (Young et al., 2013). The gap in this respect in LMICs is one of the barriers to conducting quality studies, especially in the domain of public health. As evidence-based practice has evolved in just the last century, the traditionally modeled health systems in developing countries are still resistant to adopt the new approach and changing the health system processes accordingly (Young et al., 2013). For this reason, translational research is gaining importance in the scientific scene. LMICs are not only challenged by the limited involvement in the generation of evidence but are also hindered by the inefficient information dissemination and adoption of new practices.

The WHO has established systematic review centers in Bangladesh, Chile, China, Lebanon, South Africa, and Uganda under the Alliance for Health Policy and System Research. These centers work on ways to improve the performance of health systems. Approximately 20 systematic reviews and review protocols have been produced, and more are in process. The identification of this and other available resources and collaboration to ensure capacity building are necessary initial steps for LMICs to participate in the evidence synthesis process (International Initiative for Impact Evaluaton-3ie, 2018).

Use of Standard Protocols

Standardized methodologies and research protocols are a valuable tool to produce good quality evidence with less possibility of methodological flaws and bias. The WHO/INRUD methodology for assessing the rational use of medicine and drug utilization review is one such example. It has also been identified in this chapter that the largest number of studies were carried out under the WHO/INRUD protocol. This also leads to less heterogeneity in the data, allowing more room for qualitative analysis. However, proper conduct of these protocols may involve training of researchers. Moreover, like INRUD, these methodologies must be disseminated through interactive forums, research organizations, and public institutions to create interest and awareness of the importance of generating primary data on the subject. Another example of standardized methodologies is the Health Action International (HAI) methodology to measure drug prices. While more protocols are needed to be developed focusing directly on the pharmacy practice areas, the existing protocols need to be constantly circulated and encouraged for use. One important area of such template research is undergraduate student projects. The expertise and close mentorship needed to design an entirely new project for pharmacy students is a demanding task in a system where there is limited faculty; many of whom are overburdened or lack the necessary pharmacy practice research skills. With time, more schools are adopting research projects as part of undergraduate curricula. The use of standardized study designs in themes pertinent to basic pharmacy practice data and drug use indicators as well as other key issues in LMICs will help expose young researchers with locally relevant research themes and quality research design.

Completeness of Search in Reviews

Language is one of the factors limiting the collection of primary research and ensuring the completeness of the literature search. Almost all the discussed reviews included only English language publications. Even studies by international bodies such as the WHO were limited to English (World Health Organization, 2017a). Very few studies included all languages (Salmasi et al., 2018) or additional languages along with English. This is particularly important for the incorporation of literature that is present in popular languages in LMICs, including Chinese, French, Spanish, and Arabic. Translation assistance initiatives or specialized digital aids are needed in this respect. The need for an index catalog for pharmacy practice was discussed earlier, and the availability of accessing the terms in multiple languages can be a valuable tool for ensuring the completeness of the review. Moreover, it is very rare to include gray literature, such as thesis and dissertation catalogs, in the search methodology (Evans et al., 2011). Poorly funded and unfunded studies are more prone to end up in unindexed journals or have limited dissemination through conferences and poster presentations.

Source of Research Funding

Among the 17 reviews, 1 conference proceeding and 1 article on the development of the Basel Statement that was discussed in the current chapter, 6 were funded projects. The regional and national professional bodies, public universities, and regional research centers must be encouraged to develop a mechanism for funding pharmacy practice research in LMICs. Professional bodies in LMICs can carry out advocacy with funding institutions to promote pharmacy practice research by highlighting the gaps and it's potential to inform policy for developing evidence-based policies and improving people's health.

One of the novel mediums of the arrangement of funding is the use of a central fund under the Community Pharmacy Agreement in Australia. The community pharmacy contract global sum is a model practiced in Australia for the integration of pharmacy practice and research. The successful implementation of home medicine reviews has been established and refined through research using these funds (Bond, 2015). Regulatory or professional bodies of practicing pharmacists can generate a similar funding mechanism to promote research in pharmacy practice and to aid capacity building projects in this regard. However, close collaboration of policymakers, practitioners, and researchers is needed to design and implement such initiatives.

Gaps in Academic Training in Research Methodologies

Knowledge of sociobehavioral sciences constitutes an integral segment of pharmacy practice; for example, medicine use, counseling, adherence by the patient, and interaction with prescribers to influence prescribing to promote rationality and evidence-based practice need the additional knowledge of communication, interaction, and effective dissemination of knowledge. Socio-behavioral sciences were introduced in western curricula in the 1950s to early 2000s (Mohamed Ibrahim and Wertheimer, 2018); however, they are still not present in the courses taught in many LMICs. Moreover, adequate capacity building at the postgraduate level and encouragement of postgraduate diploma courses in research methodologies in pharmacy practice are critical to ensure the development of quality evidence from LMICs. The research methodologies in pharmacy practice are not adequately taught in the pharmacy schools of LMICs.

Take Home Message

- The goal of health-care professionals globally is to ensure evidence-based practice.
- The stakeholders including practitioners, researchers, academicians, funding agencies, and the policy makers must identify "The type of EVIDENCE" that matters for uplifting the standards of care and improvement in health-care indicators of the LMICs (based on their indigenous needs and they are in many ways different from HICs).

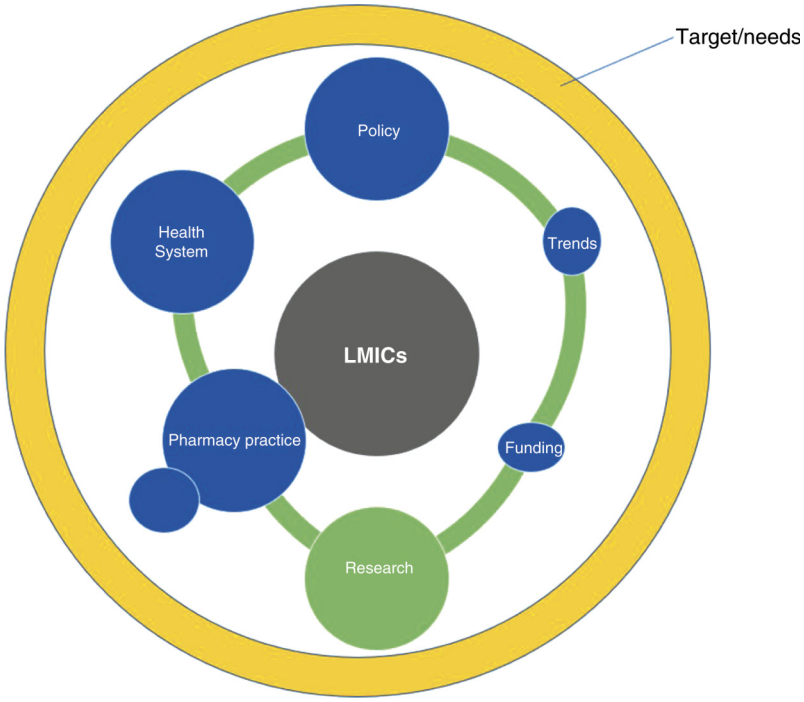

Figure 1 Proposed components of action plan for improvement in pharmacy practice research evidence in LMICs. (The outer circle refers to global trends and advancement in pharmacy practice. The central sphere refers to the indigenous needs. The magnitude of the blue green circles refers to the quantity/magnitude of progress in the related sector. The color of circles may represent the quality of the component. The closer the circle moves to the central sphere the more it caters to indigenous needs)

- The chapter identifies the gaps in pharmacy practice and evidences needed to deliver these goals and elaborates on the barriers faced in developing such evidences.
- The key stakeholders should develop a clear action plan to facilitate the process by focusing on their individual roles. Proposed components for a possible plan are shown in Fig. 1.
- In short, the global picture of evidence in pharmacy practice research cannot be built without active contribution of the LMICs that constitute 80% population of the world.

Conclusion

It is clearly depicted from the discussed analysis that the contribution of LMICs to the overall evidence synthesis process in pharmacy practice is quite low. Only a few countries have conducted quality research to be included in the systematic reviews by indexed journals. These countries include China, South Africa, Brazil, and Malaysia followed by Jordan and India (Table 1). Of the low-income countries, Nepal, Bangladesh, and Tanzania were the main contributors. A clear action plan is needed to proactively and effectively engage LMICs in quality research on pharmacy practice.

Along with the above-suggested recommendations, it is reiterated by the authors that a methodology of systematic reviews in pharmacy practice must include the identification of contributing countries from which the primary data were collected. A short analysis should be conducted with respect to country income groups to ensure appropriate interpretation of the review in different health systems and country settings.

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Implementation Science

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Introduction

The road to evidence-based practice (EBP) is long and complex. In medical disciplines, the traditional research pipeline usually begins with biomedical inquiry and preclinical or animal studies. Translational research follows, involving phase I and II clinical trials and case studies, moving discoveries to human trials, from "bench to bedside". Next, a second translational stage, involving phase III and IV human clinical trials and controlled observational studies are conducted, moving the evidence to clinical practice. However, it has been proposed that this second translational stage is sufficiently complex to warrant further division: translation to patients (synthesizing the evidence including systematic reviews and guidelines), translation to practice (diffusion, dissemination, implementation, and sustainability), and translation to population (scale-up and spread) (Colditz, 2012; Westfall et al., 2007). Each one of these translations is a research field that require theoretical bases, study designs, and indicators for evaluation. Studies are required to understand and improve the evidence of each phase of the pathway.

A similar evidence pathway is promulgated for human services, including health services and professional pharmacy services. Research begins with developing a service and testing its efficacy and effectiveness in improving patient outcomes (health and quality of life) and economic outcomes (cost-effectiveness) from the perspective of the [pharmacy] organization and health care system. Next, diffusion and dissemination (communication) studies are required, to gather evidence of how to spread the research findings in order to increase awareness and interest. Finally, the service is expected to be adopted, implemented, and sustained into routine practice. As with the traditional medical research pipeline, this "implementation process" has been posited as being sufficiently long and complex to consist of multiple phases rather than being a single event. Furthermore, each portion or subphase of the service evidence pathway is a research field that requires theoretical bases, study designs, and indicators for evaluation.

Service developers and researchers should consider the final goal, of integration and sustained delivery, and the factors influencing the achievement of this goal, throughout the evidence pathway. As an example, when an innovation or service is developed, consideration should be given to, "how will the service be received?" and, "how difficult will the service be for practitioners to apply in practice?" Such questions are crucial to achieving sustainment and scale-up. In addition, the move for integrated implementation involves collaboration or coproduction, alternative research approaches, and the measurement of novel outcomes. For many years, services were created by researchers, with the primary objective of attaining evidence of efficacy (Glasgow et al., 2003). As such, study

designs such as randomized-controlled trials were used, but which may not have been reflective of the real-world, nor considered future wide-spread implementation.

The evidence pathway and research focus of other human service disciplines are analogous to pharmacy practice research. Internationally, community pharmacy is attempting to introduce and integrate pharmacy and professional pharmacy services (Moullin et al., 2013). Numerous professional pharmacy services have been conceptualized, and in some cases, their clinical effectiveness, cost-effectiveness, and remuneration structures studied, yet many have failed to be successfully implemented (Patwardhan et al., 2014). So on the one hand, there is scope for improvement in the development and testing of services. Service developers would benefit from using implementation science and conducting research that integrates implementation principles across the entire evidence pathway, such as expanding the contexts and stakeholders involved in the studies to develop new services. On the other hand, there are developed services ready to move onto practice, and researchers should consider conducting implementation research to investigate their diffusion, dissemination, and implementation, and subsequently develop theoretically based implementation programs.

Foundations of Implementation Science

There is increasing recognition and priority being placed on dissemination and implementation research around the World (Eccles and Mittman, 2006). Internationally, across multiple disciplines, there is a realization of gaps between research and impact and disconnections in the innovation and research processes. "Science to service", "research to reality", "evidence to practice," "know-do", are all terms used to indicate gaps in the approval and application of innovations (Brownson et al., 2018). More recently there has been discussion of an "implementation gap" and a "quality chasm" referring to services not being implemented and/or sustained over time and not being delivered with fidelity to how they were originally designed and intended (Fixsen et al., 2013). An extension of this fidelity debate is whether it is necessary to safeguard results achieved in controlled clinical trials by pushing fidelity, versus allowing and encouraging adaptation, which has been shown to assist introduction and integration (Durlak and DuPre, 2008).

Implementation science and knowledge translation have arisen to move innovations into practice, drive research utilization and EBP, and by doing so improve the value of research. Implementation involves change but is further complicated by necessitating change within and across multiple contextual levels, by multiple stakeholders (Kitson et al., 2018; Wandersman et al., 2008). Implementation may require innovation adaptation/change, behavioral change, organizational change, and systems change. In light of this, it is not surprising that there is an implementation challenge nor that this challenge is not unique to pharmacy practice, but is shared among all human services (Fixsen et al., 2005). Implementation science is a cross-disciplinary field that engages practitioners, service providers, policymakers and researchers from clinical, education, community, and policy contexts. Implementation science is about opening the "black-box" of implementation to develop logical, useable approaches that can be easily understood and utilized by researchers and practitioners to close the implementation "gaps".

Implementation science is a research field directed toward building evidence on how (effective implementation strategies and programs), by whom (facilitators/coaches, purveyors, intermediaries, and stakeholders), where (enabling contexts including policy, clinical and community settings) and for whom, any innovation, in any given situation, may be introduced and integrated into practice (Fixsen et al., 2005). Implementation research is needed for all these implementation questions while incorporating implementation evidence across the whole research pipeline to create professional services that are more marketable, acceptable, and workable.

The propagation of implementation science is widely attributed to Everett Rogers's seminal "Diffusion of Innovations," although its advent is traced to much earlier anthropology and social science research (Rogers, 2003). Roger's work was based on initial research conducted in 1943 on the adoption, or lack thereof, of hybrid corn seed by farmers in Iowa USA, together with a synthesis of other studies, from diverse fields, which also utilized the diffusion of innovations theory. The diffusion process and rate of adoption are explained by innovation attributes, adopter innovativeness, innovation-decision process, communication channels, and the social system. The popularity of diffusion studies spread from rural sociologists into general knowledge utilization by social and political scientists, where policymakers were the adopters, as well as to technology transfer and knowledge translation in large organizations (Dearing and Kee, 2012). At a similar time concepts and theories on research utilization, and evidence-based medicine/practice were gaining momentum (Estabrooks et al., 2008).

In many ways, the principles from diffusion theory have remained constant, but have been explored further and subsequently expanded, with research investigating the ensuing stages, post the adoption decision, of the implementation process (Rycroft-Malone and Bucknall, 2010). With time and further evidence, multiple other approaches have been added to the communication-based diffusion theory, and frameworks and models have proliferated (Moullin et al., 2015; Nilsen, 2015). Interest in the diffusion of innovations continues, as is recognition of the importance of the ensuing introduction and integration stages postawareness of the innovation. These stages or phases have been termed the implementation process and the study of this process, its influences and the strategies to improve successful implementation, called implementation science. Implementation science amalgamates different theories and various lenses are offered to view processes and outcomes. Regardless of the lens, the notion is moving an innovation or knowledge among individuals and contexts by various means to achieve outcomes.

Terminology

Alongside implementation science, the term knowledge translation is commonly used, particularly in the health and policy sectors in Europe and Canada. Knowledge translation was used by the World Health Organization (WHO) in their policy to close the "know-do-gap" (World Health Organization, 2006). Subsequently, WHO have released a practical guide to implementation research in health, blurring the terminology boundaries (Peters et al., 2013). Initially, knowledge translation included a greater focus on problem identification or needs assessment, and the creation and/or synthesis of knowledge; however, implementation science has broadened to include these areas. Other distinct, but similar terms regularly used interchangeably to knowledge translation include research or knowledge, utilization, transfer, mobilization, or exchange (Ottoson and Hawe, 2009). Within these fields, the terminology and inclusion of concepts within their frameworks vary; however, the goals and principles are largely analogous.

The terminology of the implementation fields can be confusing. Not only does implementation science use different terms to knowledge translation (KT), but within the fields and within the same disciplines different terms are often used to mean the same thing (synonymy), or the same term is used to indicate different things (homonymy). For example, the word "intervention" may refer to an "implementation intervention" or a "clinical intervention". Another example is the end-user, which in implementation usually refers to the individual who will deliver the innovation (i.e. pharmacist), as they are the end-user of the implementation intervention. Whereas in pharmacy practice, other health services, and public health disciplines, the end-user is the individual receiving the innovation (i.e. patient). A small glossary of terms has been included at the beginning of the chapter and further implementation science-based pharmacy practice definitions have been published (Moullin et al., 2016a, 2016b).

Theoretical Approaches: Frameworks, Models and Theories

One valuable aspect of implementation science is that it incorporates concepts from an array of disciplines and theories to provide a holistic view of the implementation process and its determinants. Disciplines drawn upon include sociology, psychology, political science, business, and communications (Nilsen, 2015). Theories include cognitive, behavioral, organizational (Davies et al., 2010) and complexity, network and systems thinking cross-social ecological boundaries (Foster-Fishman and Watson, 2012; Kitson et al., 2018).

There has been increased recognition of the importance of using established change theories, models and/or frameworks, as well as developing theoretical bases from within the implementation science discipline. Theoretical grounding may be used to determine and assess factors, create and evaluate strategies and develop tools and measures to gain evidence into the mechanisms of implementation and how implementation is more likely to succeed (The Improved Clinical Effectiveness through Behavioural Research Group, 2006). It is largely accepted that research should be theoretically driven and implementation research is no exception; however, the debate on frivolous theory over common sense and empirical evidence lingers (Bhattacharyya et al., 2006; Oxman et al., 2005).

Implementation theories, models, and frameworks have been classified as being concentrated toward, content and context (determinant frameworks, classic theories or implementation theories), process, or evaluation (Nilsen, 2015). Within these classifications there are broach overarching frameworks (e.g. lists of factors, strategies or measures; stages, steps or evaluations across the entire implementation process; multi-level context derivations; general theory of implementation). Additionally, there are frameworks for specific concepts (e.g. fidelity, organizational readiness, implementation climate, adoption stage, and sustainability stage). Moreover, frameworks, models, and theories from related fields are used (e.g. intervention development models such as intervention mapping; behavioral motivational, action or stage theories; organizational or quality improvement theories; systems, complexity, and network thinking). There is an occasion for all frameworks, models and theories depending on the research question, the contextual level being targeted, setting and point in the evidence pathway.

Along with realization of the importance of the later dissemination and implementation phases of the evidence pathway, there has been insight that for successful implementation, implementation evidence should also be considered during the early, innovation, or service development phases (Kitson et al., 2013; Kothari and Wathen, 2013). Examples of frameworks that incorporate principles of implementation into the development phases include: the Medication Research Council of UK's Framework for Complex Interventions (Craig et al., 2008, 2013); knowledge translation frameworks that are based around theories of planned action such as Knowledge to Action (KTA) (Graham et al., 2006); the KT complexity network model (Kitson et al., 2018); and intervention mapping (Bartholomew et al., 1998).

Core Concepts of Implementation Science

In basic terms, implementation success (**Fig. 1**) is impacted by

- What is to be implemented (the innovation)
- Where and for whom is the innovation to be implemented (the context)
- How and by whom is the innovation to be implemented (the implementation process and program)

Figure 1 Active implementation framework formula for success (Fixsen et al., 2013).

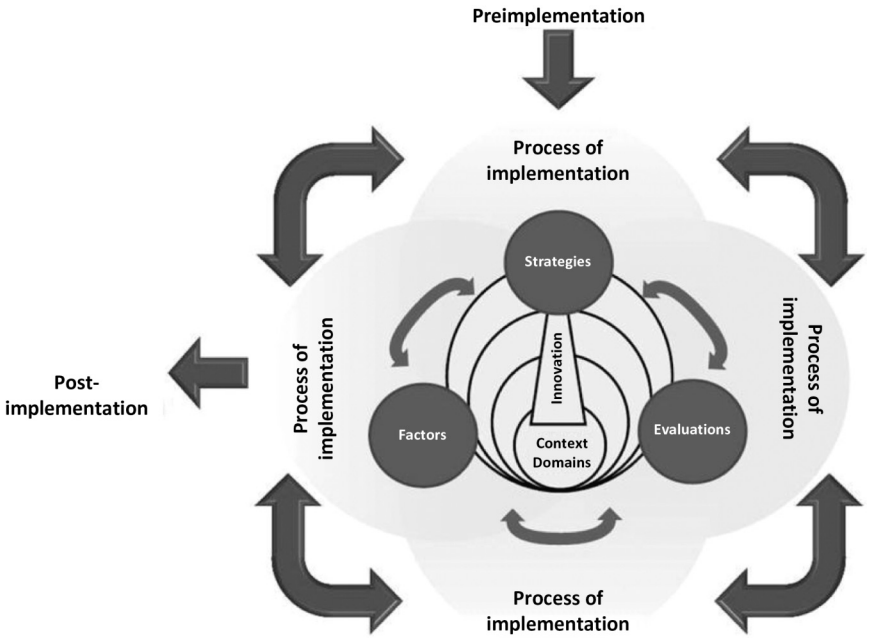

Figure 2 Generic Implementation Framework (GIF) (Moullin et al., 2015).

Developing evidence on what constitutes effective implementation, for which innovations, in which contexts, is the primary focus of implementation science. Knowledge translation has mirrored concepts, where successful implementation has been postulated to be calculated from evidence, context and facilitation in the Promoting Action on Research Implementation in Health Services (PARIHS) framework (Kitson et al., 2008). Similar components have also been voiced as the essential ingredients of change management and organizational change (Worren et al., 1999). By being multiplications, the implementation equations signify that all components are imperative and must be considered and that if any component equals zero, the outcome of the equation will be zero, i.e. unsuccessful implementation.

Generic Implementation Framework (GIF)

The GIF collates the key components involved in implementation (Fig. 2) (Moullin et al., 2015). These components are described as (1) the innovation (e.g. professional pharmacy service), which is being implemented into (2) a multi-level context, which consists of and is influenced by a number of (3) implementation factors, throughout a (4) multi-phase implementation process, that is facilitated by (5) strategies and assessed with (6) evaluations and outcomes. It is a central structure into which meta-frameworks, model of theories should be added to operationalize each component.

Innovation: What is to be Implemented?

Implementation science arose as innovations, evidence-based practices (EBPs) and evidence-informed treatments, sat idle in academia and empirical evidence and knowledge were not spreading. Innovations are defined as "a novel set of behaviors, routines, and ways of working within a setting" (Greenhalgh et al., 2004). Innovations vary from a new technology or guideline to a service or program, or a novel way of working, such as continuous quality improvement initiatives or EBP. The characteristics of innovations influence the ease and likelihood of successful implementation. The innovation's attributes effect all stages of the implementation process, from exploring and appraising the service and deciding whether or not to implement (adoption decision), to how much preparation is required, how difficult the innovation is to introduce, the challenge of gathering support and integrating into practice, to finally influencing the spread across diverse settings.

It appears professional pharmacy services are largely developed prior to considering implementation and sustainability. It is therefore possible, that research projects may produce innovations that are not implementable. Integrated implementation would be desirable to increase their feasibility, acceptability, implementability, and sustainability. In addition, investigating the

components of services is recommended so that adaptations to the innovation may be made while ensuring the positive outcomes obtained in the trials are transferred to real-world practice. Pharmacy practice research could benefit from service development and optimization studies, which incorporate implementation science, as well as implementation research on services that are already developed and available for implementation.

Contextual Domains: Where and for Whom is it to be Implemented?

The context into which an innovation is to be implemented is gaining increasing attention in implementation science literature. The notion of contextual domains is to acknowledge and embrace the complexity of the system and consider influences across all social-ecological levels, at all stages of the process. Contextual domains may be defined as groupings of related influences regarding the circumstances that surround the innovation to be implemented (Aarons et al., 2011; Damschroder et al., 2009).

Ideally, throughout the implementation process consideration would be given to: the characteristics and readiness of all stakeholders involved with an innovation and/or the implementation process; the conditions and characteristics of the setting(s) in which the innovation is to operate; the circumstances immediately surrounding the organization(s) including the community, and patients (for whom the innovation is targeting) and their social network; and finally the economic, political, and professional milieu (Moullin et al., 2016a). Mendel et al. (2008) use complexity theory in their framework to include multiple levels of context and illustrate the importance of capacity building. The Interactive Systems Framework (ISF), a community service implementation framework, also focuses on building the capacity of the service delivery system and the service support system, as well as acknowledging the interrelationships between these levels (Wandersman et al., 2008). Their latest framework the Evidence-Based System for Innovation Support (EBSIS) builds on the ISF by delineating an implementation program specific for capacity building (Leeman et al., 2015). Implementation science emphasizes the importance of considering and involving stakeholders from both the inner and outer context (Aarons et al., 2011) such as community, patients and policy-makers (Kitson et al., 2018, 2013).

Implementation factors

Implementation factors are the variables that may affect the implementation process. Also termed influences, facilitators and barriers or determinants of practice (Flottorp et al., 2013). List-style frameworks of factors include the Consolidated Framework for Implementation Research (CFIR) (Damschroder et al., 2009), integrated checklist to identify determinants of practice (TICD checklist) (Flottorp et al., 2013), Theoretical Domains Framework (TDF) (Michie et al., 2005), and Behavioral Change Wheel (BCW) (Michie et al., 2014). The CFIR list of factors influencing the implementation process has been adapted for community pharmacy in a paper by Moullin et al. (2016a). Some researchers have narrowed down the scope of the factors and developed models that link to aid in the selection of strategies, such as the PRECEDE-PROCEED (Green and Kreuter, 1999).

Use of factor frameworks facilitates consistent terminology across disciplines, linkage to theories, and impact evaluation, where mechanisms of action and determinants of implementation are evaluated. Factors may act as moderators, where they modify direction or strength of an effect, or as mediators, where they account for part of an effect (Flottorp et al., 2013). Once target factors have been determined, appropriate strategies may be chosen, including the operationalization and reasoning of the strategy, so that the proposed mechanism of action may be tested (Dalkin et al., 2015; Eccles et al., 2005). As mentioned, barriers and facilitators to professional pharmacy service implementation have been tested, however using a typology that links to strategies, and assessing the factors influencing the implementation by multiple stakeholders, at different time points may advance implementation evidence for the implementation of professional pharmacy services (Moullin et al., 2016a).

Tools and theories of contextual factors have been developed and tested, such as implementation climate, leadership, implementation citizenship behavior, organizational readiness, organization context (Aarons et al., 2018). The "fit" of the innovation to context (innovation fit) is an example of one factor associated with implementation that may be evaluated to guide tailoring of implementation strategies and adaptations of the innovation and/or the context (Aarons et al., 2012).

Implementation Process: How and by Whom is it to be Implemented?

The crux of implementation science is to answer the question, "How and by whom should an innovation in a particular context be implemented?" Or "What constitutes effective implementation?" The answer is not simple. Implementation consists of a complex process, often to implement complex innovations, across complex social systems.

It is widely accepted that implementation is not a single event, but a long and complex process. The process is delineated into numerous different arrangements and typologies of stages. In addition, in some derivations, the stages are further divided into a series of activities or steps, as is the case for the Framework for Implementation of Services in Pharmacy described later in this chapter.

Examples of the implementation process stages include:

- Knowledge, persuasion, decision, implementation, and confirmation (Innovation-decision process up until point of adoption) (Rogers, 2003).
- Knowledge creation (tailoring knowledge): knowledge inquiry, synthesis, product tools; Action cycle (application): identify problem, identify, review, select knowledge, adapt knowledge to local context, assess barriers to knowledge use, select, tailor,

implement interventions, monitor knowledge use, evaluate outcomes, sustain knowledge use (Graham et al., 2006; Straus et al., 2009).
- Problem identification, knowledge creation, knowledge synthesis, implementation, and evaluation (Kitson et al., 2018).
- Awareness, adoption, implementation, and institutionalization (Steckler et al., 1992).
- Exploration, installation, initial implementation, full implementation (Fixsen et al., 2005).
- Exploration, preparation, implementation, and sustainment (Aarons et al., 2011).
- Training, adoption, implementation, and practice improvement (Simpson and Flynn, 2007).
- Development or discovery, exploration, preparation, testing, operation, and sustainability (Moullin et al., 2016a).

The stages and steps are criticized for their linear derivation, as the process appears to be iterative. Frameworks, such as Greenhalgh et al. (2004), are less linear in appearance, where system antecedents and system readiness occurring parallel to diffusion and dissemination, both leading to adoption/assimilation, followed by implementation and finally consequences. Conversely, Kitson et al. (2018) removed the linear representation all together depicting only separate domains. Regardless, for illustrative and planning purposes many frameworks do take a temporal, stage-based approach. And branded implementation programs and frameworks that include the development or synthesis phase, such as in knowledge translation, quality improvement and intervention mapping, appear to be more prescriptive of the implementation process.

The second aspect of the implementation process is the individuals involved in the implementation effort (those delivering the implementation strategies) as well as those in the enabling context(s) (those delivering the innovation). Staff selection, implementation teams and leadership are particularly prominent implementation topics. In addition, the use of knowledge brokers, purveyors and intermediary organizations has received attention (Gagnon, 2011; Oosthuizen and Louw, 2013). Research, funding and use of implementation facilitators may be valuable for professional service implementation.

Implementation strategies

Implementation strategies are the efforts (method, technique, or activity) designed to enhance the movement of an innovation into use and its integration into routine practice (Curran et al., 2012; Flottorp et al., 2013). "Implementation strategies are inherently complex social interventions, as they address multifaceted and complicated processes within interpersonal, organizational, and community contexts" (Proctor et al., 2013, p. 3). In a similar vein as clinical interventions being designed to affect behavioral or environmental determinants of patients' health, implementation strategies are designed to affect the behavioral or environmental determinants of practitioners' practice. Strategies may need to adapt innovations, behavior, organizational structure, climate, culture, shift perceptions of communities or enable policy amendments. Implementation strategies include:

> 'how to translate interventions to encourage uptake and implementation in ways that preserve scientifically validated components of evidence-based practices, how to obtain buy-in of various stakeholders in settings over which researchers have little control, and how to sustain interventions beyond initial demonstrations and funding, particularly in settings with highly constrained resources'.
>
> (Mendel et al., 2008, p. 22)

Taxonomies and frameworks of implementation strategies include the EPOC checklist (Cochrane Effective Practice and Organisation of Care Group, 2010), Behavioral Change Techniques (BCT) (Michie et al., 2013) and Expert Recommendations for Implementing Change (ERIC) discrete strategies list (Powell et al., 2015). Other frameworks which combine a number of discrete strategies have been termed branded, manualized, multifaceted implementation strategies or implementation programs (Proctor et al., 2013). These include the Availability, Responsiveness and Continuity model (ARC) (Glisson and Schoenwald, 2005), Replicating Effective Programs (REP) (Kilbourne et al., 2007), Getting to Outcomes (GTO) (Chinman et al., 2004), Quality Implementation Framework (QIF) (Meyers et al., 2012), and Leadership and Organizational Change for Implementation (LOCI) (Aarons et al., 2017). Examples of commonly used implementation strategies include education, audit & feedback, outreach (opinion leaders, knowledge brokers, facilitators/coaches, and purveyors) infrastructure & technology, and financial incentives.

Implementation science has shown that generally neither changing a single implementation factor nor employing a single implementation strategy is sufficient for successful, sustained implementation (Grimshaw et al., 2001; Scott et al., 2012). In other words, factors such as a strong desire, motivation and knowledge alone are not sufficient to drive implementation (Green et al., 2009). Neither are strategies such as payment, training, continued professional development (CPD) including conferences, or mass mailings of clinical guidelines (Forsetlund et al., 2009; Grimshaw et al., 2001; Hakkennes and Dodd, 2008). In pharmacy practice, great emphasis was placed on securing payment and providing CPD, believing this would be sufficient to drive implementation. From the experiences in many countries, it can now be seen that although a benefit must be realized for the pharmacy business, remuneration and training alone are not going to lead to successful implementation. Implementation science deems that theoretically driven strategies are needed to target key factors that influence implementation for a particular setting for a particular service (Palinkas et al., 2011). On the contrary, the evidence for tailored interventions is currently mixed (Baker et al., 2015).

A research team headed by Susan Michie at University College London have combined psychological frameworks and models for determining factors and tailoring implementation strategies. The factors determined from the Theoretical Domains Framework (TDF) or Behavioral Change Wheel (BCW) may be mapped to the COM-B model (Capability, Opportunity,

Motivation – Behavior) (French et al., 2012; Michie et al., 2014). This model determines whether greater capability, increased opportunity, and/or stronger motivation is required to drive behavioral change. From the results, strategies and finally techniques, the active ingredients that may achieve the desired change to the determinants, are identified (Michie et al., 2014). Although COM-B and the BCW have been used in policy and organizational contexts, as the name suggests, the associated models are largely focused on individual behavior.

Quality improvement approaches such as UK's Institute for Healthcare Improvement (IHI) breakthrough series (Institute for Healthcare Improvement, 2003) and US Department of Veteran's Affairs, Quality Enhancement Research Initiative (QUERI) projects (Stetler et al., 2006) are particularly helpful at the organizational level. Alternatively, an option is to follow an intervention development framework (e.g., Medical Research Council (MRC) guidance, intervention mapping, IHI etc.), but for the development of an implementation strategy or program, rather than the clinical intervention.

The design of implementation strategies should be deliberated, strategically and systematically, and this design process explicitly reported. When researching implementation programs, it is essential to report each strategy as would a clinical intervention. In this way, the fidelity of implementation and essential strategies for a particular innovation in a particular context may be evaluated. In addition, it allows for replication and meta-analyses (Michie et al., 2009; Proctor et al., 2013). Recommendations, manuals and protocols have been made by the Workgroup for Intervention Development and Evaluation Research (WIDER) group for the reporting of behavioral change interventions and implementation strategies, for quality improvement interventions standards have been developed (Standards for Quality Improvement Reporting Excellence (SQUIRE checklist)), and a statement of Standards for Reporting Implementation Studies (StaRI) (Pinnock et al., 2017) has been published.

Implementation evaluation/outcomes

All implementation efforts and implementation studies should include a plan to evaluate the impact of the chosen implementation approach and ways to measure success. Implementation evaluations measure the effects of implementation and may include: process evaluation of progression, impact evaluation of factors, formative and summative evaluation of strategies, as well as the degree of implementation, and innovation outcomes. Frameworks based on implementation evaluations include Glasgow et al. (1999), Green and Kreuter (2005), Lehman et al. (2011), Moullin et al. (2016b), Proctor et al. (2011), Stekler et al. (1992), and Stetler et al. (2006).

In recent years, implementation science has focused heavily on the development and testing of implementation measures and large databases have been developed as repositories (Lewis et al., 2015; Rabin et al., 2012). Over 500 measures have been described. Literature reviews on implementation tools have been conducted, tools developed for particular implementation concepts (e.g. Stages of Implementation Completion), specific factors (e.g. implementation climate), theory suitable for formative evaluation of normalization and models of particular outcomes (e.g. implementation fidelity).

Formative evaluation is an assessment process designed to identify influences on the progress and effectiveness of implementation to guide ongoing tailoring of implementation strategies. Formative evaluation is often used as part of an audit and feedback implementation strategy and in quality improvement. Four progressive, integrated stages of formative evaluation are described by Stetler et al. (2006): (1) developmental evaluation prior to implementation to explore and assess current practice: determinants of current practice, barriers and facilitators to implementation, and feasibility and tailoring of implementation strategies; (2) process focused evaluation to monitor the progress; (3) implementation focused evaluation to reduce type III errors and enhance result analysis, assess modifiable barriers to refine implementation strategies, and assess innovation adaptation, critical components and/or strategies to replicate outcomes; (4) interpretative evaluations postimplementation to explain the summative implementation and innovation outcomes, assess evidence of the factors and strategies, develop tools for wider spread and scale-up, and develop hypotheses for future studies.

RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance), is one implementation evaluation framework that may be used to guide implementation science protocol design and measurement (Glasgow et al., 1999, 2005, 2006). This framework includes effectiveness testing (of the professional service and/or implementation program), in combination with reach (participation rate and representativeness of the participants), organizational measures of adoption (uptake by providers and organizations, including proportion and representativeness), implementation (quality, consistency and integrity of provision, and implementation cost) and maintenance of both health benefits in patients (or determinants of benefits such as behavioral changes) and changes in the organization in terms of integrating the service as routine. Another useful tool is the Stages of Implementation Completion (SIC), which may be used as both a formative and summative tool to measure the rate and depth of implementation (Chamberlain et al., 2011). It may be used to investigate which steps or strategies are essential for implementation success. These frameworks have been used to help guide the development of an evaluation model for implementation programs and pharmacy services as described in the next section.

Framework for the Implementation of Services in Pharmacy (FISpH)

For application in pharmacy practice, the Generic Implementation Framework (GIF) was contextualized and operationalized from the results of a qualitative study (Moullin et al., 2016a). The Framework for the Implementation of Services in Pharmacy (FISpH) demarcates the stages and activities of the implementation process, the contextual domains or ecological levels, implementation influences, tailored from the Consolidated Framework for Implementation Research (CFIR), and provides a

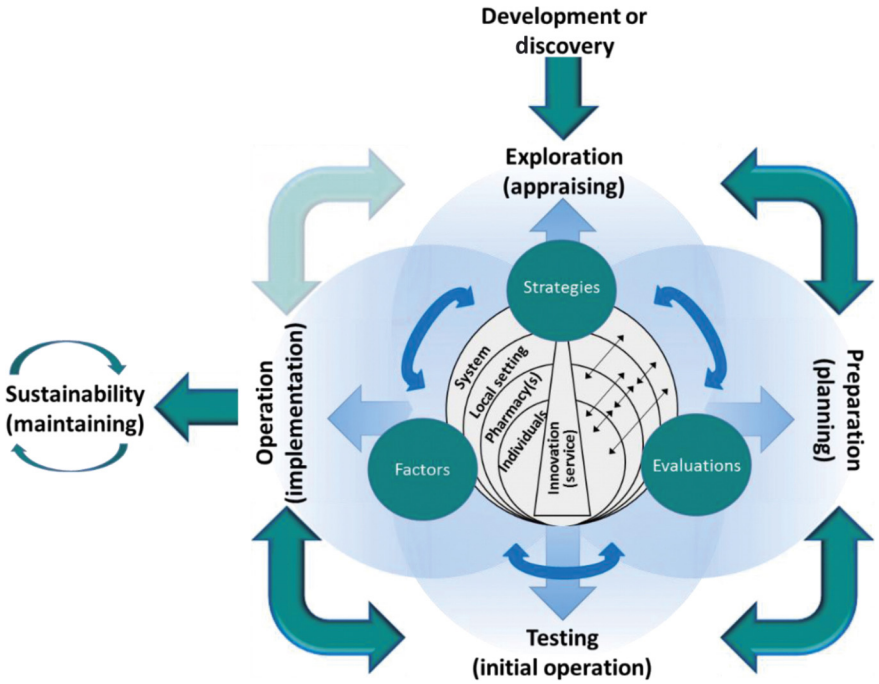

Figure 3 Framework for the Implementation of Services in Pharmacy (FISpH) (Moullin et al., 2016a).

model for evaluation of the service and the implementation program for pharmacy practice (Figs. 3–5). Other models or theories are currently required for selecting implementation strategies. Thus far the framework has been applied in Australia (Roberts et al., 2015), New Zealand (Pharmaceutical Society of New Zealand and New Zealand Medical Association, April 2017), Spain (Moullin et al., 2014), Belgium (Lelubre et al., 2018), Switzerland, and Mexico.

At the center of the framework is the innovation or professional pharmacy service to be implemented. A professional pharmacy service has been defined as "an action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population or other health professional, to optimize the process of care, with the aim to improve health outcomes and the value of health care" (Moullin et al., 2013).

Surrounding the professional pharmacy service to be implemented are the contextual domains specific to pharmacy practice, defined as:

- Individuals: the people involved in the implementation process including the pharmacy owner, the service provider (often a pharmacist), and other pharmacy staff such as technicians and assistants. It may also include individuals from the pharmacy group, such as a professional services manager, or external assistance sought to aid the implementation effort.
- Organization: the characteristics of the pharmacy or group of pharmacies.
- Local setting: the environment surrounding the pharmacy including patients, friends and relatives, clientele, the community and other health care professionals.
- System: the political and economic context, as well as the professional situation (such as the pharmacy bodies and the organizations of other health care professionals).

The process of implementation in the FISpH is divided into six stages. These stages are development or discovery, exploration, preparation, testing, operation, and sustainability. The preimplementation stage of development or discovery is where a pharmacy or pharmacy group internally develops a service(s) and/or discovers an externally developed service. Once a pharmacy is aware of a service they move into the exploration stage where they are deliberating or appraising the service, and deciding whether or not they want to take it up (adopt). If the decision is to go ahead, they move to preparation, where the pharmacy, pharmacist and all other factors are planned and primed for service delivery. The service is then trialed, by being delivered either for a short, defined period, with a limited number of patients, or by a single pharmacist, rather than the whole team. From here a pharmacy may move back into preparation stage to make improvements or move directly into the operation stage. The operation stage is the long process of integrating the service into routine practice. During this stage, staff need to gain confidence while trying not to revert back to their old habits and way of working. Finally, moving from operation to sustainability occurs when service delivery continues after a period of time or when any implementation program (or external assistance) has ceased. This displays that the service is integrated as a routine in the pharmacy, there is ongoing support and capacity, and outcomes persist both for the patients and the pharmacy business.

During the stages, a range of activities were exposed from interview data (Fig. 4) (Moullin et al., 2016a). The activities were *Exploration*: Organizational fit assessment, value assessment (relative advantage), service assessment (service characteristics), organizational capacity assessment (supporting conditions & staff capacity), community fit assessment, decision; *Preparation*: Assign leader, research requirements, organize supporting conditions, plan service procedure, rearrange workflow, staff arrangements, team communication (buy-in and foster climate), training, community awareness & recruitment; *Testing*: Initial adaptations, familiarization & improve staff conviction, test patient demand; *Operation*: Modification of plans & procedures, maintain patient demand, staffing, teamwork, team input and internal communication, integration tactics, ongoing training, goal setting, monitoring, adaptation, improvement; *Sustainability*: Few pharmacies had reached sustainability however activities were posited as continuing the last three activities of the operation stage: monitoring, adaptation and improvement.

The stages nor activities are not mutually exclusive, nor linear. There will be wide variation in the duration of stages, movement back and forth between stages, differences in the order of performing implementation activities and not all activities will be completed. The framework, however, provides a structure to the process and guidance on some useful activities to target for an implementation program [Fig. 4].

Analysis of the factors influencing the implementation of professional pharmacy services, revealed five influences that affected all stages of the implementation process: a pharmacy's direction and impetus, internal communication, staffing, community fit and support. However, many other factors influence the process profoundly at various stages. A refined list of the implementation factors for community pharmacy has been developed and published (Moullin et al., 2016a). This adaptation of the Consolidated Framework for Implementation Research for pharmacy practice provides a typology of influences that can be used to code qualitative studies and to develop implementation hypotheses, models, and measures.

Conceptual frameworks are a perpetually evolving through revisions and enhancements. In addition, it is possible to contextualize and adapt frameworks for individual situations, such as further dividing the context domains depending on the desired analysis and research question. As an example, the domain of the local setting surrounding a pharmacy may be split into three subdomains: patients, community, and local health care professionals. Adaptations may also be required as pharmacies within and across countries will show cultural and contextual differences. For example, compared to Australia, Spanish pharmacies are commonly owned by single proprietors, who can only own one pharmacy, are smaller in size and have longer employer tenure. Therefore, an example of theoretical adaptation would be removing "team" based strategies or evaluations as they may not be applicable or suitable for Spanish pharmacy settings.

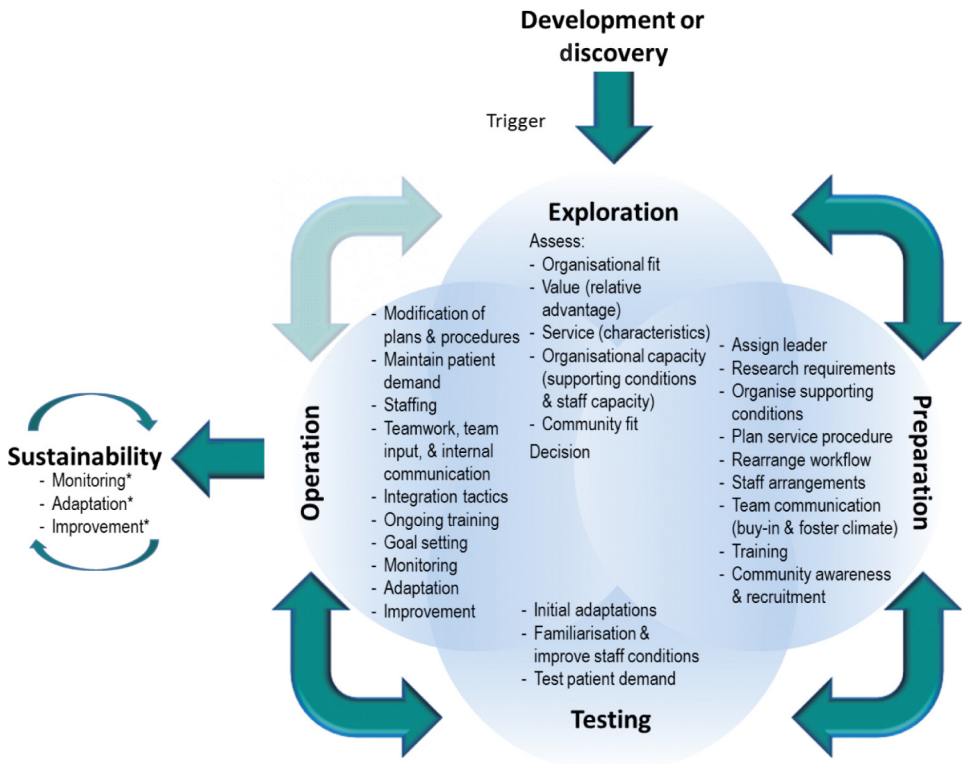

Figure 4 Implementation process of the Framework for the Implementation of Services in Pharmacy (FISpH) (Moullin et al., 2016a) *Source: Reproduction of Figure 4 has been granted by Elsevier.*

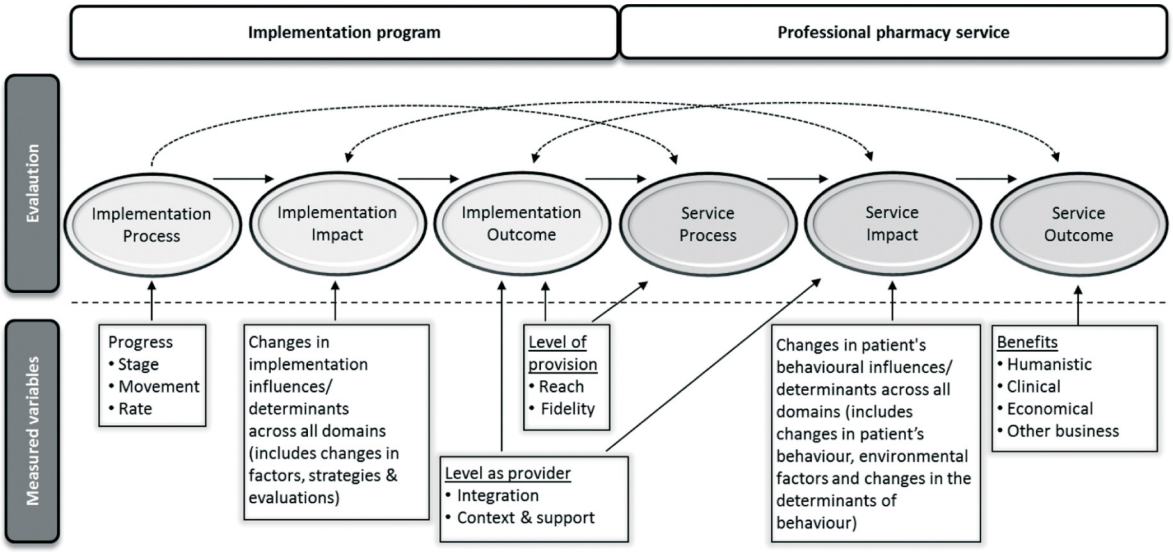

Figure 5 Model for the evaluation of implementation programs and professional pharmacy services (reprinted from Research in Social Administrative Pharmacy, Vol 12, Moullin, J. C., Sabater-Hernández, D. & Benrimoj, S. I. Model for the evaluation of implementation programs and professional pharmacy services, pages no. 515-522, 2016, with permission from Elsevier)

Note: Domains are the divisions or categories of the implementation influences and determinants of a patient's behavior, they include characteristics of the service being implemented, and the context (individuals, organization/pharmacy, local setting and system).

Model for the Evaluation of Implementation Programs and Professional Pharmacy Services

Based on the FISpH and implementation science literature (Carroll et al., 2007; Glasgow et al., 1999; Lehman et al., 2011; Proctor et al., 2011; Slaghuis et al., 2011; Steckler et al., 1992) a model for the evaluation of implementation programs and professional pharmacy services was developed (Fig. 5) (Moullin et al., 2016b).

The evaluation model involves indicators for both implementation process, impact, and outcome evaluations as well as service process, impact and outcome. The model recognizes evaluations for implementation, including indicators of (1) movement through the implementation stages (formative and summative implementation process evaluation), (2) influencing factors and changes in factors over-time (implementation impact), and (3) overall measures of implementation (implementation outcomes). The arrows indicate the flow of effect, while the curved arrows hypothesized relationships between the implementation and service evaluations.

The evaluation model may be used to evaluate the level of implementation by assessing the level of service delivery (reach and fidelity) and the level as a service provider (integration and strength of support in the service environment). The level of service provision may be described as "how much and how well" the service is performed, while the level as a service provider explains the extent to which the service is integrated into the pharmacies' principles and practice, their capability, and the support throughout the service environment.

Pharmacy practice research has been heavily focused on patient outcomes and cost-effectiveness in a bid to gain recognition and remuneration for professional services. As such, studies have needed to be conducted in controlled conditions, often prior to real-world implementation. Exacerbating the issue is poor monitoring within the pharmacy profession (Australian National Audit Office, 2015; Patwardhan et al., 2014). This combination has led to governments pushing for an increase in implementation and impact evaluations, both within academic research proposals and reports, and by the profession. To conduct implementation research, quality assurance, performance assessment and impact evaluations, evaluation models and practical tools to assess implementation indicators should be used.

Implementation Science Research Methods

The objective of implementation science is to understand the mechanisms required to improve adoption, utilization, sustainment, and scale-up. This has been described as seeking 'to understand the processes and factors that are associated with successful integration of evidence-based interventions within a particular setting' (Rabin et al., 2008, p. 119). It therefore can be seen that dissemination and implementation research addresses different questions to clinical research. Implementation research is specific for researching the effect of implementation strategies and programs, while health services and clinical research revolve around developing health innovations and clinical interventions, and studying the efficacy and effectiveness of such interventions. In other

words, implementation science is focused on the processes, influences and outcomes of implementation, rather than the processes, determinants or outcomes of the innovation. The study of implementation strategies needs to be scientifically tested, as would a clinical intervention. A group has been formed at the Cochrane Institute to evaluate the effectiveness of implementation strategies (Cochrane Effective Practice and Organisation of Care Group, 2010).

To produce rigorous implementation evidence study designs, tools and analyses need to relate to implementation objectives and indicators. A prerequisite for this to occur is for implementation strategies to be recorded and reported in detail as would clinical interventions (Bartholomew et al., 2011; Michie et al., 2009; Proctor et al., 2013). This also will facilitate future replication, comparison and assessment across studies. Proctor et al. (2013) describe the principles of naming, conceptually defining, and specifying (actor, action, target, temporality, dose, implementation outcome affected, justification) to operationalize and contextualize implementation strategies. Ideally, implementation strategies should follow an evidence path, from theory building to phase I modeling, Phase II exploratory studies before phase III implementation and phase IV sustainability trials (Eccles et al., 2005).

External validity and generalizability are central to implementation science as the research addresses the introduction and integration of innovations within real-world, complex, service systems. While in many health service fields, including pharmacy practice research, internal validity has been emphasized in order to look at the extent to which the innovation produces an effect. This has led to the reliance on randomized control trials (RCTs), testing in restricted populations with narrow interventions, and meta-analyses that exclude nonrandomized trials to strengthen causal inference. Subsequently, moving innovations into diverse settings became a haphazard process as was unknown if the innovations would be feasible, or even if they would produce the outcomes shown in the controlled setting (Eccles et al., 2009). The Consolidated Standards of Reporting Trials (CONSORT) statement recommends researchers summarize the extent a study is pragmatic versus explanatory to increase the external validity data available for systematic reviews (Zwarenstein et al., 2008), and the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) has been developed to provide guidelines (Loudon et al., 2015). In addition, the extended Consolidated Standards of Reporting Trials statement (CONSORT statement) includes recording recruitment (reach) and maintenance (sustainability) details (Calvert et al., 2013). It follows that future pharmacy practice research should also consider the addition of reporting implementation indicators and outcomes.

Study Design

The overall implementation research process mimics efficacy and effectiveness research. Similarly, the use and reporting of theory to guide implementation research is recommended. Study designs for implementation research include an array of experimental, quasi-experimental/observational, alternative randomized (staging), hybrid (effectiveness-implementation combination designs), adaptive protocols, and designs that allow for collaboration with stakeholders (Brown et al., 2017). While RCTs and cluster RCTs predominate implementation research (Mazzucca et al., 2018), alternative designs offer advantages. For example, the interrelationships within and across social-ecological levels require novel study designs that offer flexibility during innovation development, dissemination and implementation (Lindamer et al., 2009; Mendel et al., 2008).

Experimental Design

Although RCTs are possible and suitable for some implementation research studies, there are some issues that should be considered. These issues include the unit of observation, possible contamination, breakdown of randomization, and statistical power. Furthermore, in implementation research, randomization may be precluded by ethical, legal, practical, or policy concerns.

Quasi-experimental and/or Observational Design

Quasi-experimental and/or observational study designs are often suitable for conducting implementation research as external validity is prioritized. These designs may be useful when randomization is not feasible or appropriate. In addition, they may provide useful information on the implementation context. Three types of quasi-experimental and/or observational designs are frequently used in implementation science to enable causal inference: controlled before and after study, interrupted time series, and regression discontinuity designs.

Controlled before and after study designs involve non-randomized allocation of intervention and control site/groups and the measurement of outcomes preintervention (baseline), and postintervention. Pre- and postintervention periods for intervention and control sites should be equivalent, and comparable sites should be selected based on their characteristics, script volume, setting, staffing, patient population, etc. Two sites are a minimum.

Interrupted time series designs involve measurements of the outcome variable at equally spaced intervals (i.e., daily, monthly, annually) over a long period of time. An innovation and/or implementation strategy is introduced at a specified point in time and is expected to affect the outcome variable(s), often indicated by a change in slope of the outcome measured over time, as a function of the innovation and/or implementation strategy being introduced.

Regression discontinuity design is where a clinical intervention or implementation strategy is assigned based on a cut-point on a quantitative measure. For example, the number of medication reviews a pharmacy completed in the previous three months may be used to assign pharmacies to the intervention or control implementation strategy conditions. In this case, it may be that pharmacies who conducted less than 15 reviews would be assigned to a tailored implementation strategy, whereas those who performed more

than 15 reviews are assigned to an implementation-as-usual control condition. The outcome of interest could be the number of medication reviews performed in the next 3 months as a function of implementation strategy condition.

Alternative Randomized Design

Traditionally, implementation occurs as the final stage of the translational evidence pipeline. This depiction although still prevalent, has received criticism, and led to more integrated approaches and consequently, alternative research study designs. In addition, as discussed previously to address concerns regarding generalizability designs that attempt to increase the strength of external validity while maintaining the strength of internal validity are common in implementation research.

Effectiveness-implementation hybrid study designs are one alternative randomized design where both implementation and clinical data are gathered (Curran et al., 2012). Hybrid designs are categorized into three types. Type 1 hybrid designs occur when the primary outcomes collected relate to the clinical effectiveness of the clinical intervention/innovation, while secondary data are collected on implementation. In type 2 hybrid designs equal emphasis is placed on clinical effectiveness and implementation. Finally, in type 3 hybrid designs the primary focus is investigating the implementation strategy and thus primary outcomes are implementation indicators, while secondary information is collected on the clinical intervention's impact.

Roll-out designs, such as the stepped wedge design, are another useful alternative design to RCTs. In these designs, all pharmacies/pharmacists would begin the study simultaneously, either all receiving an implementation strategy or continuing practice as usual. Next, at randomly assigned time intervals, pharmacies would cross over to a new implementation strategy/condition, resulting in between-unit (comparing those with practice as usual versus the implementation strategy) and pre-post within unit comparisons, at each time point.

Other alternative design options include: *Cumulative trial designs* which aim to improve intervention impact evaluation by combining a sequence of trials or replicate cohorts to increase statistical power; *Randomized encouragement trial and the randomized consent design* where participants are randomized to condition, but are offered the option to adhere to their assigned condition or switch to a preferred condition, in an attempt to strengthen external validity; *Randomized factorial designs* test combinations of two or more implementation strategies (experimental conditions) and two or more variations/levels of each implementation strategy simultaneously. For example, a 2×2 factorial design may test the implementation strategies of consultation type, with remote and in-person consultation as distinct variations, and feedback, with monthly versus as-needed variations. Pharmacies would be randomly assigned to one of the four conditions; *Sequential Multiple Assignment Randomized Trial (SMART) designs* are a type of factorial design that accommodates participant responses. For example, pharmacies that do not respond to an implementation strategy may be randomized to receive additional support from an external facilitator or both an external and internal facilitator. Then pharmacies which were randomized to receive an external facilitator only, and are still unresponsive, may be randomized again to continue with only an external facilitator or both the external and internal facilitators (Kilbourne et al., 2014).

Stakeholder Involvement

The involvement of stakeholders in all stages of research is strongly encouraged in implementation science. It is recommended that developers consider methods such as community-academic partnerships, stakeholder mapping, social network analyses, intervention mapping and/or participatory action research in their methodologies to engage stakeholders and to design services and innovations that are feasible, implementable and produce relevant outcomes for all parties.

Data Collection

The types of data collected in implementation studies emulate efficacy and effectiveness research, although a greater emphasis is placed on mixed methods where quantitative and qualitative data are combined. Mixed method designs achieve a depth of understanding often unobtainable if one approach or data source was used alone. For implementation research, mixed method designs offer particular advantages of contextualizing and understanding nuances in the implementation process, such as identifying and understanding implementation influences (facilitators and barriers), explaining implementation outcomes, and assessing the feasibility, acceptability, and utility of an innovation and/or implementation strategies.

Understanding the unique combination of factors influencing implementation in each context is crucial to implementation research. Surveys, completed either by respondents about themselves or their actions (self-report), or asking about their perceptions on a different person or phenomena, are a common collection method. However, qualitative data, as the sole data collection method or in combination, is beneficial to evoke multifaceted, rich responses, that may be unforeseen by the researcher and are needed to understand the diverse perspectives of stakeholders across settings. Furthermore, the use of mixed methods has been recommended "to enhance the value of implementation research for end users" (Neta et al., 2015). As an example, for the implementation outcome fidelity, the degree to which an innovation is delivered as it was designed or intended, it is important to consider how to collect the data. Fidelity may be evaluated in multiple ways such as quantitatively by surveys or clinical documents, or qualitatively via interviews or direct observation. Qualitative approaches may be more reliable and increase the depth of information, yet are often costly.

A distinguishing feature of implementation research is that the data includes indicators of implementation process, influences and/or outcomes, either with or without collection of economic, clinical or humanistic outcomes. Moreover, implementation outcomes may serve as intermediate outcomes to health outcomes (Moullin et al., 2016b). For instance, "reach" defined as the

absolute number, percentage and representativeness of an eligible population who receive an innovation, is both an implementation outcome and an output necessary to determine the impact of a clinical intervention (Glasgow et al., 2006).

One issue that should be considered in collecting data for implementation research in pharmacy practice is the "level" of the data. Implementation data is commonly multilevel as all contextual levels (e.g. pharmacist, pharmacy staff/team, pharmacy, local setting, and system) may influence the implementation effort. Therefore, the referent level of the data to be collected should be carefully decided. As an example, in an investigation on the implementation of a new asthma guideline, data may be collected from the pharmacist, pharmacy staff and/or patients. This data may be regarding their attitudes toward the guideline but equally it may be useful to evaluate the pharmacy team's functioning, the workflow of the pharmacy or their perceptions of asthma prevalence etc.

Finally, to cultivate implementation evidence, the timing of data collection needs to be consciously chosen. As implementation is a multistage process, ideally implementation indicators should be collected at multiple time-points. It is also encouraged to collect implementation data during effectiveness studies as this will increase knowledge on the mechanisms of action of the intervention and generalizability of findings.

Data Analysis

Evaluating complex interventions such as health programs and professional pharmacy services is challenging. There is rarely a single outcome or stakeholder, but a large number of groups and individuals with an interest and consequently a large pool of potential measures of success. Funders are often interested in "reach," wanting to know the number of participants and if the service has reached those most in need. Program developers may be interested in milestone attainment such as the level of "adoption" and "implementation". These measures may be further augmented by indicating if practitioners accept the innovation and subsequently use the innovation with fidelity. To correctly attribute observed outcomes of an innovation to those achieved in efficacy or effectiveness studies, the researcher should have empirical evidence on the extent to which innovation components were implemented, known as the degree of fidelity. Only by understanding and measuring whether an intervention has been implemented with fidelity can researchers and practitioners gain a better understanding of how and why an intervention works, and the extent to which outcomes can be improved.

As with data collection, data analyses in implementation science largely mimic that of efficacy and effectiveness research. However, some considerations are more pertinent due to the increased use of alternative research designs. Firstly, statistical methods to enhance internal validity and reduce inferences being made because of differences between groups in nonrandomized designs, such as covariate analysis, propensity score analysis, and sensitivity analysis, may be beneficial. Secondly, mediation, moderation, and path analyses, as well theoretical process evaluation techniques, are often employed. Finally, as data collected is often multilevel, statistics to analyze the nested structure of data are needed. Common techniques include intra-class correlation coefficient (ICC) and within group agreement (rwg and rwg(j)) analyses. If a nested data structure is present and aggregating data to a higher level is indicated data analyzes such as multilevel modeling and multilevel structural equation modeling are useful methods for assessing quantitative data.

Pharmacy practice research needs to disentangle the effectiveness of implementation strategies. As with complex clinical interventions with patients, implementation strategies are complex interventions with pharmacists or other stakeholders across the ecological contextual domains. Therefore delineating the core components of implementation strategies is an area requiring attention. One method being used to analyze implementation is realist evaluation. This approach is based on program theory where the focus is on studying the mechanism or the response implementation strategies trigger in stakeholders, and the resulting outcome (Dalkin et al., 2015). Realist evaluation investigates the causes, mechanism and factors associated with an outcome, rather than just the outcome, and therefore is an approach targeting the questions that consume implementation "what works, for whom, in what circumstances?" (Salter and Kothari, 2014, p. 2)

Summary

EBP, programs and services must be widely available and offered to achieve improved economic, humanistic and clinical health outcomes. Internationally professional pharmacy services and health innovations are being developed, disseminated and being implemented into pharmacy practice; however, there appears to be a pervasive challenge to achieving timely implementation, widespread incorporation and sustainment. Both a lack of implementation research and the compartmentalized nature of research in other stages of the evidence pipeline may be implicated. Implementation science aims to increase the evidence base on the process and influences affecting implementation including the support required to assist pharmacy practice move services into reality. Conducting implementation studies, using implementation frameworks and models, employing suitable research methodologies, and assessing implementation indicators may assist community pharmacy move toward the ultimate goal of integrated service provision and improved health outcomes for the communities they serve.

Endnote: Sections of this chapter have been modified from the doctoral thesis "Implementation in community pharmacy: development of frameworks, models and tools for the introduction and integration of professional services," stored in the online library repository of the University of Technology Sydney.

Glossary

Implementation science The scientific study of the influences and mechanisms that promote the systematic uptake, utilization and integration of innovations and research findings into routine practice.
Implementation process The progression of commencing to use and integrating a novel innovation. The implementation process consists of multiple nonlinear, recursive phases.
Implementation factors Variables that influence the implementation process, either positively or negatively. Also termed facilitators and barriers, influences, or determinants of practice. Factors may be grouped as domains of related implementation influences across contextual levels.
Implementation strategies Targeted efforts (methods, techniques or activities) to enhance the movement of an innovation into use and integration into routine practice. Packages of implementation strategies form an implementation program.
Implementation evaluations Indicators of the effects of implementation efforts including both formative and summative evaluations of the implementation process, impact (mediator and moderator analyses), and outcomes.

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Proctor, E., Silmere, H., Raghavan, R., et al., 2011. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm. Policy Ment. Health 38 (2), 65–76.

List of Relevant Web Pages

The Society for Implementation Research Collaboration (SIRC): https://societyforimplementationresearchcollaboration.org/
Global Implementation Initiative (GII): https://globalimplementation.org
Implementation Science, journal: https://implementationscience.biomedcentral.com/
European Implementation Collaborative: http://www.implementation.eu/
Knowledge Translation Canada: http://ktcanada.net/
Centre for Implementation Science (UK): http://www.clahrc-southlondon.nihr.ac.uk/centre-implementation-science
National implementation research network (USA): http://nirn.fpg.unc.edu/
Centre for Dissemination and Implementation (USA): https://publichealth.wustl.edu/centers/dissemination-implementation/
Human Behaviour Change Project (UK): http://www.ucl.ac.uk/human-behaviour-change
RE-AIM: http://www.re-aim.org/

Network Meta-Analysis in Pharmacy Practice Research

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Introduction

Using best evidence in decision making is crucial in health care. Randomized controlled trials (RCTs) are typically considered to provide high-quality empirical information. They are the standard approach to evaluating efficacy of medications, interventions, and services in a controlled condition. Randomized controlled trials compare one or more standard treatment or placebo (control arms) with one or more alternative/new treatments (intervention arms) by randomizing treatment allocation to minimize bias and confounding. Nonetheless, comparing multiple treatments by conducting a large RCT with multiple arms or a mega-trial is difficult to conduct and require greater resources (Shrier et al., 2007). They are also complex in design, analysis, and reporting (Baron et al., 2013).

In addition to RCTs, systematic review and meta-analysis are considered to produce high-quality evidence by summarizing empirical evidence from previous studies (e.g., RCTs). Meta-analysis is a statistical tool used in a systematic review to provide summarized quantitative evidence. Traditional meta-analysis (pairwise meta-analysis) of RCTs generates pairwise comparisons or comparing two treatments at a time. Comparing treatments in a pair but not simultaneously in a traditional meta-analysis limits its ability for decision making. Therefore, statistical techniques that are able to compare all treatments simultaneously are needed, and network meta-analysis (NMA) addresses this problem.

Network Meta-Analysis

Concept

Network meta-analysis (NMA) is also called indirect comparison, multiple treatments meta-analysis, and mixed-treatment comparison (MTC) and is a new statistical tool to compare and rank multiple treatments at a time (Salanti, 2012). Conceptually, NMA creates a network of multiple pairwise-comparison analyses and calculates relative effects between different treatments from direct comparisons found in studies (mostly from RCTs). This also indirectly makes comparisons through one or several common comparators. A common comparator is an anchored arm served as a linkage to enable all treatments, which are not compared directly in studies to be compared indirectly. For example, if there is a trial comparing treatment A versus treatment B and a trial comparing treatment B vs treatment C, treatment B is a common comparator. Most common comparators are placebo or a standard treatment. A comparison between treatments that is not done directly by experiment but through a statistical method is referred as an indirect comparison. Network meta-analysis needs at least three treatments in a network. Network meta-analysis connects control arms and treatment arms together based on a selected collection of RCTs.

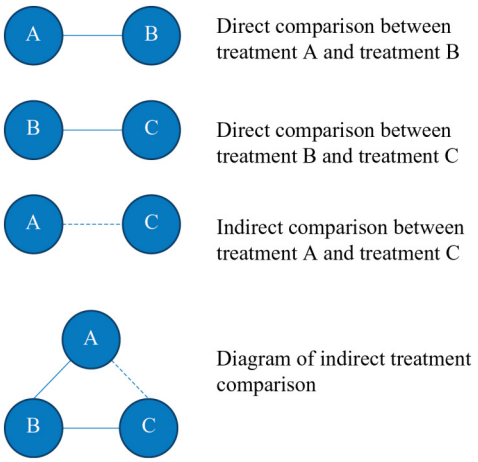

Figure 1 Examples of evidence networks.

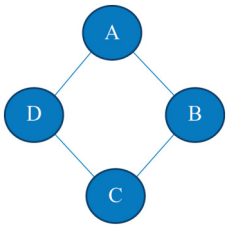

Figure 2 A closed-loop network.

History

Historically, the first model of NMA was the indirect treatment comparison (ITC), and it was proposed by Bucher et al. (1997). The model explains that if treatment A is directly compared with treatment B and treatment B is directly compared with treatment C from RCTs, an indirect comparison between treatment A and treatment C via treatment B can be performed by a statistical method. In other words, the ITC of treatment A and treatment C is anchored on treatment B or linked through treatment B. Fig. 1 shows the diagram of the aforementioned direct and indirect comparisons of treatments A, B, and C; a node represents a treatment and a line means a direct comparison or a head-to-head comparison obtained from RCTs. A dashed line represents the indirect treatment comparison between A and C.

Thomas Lumley published an article in 2002 to present ITC methods and to address the problem of differences in treatment effects estimated from ITCs when there are multiple sources of information (Lumley, 2002). Lumley created a diagram of networks of evidence from RCTs, hence coined the term NMA. Fig. 2 shows an example of a closed-loop NMA where there are direct comparisons between A vs B, B vs C, C vs D, and D vs A. The indirect comparison of AC can be obtained through B or D. When there are multiple pathways in a closed-loop NMA to estimate indirect treatment effects, it is possible that these estimates differ or disagree.

Subsequently, Lu and Ades further developed a method to combine relative effects from both direct comparison from RCTs and indirect comparison in NMA (Lu and Ades, 2004). Due to this combination, it is called MTC. This type of NMA particularly helps to add to direct-comparative evidence and allow simultaneous comparison of all treatments and ranking.

Fundamentals of Network Meta-Analysis

Based on the history, NMA can be categorized into two groups (Fig. 3). First, ITC is referred to open-loop networks or star-shaped networks (treatments are compared with a standard treatment/placebo but not with each other). Second, MTC contains at least one closed-loop network of evidence (Jansen et al., 2011; Tonin et al., 2017).

Using the network of evidence from Fig. 3A, a relative effect of ITC between treatment A and treatment C is calculated from the difference between the relative effect of treatment A vs B and the relative effect of treatment B vs C (Chaiyakunapruk et al., 2014). Suppose $D_{AB\text{-}direct}$ represents the relative effect of treatment A compared with treatment B from a study, and $D_{BC\text{-}direct}$ represents the relative effect of treatment B compared with treatment C from a study. Then, $D_{AC\text{-}indirect}$ represents the indirect effect of treatment A compared with treatment C in Eq. (1).

$$D_{AC-indirect} = D_{AB-direct} - D_{BC-direct} \quad (1)$$

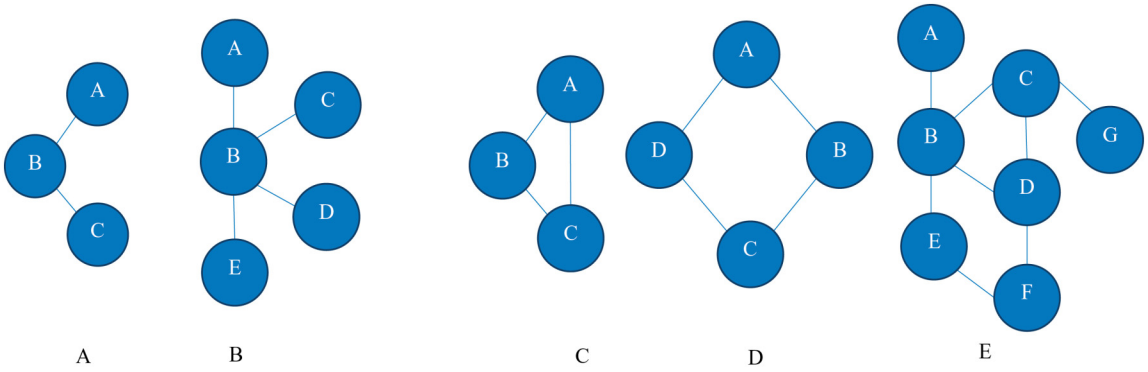

Figure 3 Open-loop networks and closed-loop networks.

Fig. 3C is a closed-loop network of evidence where there are direct comparisons of AB, BC, and AC. The pooled relative effect of treatment A vs treatment C is weighted from both direct and indirect comparisons (Chaiyakunapruk et al., 2014). Suppose $D_{AC\text{-}direct}$ represents the direct relative effect of AC from an RCT, and $D_{AC\text{-}indirect}$ represents the indirect relative effect of treatment AC from Eq. (1). $W_{AC\text{-}direct}$ represents the weighted relative effect of $D_{AC\text{-}direct}$ calculated by an inverse variance of studies, while $W_{AC\text{-}indirect}$ represents the weighted relative effect of $D_{AC\text{-}indirect}$ calculated by an inverse variance of the indirect comparison. $D_{AC\text{-}pooled}$ is the relative effect derived from both direct and indirect comparisons and is shown in Eq. (2).

$$D_{AC-pooled} = \frac{(W_{AC-direct} * D_{AC-direct}) + (W_{AC-indirect} * D_{AC-indirect})}{(W_{AC-direct} + W_{AC-indirect})} \quad (2)$$

Assumptions of Network Meta-Analysis

Two assumptions, namely transitivity and consistency assumptions, are required in NMA to provide valid results. Transitivity is defined as being able to apply in a successive object of a sequence. For example, if treatment A is better than treatment B and treatment B is better than treatment C, then treatment A will be better than treatment C. In NMA, transitivity is the ability to apply an indirect comparison through a common comparator. Transitivity assumption (or similarity assumption in some literature) aims to state that this indirect comparison is valid. Transitivity assumption cannot be tested quantitatively. It needs to be carefully examined by both logic and similarity in study characteristics (Salanti, 2012). To explain, studies that are included in systematic review and meta-analysis need to be similar in terms of effect modifiers. Effect modifiers are defined as factors that affect study outcomes, and these include study design, study population, treatments, and outcome measures. It is best to have homogeneous study characteristics and if not the level of heterogeneity should be similar across pairwise comparisons. Consistency assumption requires that the relative effects from the direct evidence are aligned with those obtained from the indirect evidence.

Analytical Methods

To conduct an NMA, a general process involves writing a research and statistical analysis plan, conducting a systematic review, creating networks of evidence, carrying out statistical analysis for checking assumptions and estimation, evaluation of quality of NMA results, and reporting.

Network meta-analysis can be performed by using either frequentist or Bayesian approach to give a point estimate of relative treatment effect. The effect measures commonly used in NMA are relative measures such as odds ratios (ORs), relative risk (risk ratios) (RRs), difference in change from baseline or hazard ratios (Jansen et al., 2011). In addition to the effect measures, rankings of treatments can be generated by both approaches (Jansen et al., 2008; Rucker and Schwarzer, 2015).

Frequentist approach is a traditional way in which statistical hypothesis testing and confidence intervals are carried out. It takes the sample data to test against the null hypothesis stating that treatment effect is null for all studies by using the probability calculated from the sampling distribution compared with the predetermined significance level (e.g., 0.05). Probability in frequentist approach is viewed as a fixed value. On the other hand, Bayesian approach considers probability as likelihood that is expressed prior to a trial, and then it is updated after gaining more information from the trial.

Bayesian probability takes into account of both prior information, which can be taken from opinion or previous studies and empirical data. Due to the differences in probability view when compared with frequentist approach, Bayesian approach treats treatment effects obtained from RCTs as random variables, which require prior probability distributions. Bayesian approach is

done by using Markov Chain Monte Carlo simulation. The simulation creates a random sample by taking a value of a parameter (e.g., treatment effect) from a specified prior probability distribution and calculates a result. The simulation is repeated in a predefined number of times (e.g., 1000 times), and eventually an aggregate result of each random sample is produced (Salanti, 2012).

Several methods attempt to detect and improve consistency in NMA. Investigators should put effort to explain observed inconsistency and explore the causes. Inconsistency can be detected by comparing estimates or posterior distributions using statistical tests (Hoaglin et al., 2011).

Critical Appraisal of Network Meta-Analysis and Findings

Evaluating quality of NMA results is very important because simply looking at statistical results such as odds ratio or ranking from NMA results without any judgment can be misleading. For example, teriparatide is concluded to be the best treatment for reduction in bone fracture by the statistical numbers; however, when applying quality assessment on NMA, it shows that the quality of this information is very poor (Puhan et al., 2014). Decision makers, especially clinical guideline developers, policy makers, and clinicians, need to assess quality of NMA studies prior to making decisions.

Several guidelines of NMA reports are available to assist NMA appraisal. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides a checklist to evaluate an NMA (Jansen et al., 2011). The checklist suggests what to look for in an NMA article and to examine essential components. The PRISMA-NMA extension was published in 2015, and it provides guidance for reporting systematic reviews comparing multiple treatments using direct and indirect evidence in a network meta-analyses (Hutton et al., 2015).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group devised a guideline to rate quality of evidence in NMA into four levels including high, moderate, low, and very low reflecting a degree of confidence of how the true effect lies close to the estimate of the effect (Puhan et al., 2014). Further detail and examples can be found in the literature (Puhan et al., 2014; Salanti et al., 2014).

Reporting and Interpreting Results

This section focuses on report on network geometry, consistency and transitivity assumptions, relative treatment effects, and treatment rankings.

Network geometry is strongly recommended to present in NMA results (Hutton et al., 2015; Mills et al., 2012). Network geometry is a network graph or a network plot showing the interactions among the articles included in NMA. An NMA graph provides important information in establishing analytic strategies and interpreting the results such as the presence of direct or indirect evidence. The directly compared interventions are linked with a line. The size of the nodes and the thickness of the lines are weighted according to the number of studies assessing each treatment. An example of network geometry is shown in Fig. 4 (Kengkla

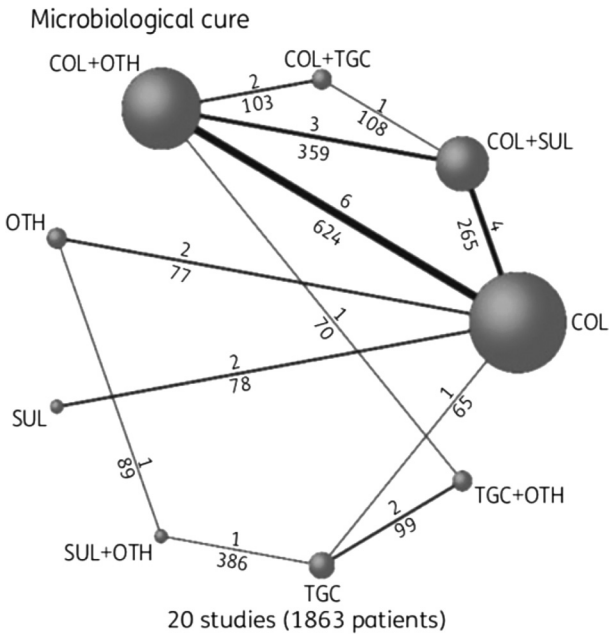

Figure 4 Network comparisons of studies included in the analyses for the microbiological cure outcome. The numbers above and below the lines indicate the number of studies and the number of patients, respectively. *COL*, colistin; *OTH*, other antibiotics; *SUL*, sulbactam; *TGC*, tigecycline (Kengkla et al., 2018).

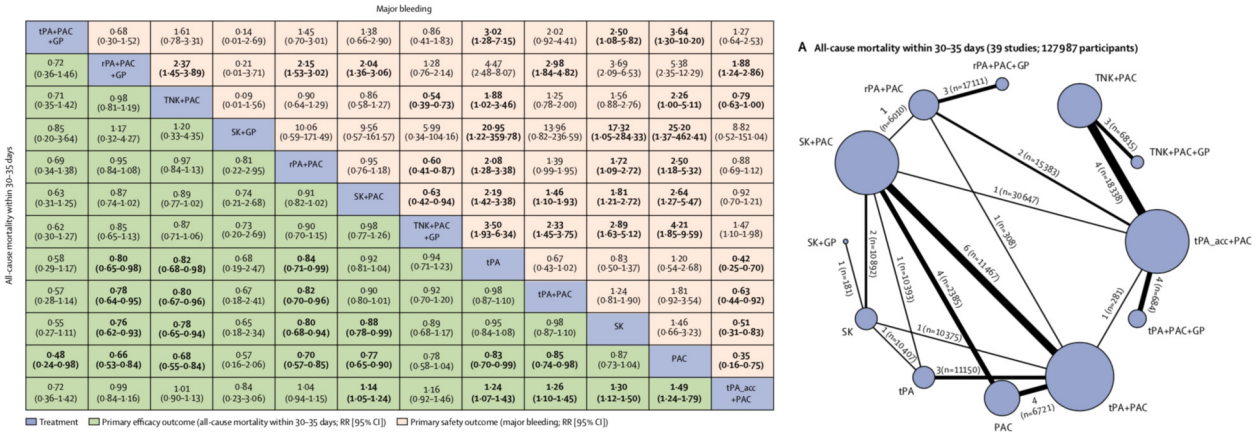

Figure 5 NMA results (on the left) of primary efficacy (all-cause mortality within 30–35 days) and safety (major bleeding) with the network geometry (A; on the right). Interventions (in violet color) are ordered by ranking for all-cause mortality within 30–35 days. Results are the RRs (95% CIs) for all-cause mortality within 30–35 days (green) and major bleeding (pink). Comparisons must be read from left to right. The text in bold represents statistically significant results. *tPA*, alteplase (nonaccelerated infusion); *PAC*, parenteral anticoagulants; *GP*, glycoprotein IIb or IIIa inhibitors; *rPA*, reteplase; *TNK*, tenecteplase; *SK*, streptokinase; *tPA_acc*, alteplase (accelerated infusion); *RR*, risk ratio (Jinatongthai et al., 2017).

et al., 2018). In this figure, 1863 patients from 20 studies were included in the network and used for performing both direct and indirect comparisons. This network has nine interventions including colistin, colistin plus sulbactam, colistin plus tigecycline, colistin plus other antibiotics, tigecycline plus other antibiotics, tigecycline, sulbactam plus other antibiotics, sulbactam, and other antibiotics.

Consistency and transitivity assumptions are also another important area of NMA because the validity of results in an NMA relies on the assumptions made (Salanti, 2012). Inconsistency can arise from effect modifiers such as baseline patient characteristics. An example of patient characteristics reported in an NMA study is shown in **Table 1** (Bunmark et al., 2018). This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distributions of potential effect modifiers across trials.

Treatment effects or effect sizes reported in relative measures such as ORs, RRs, or mean difference with 95% confidence intervals (CIs) for frequentist approach or 95% credibility intervals (CrIs) for Bayesian approach are usually presented in a league table (Jinatongthai et al., 2017). As exhibited in **Fig. 5**, the network geometry shows 12 interventions, and the reference regimen is tPA_acc + PAC. Both direct and indirect comparisons were performed, and the combined results were presented in the league table. Based on the league table, comparisons between treatments must be read from left to right such as a comparison of tPA + PAC + GP versus rPA + PAC + GP. This example shows the negative outcomes including all-cause mortality (the lower part of the table) and major bleeding (the upper part of the table). Therefore, the RR less than 1 means that the left-hand-side treatment produces fewer negative outcomes, whereas the RR more than 1 means that the left-hand-side treatment produces more negative outcomes. For instance, the RR of PAC versus tPA_acc + PAC for the all-cause mortality is 1.49 (95%CI: 1.24–1.79). It means that the all-cause mortality from PAC is statistically significant and is 1.49 times more than that from tPA_acc + PAC.

By Bayesian approach, interpretation of 95% CrIs is similar to that of 95% CIs, but it is in terms of probability. For example, if the RR of treatment A versus B is 0.40 (95% CrI: 0.10, 0.70), it means that the probability of treatment A is 40% less likely to produce an outcome compared with treatment B and there is a 95% chance that the true likelihood will be between 10% and 70%.

In addition to a league table, NMA results can be presented in a forest plot (**Fig. 6**). The interpretation of the results is similar to those from traditional meta-analysis by illustrating the relative treatment effects of each pair. In **Fig. 6**, the RR of OCA compared with placebo is statistically significant and is 1.91 times higher than the placebo (Sawangjit et al., 2016).

Clinicians and pharmacists should carefully interpret results of rank orders and use the information with caution when making decision analyzing both clinical and statistical significance.

In addition to report rankings by such as efficacy of treatments, cluster rank plots can simultaneously portray rank positions based on multiple aspects such as risk (e.g., a side effect) against benefit (e.g., efficacy of treatment). **Fig. 7** depicts the scatter plot based on reduction in mortality presented in terms of risk of mortality on the graph (representing benefit) and risk of major bleeding (representing risk) (Jinatongthai et al., 2017). Based on this figure, treatment options in the lower left quarter comprising tenecteplase (TNK) plus parenteral anticoagulants (PAC), reteplase (rPA) plus PAC, and alteplase accelerated infusion (tPA_acc) plus PAC should be recommended in patients with myocardial infarction. This is because these regimens show the reduction in mortality and the low major bleeding. Also, among these three treatments, TNK plus PAC is preferred because it has the lowest risk of bleeding with the similar efficacy.

Table 1 Characteristics of participants of included RCTs (Bunmark et al., 2018)

Study group/First author	*Regimen*	*Age (year)*		*Male (%)*	*DM (%)*	*HTN (%)*	*DLP (%)*	*Smoking history (%)*	*Previous MI (%)*	*Previous PCI (%)*	*CKD (%)*	*Bleeding history (%)*	*Ejection Fraction (%)*	
WOEST (Dewilde et al., 2013)	A + C + VKA	69.5 ± 8	Mean	82	25	68	72	15	35	36	17	5	47 ± 13	Mean
	C + VKA	70.3 ± 7	Mean	77	24	69	68	22	34	31	18	5	46 ± 15	Mean
PIONEER AF-PCI (Gibson et al., 2016)	A + C + VKA	69.9 ± 8.7	Mean	73.4	31.3	75.4	44.8	6.8	22.2	NA	NA	0.7	NA	–
	A + C + r	70 ± 9.1	Mean	75.5	28.1	73.2	41.6	7.9	25.4	NA	NA	1.3	NA	–
	C + R	70.4 ± 9.1	Mean	74.5	28.8	73.3	42.6	5.2	19.8	NA	NA	1	NA	–
REDUAL-PCI (Cannon et al., 2017)	A + C + VKA	71.7 ± 8.9	Mean	76.5	37.9	NA	NA	NA	27.3	35.4	19.2	NA	NA	–
	C + d	71.5 ± 8.9	Mean	74.2	36.9	NA	NA	NA	24.2	33.2	16	NA	NA	–
	C + D	68.6 ± 7.7	Mean	77.6	34.1	NA	NA	NA	25.4	31.3	15.2	NA	NA	–

NA, Not available; *DM*, diabetes mellitus; *HTN*, hypertension; *DLP*, dyslipidemia; *CKD*, chronic kidney disease; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *IQR*, interquartile range; *A + C + VKA*, aspirin + clopidogrel + vitamin K antagonist; *C + VKA*, clopidogrel + vitamin K antagonist; *A + C + r*, aspirin + clopidogrel + very low-dose rivaroxaban; *C + R*, clopidogrel + low-dose rivaroxaban; *C + d*, clopidogrel + low-dose dabigatran; *C + D*, clopidogrel + high-dose dabigatran.

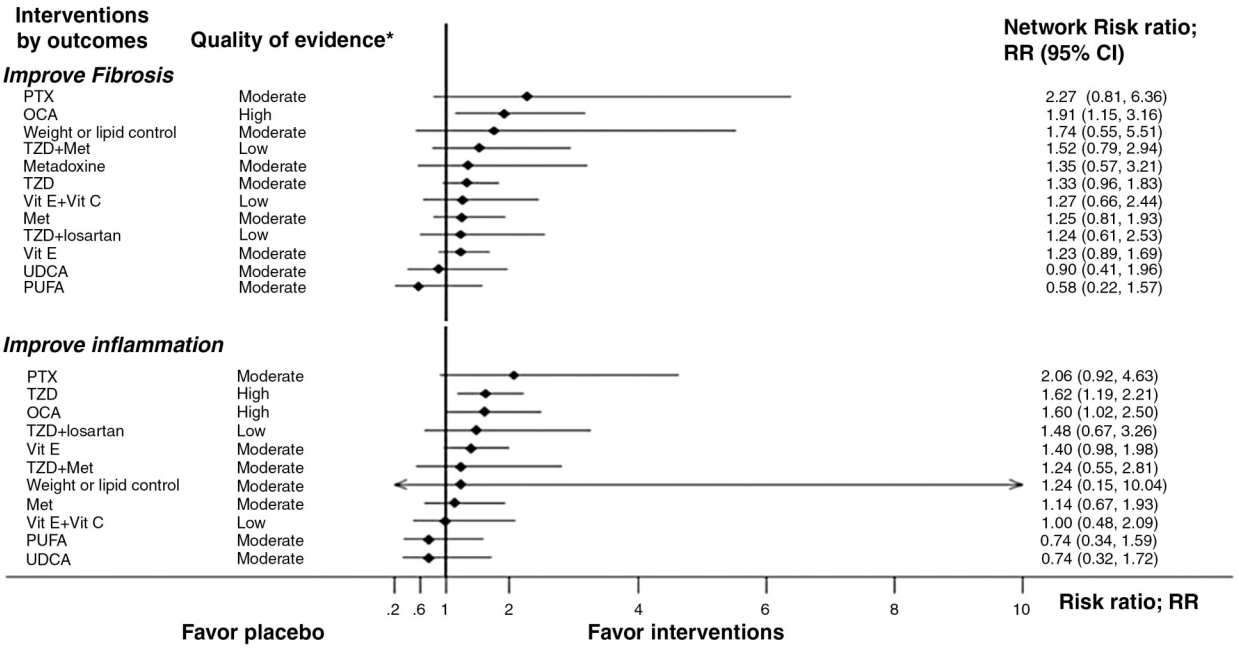

Figure 6 Forest plots showing the effects of interventions on improving outcomes on fibrosis and inflammation conditions among patients with nonalcoholic fatty liver disease (NAFLD). *RR*, risk ratio; *95% CI*, 95% confidence interval; *Met*, metformin; *PP*, phospholipid; *PTX*, pentoxifyline; *PUFA*, polyunsaturated fatty acid; *TZD*, thiazolidinedione; *UCDA*, ursodeoxycholic acid; *Vit C*, vitamin C; *Vit E*, vitamin E; *OCA*, obeticolic acid. *Quality of evidence was graded based on GRADE Working Group: high = we are very confident that the true effect lies close to that of the estimate of the effect, moderate = we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, low = our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect, very low = we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect (Sawangjit et al., 2016).

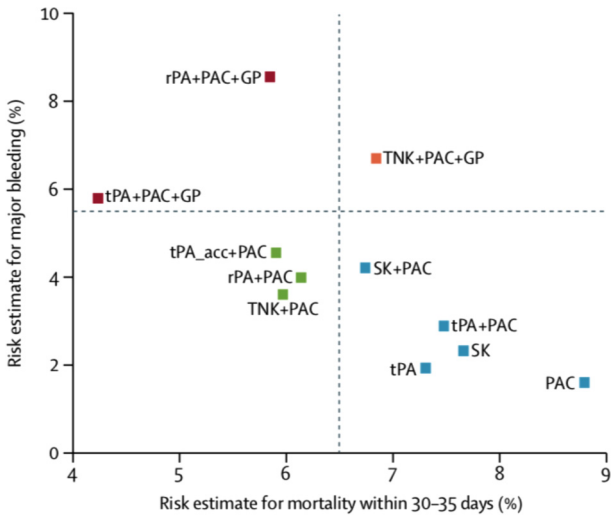

Figure 7 A cluster rank plot explaining ranking of each intervention when considering both (A) mortality reduction presented in the form of risk of mortality within 30–35 days (showing efficacy of the treatment) and (B) major bleeding (showing the safety issue). The risk estimates were estimated in percentage. The plot of treatment with streptokinase plus glycoprotein IIb/IIIa inhibitors was omitted because it was out of the range of the plot. The dashed lines represent the different quadrants of the risk estimates dividing treatments based on their risk magnitudes. *rPA*, reteplase; *PAC*, parenteral anticoagulants; *GP*, glycoprotein IIb or IIIa inhibitors; *TNK*, tenecteplase; *tPA*, alteplase (nonaccelerated infusion); *tPA_acc*, alteplase (accelerated infusion); *SK*, streptokinase (Jinatongthai et al., 2017).

Use of NMA in Pharmacy Research

Pharmaceutical Products Evaluation

To date, there are over 400 NMA studies evaluating pharmaceutical products used in Western and Chinese medicine (Tonin et al., 2018a, 2018b; Yang et al., 2018). Network meta-analysis is of interest among researchers worldwide as witnessed by those 400 NMA studies published by authors from more than 30 countries. The United States, China, the United Kingdom, Canada, and Italy are the top five countries that published such research. Additionally, the trend of use of NMA for pharmaceutical products is increasing globally. Of those NMA studies evaluating pharmaceutical products, very few studies were published prior to 2008, but over the past decade its use has markedly increased. Around 50% of the 400 studies were publications from 2014 onward (Tonin et al., 2018a, 2018b; Yang et al., 2018). A number of medicines were evaluated using NMAs, and the most commonly evaluated clinical conditions include cardiovascular diseases, oncological disorders, autoimmune disorders, mental health disorders, and infectious diseases. Among NMA studies assessing pharmaceutical products, only 33% followed the PRISMA or PRISMA-NMA guidelines (Tonin et al., 2018a; Yang et al., 2018). Since the quality of NMA research is evaluated from study reports, researchers should use PRISMA-NMA (Hutton et al., 2015) to ensure that essential features are reported. This would improve quality of research and understanding of NMA.

Evaluation of Pharmacy Services

Since network meta-analysis is considered a relatively new approach in summarizing evidence, its application in understanding the impact of various pharmacy practice models has remained limited. However, there are a few NMA studies evaluating pharmaceutical care services such as pharmacist counseling and medication reconciliation.

Van Spall et al. (2017) assessed a number of transitional care services for patients with heart failure who discharged from the hospital by comparing usual care, education-alone interventions, pharmacist interventions, telemonitoring, telephone support, nurse home visits, and disease management clinics (DMCs). A total of 43 RCTs were included in the NMA. The study found that nurse home visits and DMCs significantly decreased the mortality and all-cause readmissions relative to usual care. It was also observed that pharmacist services tended to improve the clinical outcomes in patients with heart failure; however, no statistical significance was observed.

Bukhsh et al. (2018) conducted an NMA to compare the effects of pharmacist-based education methods on clinical outcomes in adults with type 2 diabetes mellitus. Thirty-nine studies involving 6259 type-2 diabetic patients were included in the NMA. The findings revealed that the pharmacist-based education was superior in terms of reduction in glycosylated hemoglobin (HbA1c) levels, when compared to usual care. However, there was no significant difference between various diabetes education programs provided by pharmacists. In addition, the pharmacist-led diabetes education plus pharmaceutical care significantly lowered systolic blood pressure and plasma triglyceride levels when compared to other interventions. It was interesting to note that the study by Van Spall et al. (2017) compared pharmacist interventions with services provided by other health-care professionals or in the form of multidisciplinary teams, while the study by Bukhsh et al. (2018) focused on comparisons within pharmacist-based education programs.

The lack of NMA studies assessing pharmacy services might be due to several potential reasons. First, it might be that there have been a smaller number of RCTs in pharmacy services, contributing to challenges in performing NMAs. Second, the NMA approach might have been less adopted among the health service research community. Third, a lack of standardized definitions of pharmaceutical services might prohibit the use of NMA in understanding the comparative effects of all interventions.

In summary, the use of NMA in pharmacy practice-based research is still limited. There is a need to adopt this technique to better understand and evaluate pharmacy service.

Conclusion

Network meta-analysis is an extension of pairwise meta-analysis that simultaneously compares the effects of all interventions of interest. There has been an increasing trend in using such a technique to understand the effects of pharmaceutical products. However, studies investigating pharmacy services interventions remain limited. Pharmacy professionals should have a better understanding of the foundation and the interpretation of NMA.

Glossary

Pairwise comparison A comparison between two treatments at a time in meta-analysis
Network meta-analysis A statistical method to compare and provide ranking of multiple treatments at a time using both direct evidence from empirical studies and indirect evidence through common comparators.
Indirect comparison An indirect comparison means a comparison between treatments through a statistical method rather than directly from studies.

Common comparator A common comparator is an anchored arm served as a linkage between randomized controlled trials to enable treatments, which are not compared directly from studies to be compared indirectly. If there is a trial comparing A versus B and a trial comparing B vs C, B is a common comparator.
Inconsistency Disagreement in treatment effects between direct evidence and indirect evidence which are beyond chance.
Effect modifiers Factors that can affect outcomes such as a treatment dose.
Heterogeneity Differences in treatment effects across studies which are beyond chance.
Transitivity Ability to apply an indirect comparison through a common comparator in a network of evidence.

Web References

Introduction to network meta-analysis
https://training.cochrane.org/resource/introduction-network-meta-analysis-nma
PRISMA-NMA
http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx
GRADE Working Group
http://www.gradeworkinggroup.org

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Ethnography in Pharmacy Policy and Practice

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Introduction

Recently there has been an expansion in the use of qualitative methods in an effort to understand human behavior. This rise is particularly prevalent in health services research, and hence has impact on understandings of pharmacy policy and practice.

Ethnography is a qualitative research method used to understand cultures. Ethnography is rooted in anthropology and is concerned with exploring and understanding social interactions of individuals within the communities in which they work, live or otherwise regularly inhabit and participate.

Qualitative research has a number of strengths, not least, an ontological basis that truth has a number of representations. The most common form of qualitative data collection is the semi-structured interview which allows exploration of the truth from the perception of individuals. The most common limitation cited against use of such research is that it is often small scale and unlikely to be able to claim to be representative.

Ethnography represents multiple truths and overcomes the limitations of relying on individual experiences by utilizing a wide range of tools to capture a range of social experiences. Multiple perspectives of the experience are examined. Observation affords the opportunity to gain insight into cultural practices including those that are hidden or intangible. The ethnographic researcher becomes "immersed" in the setting, collecting data from a range of sources over a period of time, which are triangulated to generate transferable findings. Other methods commonly used alongside participant observation are interviews, online observations and social media, and document analysis conducted at varying and often repeated time points.

Ethnography is messy and complex and the ethnographer employs a number of techniques, from reflexivity and iterative development of approaches to triangulation and thick description, to ensure the rigor of their work. This cyclical and ongoing reflexive approach offers the opportunity to develop links between issues that arise over time and is a strength of this approach over more time limited qualitative approaches.

Ethnography is difficult and resource intensive and as a result there are a limited number of studies. Obstacles to undertaking ethnographic research include the need to spend significant time in the field, whilst managing the need to be both flexible and responsive to sites. Gilmartin (2015) suggests that although ethnography is resource intensive and "not cheap" it should not automatically be disregarded. The high research cost of ethnography is rewarded with a depth of output unrivaled by other approaches. The richness of findings from rigorous ethnographic studies makes them a valuable tool to use to understand health services from a cultural perspective.

For those interested in pharmacy practice, reading ethnographies can provide a useful insight into unfamiliar cultures and contexts. I would recommend all Pharmacy students, and interested researchers, should read van der Geest et al.'s 'Anthropology of Pharmaceuticals' (1996) to give a broad introduction to the field of Pharmacy Practice and useful insights into the relationship between anthropology and pharmacy research.

This chapter is an introduction to ethnography; it offers a brief history and outline of ethnographic research practices, and the role of this approach in pharmacy policy and practice. The aim of this chapter is to introduce colleagues in pharmacy policy and practice research to the ethnographic traditions to enable them to read ethnographic works, support ethnographers and consider using ethnographic approaches in their own work.

What is Ethnography?

Introduction

Ethnography is embedded in a naturalistic epistemology, and reflects a social constructivist approach to understanding the world. Ethnography assumes that the social world does not exist without or outside of individuals, but instead is a system created by interactions between individuals; therefore, any effort to understand people as subjects of experience is not appropriate without significant in-depth analysis of the context in which it occurs.

Defining Ethnography

Ethnography is the study of people and their interactions in cultural groups and comes from the Greek *ethnos* (people) and graphei (to write). Stories about people and how they interact in specific contexts in order to understand them is the desired outcome of ethnographic research. Beyond these broad assertions there is little consensus about what ethnography is (Reeves et al., 2013). Miller (1997) suggests that ethnography is even more than a method or methodology, since it applies to both practices and products of research. Walford (2001) suggests that the term can be understood in three ways: as a research approach, or as a set of research methods, or the product of these as a written account. In this chapter, I adopt this multifaceted definition and use the term ethnography interchangeably to mean each of these things in turn. This first section explores the development of ethnography as a methodology and different types of ethnographic methodologies. Explicit ethnographic methods (including data collection, analysis, and writing) are explored in later sections.

Origins of Ethnography

Ethnography is a derivative approach of social anthropology which aims to develop knowledge through immersion in a culture. Ethnography emerged from anthropology—the approach to understanding unfamiliar cultures made popular by those researchers (Malinowski, 1961/1922; Mead, 1961) who spent several years living as part of indigenous unfamiliar cultures to explore, explain and write about the world from the perspective of a member of that society. Malinowski is often cited as the first researcher with a declared interest in an immersed, native point of view. Others agree that the principle aim of the ethnographic approach is to "explore and represent unfamiliar cultures", to understand meaning and events as they are understood by people in those cultures. Other major authors in fields of ethnography both in the wider field (McCalla-Chen, 1996; Walford, 2001) as well as in the specific health-care fields (Murphy and Dingwall, 2003; Savage, 2000) concur with this aim. More recent developments in ethnographic studies show that unfamiliar cultures have become more widely understood to be located "closer to home" and there is now a wide range of ethnographic studies that consider familiar practices from particular cultural perspectives (Brown and Bellaby, 2002; Duckett, 2015; Harvey et al., 2015; Latif et al., 2013, 2016; Lim et al., 2011).

Different Types of Ethnography

There is a wide range of ethnographic types and whilst this list is not intended to be exhaustive or all-encompassing, it is clearly useful to outline some of the key ethnographic types and their similarities or differences. This includes full traditional ethnography, rapid ethnography, critical ethnography, feminist ethnography, auto-ethnography and the recently emerging trends toward digital or visual ethnographies.

Full traditional ethnographies tend toward longitudinal studies with long periods where the researcher is immersed in the field. This approach has the limitations of being time and resource intensive and as a result tends to be most popularized as an approach in doctoral work. Several authors of papers reviewed mention these limitations as reasons for not choosing

ethnography as a method for study despite its apparent appropriateness for investigating the area of research (Austin et al., 2010; Miller et al., 2007; Walpola et al., 2017; Wang et al., 2014). By contrast, rapid ethnography allows users to take the ethnographic approach to a shorter and often more intense period of time spent in the field (Baines and Cunningham, 2013; Reeves et al., 2013).

Critical ethnographic studies are value-laden and use existing theories with, and often to emancipate disadvantaged cultures, through challenging existing structures. The main aim in critical ethnography is reporting on not just how things are but how they could be better (Barton, 2001; Oladele et al., 2012), for example, seeking to establish why urban children do not engage with Science (Barton, 2001). Feminist ethnography takes a similar approach, focusing on areas of female culture, or applying feminist principles to ethnographic methodologies, or both (Visweswaran, 1997; Williams, 1993). This is an approach and discourse in health services research which features predominantly in the Nursing domain (Manias and Street, 2001; Muecke, 1994).

Auto-ethnography has parallels with biographical studies since they are centralized around the researcher as author of his own experiences. In differing from biographies which centralize the author within the story, in auto-ethnographic studies the culture of the author provides the focal point for the work (Denzin, 2013; Ellis and Bochner, 2000).

In the technological era, a number of new studies have emerged that seek to understand experiences of digital and online cultures (Murthy, 2008; Wesch, 2008). Visual ethnographies overlap this somewhat as they are concerned with utilizing the consideration of a wide range of visual artifacts to give insight into the culture, often utilizing analysis frameworks related to symbolic interactionism (Pink, 2013).

This section has outlined some of the key variations of ethnographic methodology, all of which can give useful insights into the culture they examine but each has its best fit with a type of research according to the broad aim, research question, and type of culture under investigation. The choice of research methodology should be context sensitive, appropriate to the research question being asked and the desired outcome (Bryman, 2015; Green and Thorogood, 2018; Lincoln and Guba, 1985).

This section aimed to give a brief introduction to and broad overview of ethnography from a theoretical perspective.

Doing Ethnography

Introduction

The previous section introduced a brief history and definitions of ethnographic methodology. This section of the chapter outlines the practicalities of using ethnography as both a set of methods (for data collection and analysis) and as an output and impact method through writing.

Sampling

Ethnography requires ongoing access to sites and participants. There are a number of ways to negotiate access to sites, which differs from other types of research as access to the setting is not a one-off event but requires ongoing negotiation by the ethnographer. Building relationships is a vital part of ethnographic research (Hammersley and Atkinson, 2007).

Choice of sampling in research methods is also context sensitive, relates to the research question being asked, and the methodology used to find the answer. In Guetterman's (2015) review of sampling approaches in qualitative research he noted that ethnographic studies tended to have a small number of sites, for example, 1–2, with a wide variance in the number of participants at the sites depending on the site, culture and research questions. The ten ethnographic studies reviewed by Guetterman had a mean sample size of 128, with variance in sampling size from 6 to 586. Whilst the main sample of an ethnographic study will be a single or small number of sites, and the participants of the culture sharing group, other opportunistic sampling techniques are often used as the study progresses to respond to emergent areas of interest. A wide range of sampling strategies are often reported in ethnographic studies including convenience sampling, snowball sampling, critical case sampling for specific subgroup sampling, and purposive or purposeful sampling for maximum variation or representation.

Immersion

The key benefit of ethnography is the depth of understanding that emerges from time immersed in a cultural setting. It is difficult, however, to specify techniques for sampling or time immersion for ethnography as this is dependent on the setting and context. Wolcott (1994) suggests that time is the critical attribute of fieldwork in the ethnographic tradition. Ethnography assumes that we can only understand cultural ways of being in detail through an "insider's view" developed over a period of time which is needed to discern both the depth and complexity of social structures and relations (Jeffrey and Troman, 2004; McCalla-Chen, 1996; Walford, 2001). There is debate about what length of time should be spent in the field to qualify a study as being in the ethnographic tradition. Early anthropologists researching rural cultures recommended an ideal of 12 months minimum to study the annual cycle of the growing season. Wolcott (1995) described an ideal fieldwork term of 2 years as the standard. As well as debate about the length of a study, there is debate about the depth of immersion that qualifies a study as ethnographic. Jeffrey and Troman (2004) described three different "fieldwork time modes" which refer to the nature of the ethnographic methodology. A compacted time mode involves a short period of intensive immersion in all activities in the community. By contrast, a selective

intermittent mode is one where the length of time is longer but a more flexible approach is taken to frequency of observations. A recurrent research mode is one where projects aim to gain a picture by sampling the same temporal phases, for example, beginnings and ends of terms. More than one of each type of mode can be used within a single study. It is important that ethnographers describe the depths of immersion in their study and the amounts of time spent in the field to confirm that this study fits the ethnographic tradition.

Data Collection Tools

This section outlines a series of data collection methods that are often used in ethnographic research. Methods relate to the specific "working" methods and process for the work. It is important to note that whilst a set of tools is outlined here, it is the way in which they are co-utilized which is a unique feature of ethnographic research.

The most common form of formal academic writing reports the research process as data collection, analysis, and interpretation in a linear style appropriate to experimental or scientific design. It is important, however, to note that in ethnographic research, whilst these processes are followed, they are not as distinctly separated in practice as they might appear in written format. Naturalistic research is reflective and iterative and data and theory can both be simultaneously collected and analyzed. Data collection, analysis, and interpretation are ongoing and overlapping throughout ethnography. In ethnographic work, it is likely that the researcher will analyze data as it is collected, and interpret it during analysis, before repeating this cycle. Malinowski (1961/1922) suggests that in ethnography relationships between data and theory are more seamless than in other approaches.

Therefore whilst a distinct set of methods for data collection and analysis is described, the need for iterative development and reflexivity are also explored, along with appropriate measures for the rigor of academic ethnographic work.

Observation

The previous section introduced the importance of time spent in the field collecting data to be "immersed" in the context being studied. It is generally agreed that observation (participant and/or nonparticipant) forms the cornerstone of ethnographic studies (Denzin and Lincoln, 2011; Lincoln and Guba, 1985; Reeves et al., 2013; Smith, 1998a).

Savage (2000) notes that on occasion ethnography is mistakenly used interchangeably with participant observation. Hammersley and Atkinson (2007) suggested that any case study using participant observation methods with case study outputs might be classified as ethnography but others contradicted this arguing that it is the length and depth of participation that defines a true ethnography (Outhwaite and Turner, 2007; Spradley, 2016).

Periods of observation in ethnographic studies are often spaced apart in time to facilitate the iterative development of the research question. Woods (2013) suggested that an intermittent approach is:

> ' . . . the flexibility to follow a particular empirical or analytical path across people and contexts and to be able to focus more and more closely on any relevant aspect of a site just as a cinematographer who gradually zooms closer and closer on to his or her preferred subject. (Woods, 2013, p. 12)

The difficulty of conducting observation studies in health services should not be underestimated. Austin et al. (2010) suggested, for example, that it is difficult to conduct ethnography where there is access to (and sensitivity around) patient records. Ward et al. (1998) acknowledged the contribution of the participants in their research.

> 'The authors would like to thank all the staff at the 10 pharmacies who took part in this study. To subject oneself to the scrutiny of strangers for five days takes both courage and a sense of commitment to the development of the profession of pharmacy.' (Ward et al., 1998, p. 214)

While observation allows for a level of researcher immersion in context, it is inherently researcher-centric and in the majority of ethnographic studies it is used alongside other data to explore multiple perspectives.

Interviews

Whilst qualitative interviews alone do not constitute an ethnography, ethnographic studies often use interviews alongside periods of observation. The key aim of the qualitative interview is to gain insight into the participant's view of the research topic (Smith, 1998b). Interviews are often used to explore areas of interest which have emerged from observations and can occur at multiple time points and be either preplanned or spontaneous. Life history interviews focus on individuals and are often used in the early stage of ethnography as a tool to build relationships with participants, understand their social history and extend the research out to understandings beyond the fixed time period for the research. Semistructured interviews are most commonly used as they allow the researcher to have broad areas of questioning with underlying prompts but can also follow areas of emergent interest.

Ethnographic Content Analysis

Documents, an output of human creation, related to the context for study, can often provide useful insights as part of an ethnographic study. This method is called ethnographic content analysis and involves locating, identifying and analyzing documents for their meaning and significance to the context of the research study and their relationship to the emerging research question (Altheide, 1987). Visual artifacts including media items can also be analyzed (Glinert, 2005; Pink, 2013).

Mixed Methods and Ethnography

Some argue that ethnography is an inherently mixed methods approach since, as outlined above, ethnographic studies most often utilize a combination of qualitative data collection methods (Schensul et al., 1999).

A number of studies have emerged recently which take a broader approach and suggest that the qualitative tools of an ethnographic study can be used alongside quantitative methods to give a broad mixed methods overview and understanding of a context. This is complex since both are epistemologically opposed, nonetheless, this can give a holistic understanding of complex situations and as such has gained popularity as a combination of methods, for example, in implementation science in healthcare settings (Bunce et al., 2014; Palinkas et al., 2011; Rowley and Waring, 2011).

Data Analysis Process

The research process of ethnography is not linear in the same way as other types of studies and therefore it is unlikely for there to be a clear and distinct period of data collection and analysis.

Theory in Ethnography

There is broad agreement about the fact that there are variations in analytical approaches used in ethnography (Bryman, 2015; Hammersley and Atkinson, 2007; Walford, 2001). Any broad review of ethnographic literature will find a range of approaches on the deductive to inductive scale. At one end of the scale, there are fully inductive studies which explore an area and develop a theory according to the data, often using a broad thematic analysis. Some such studies take a grounded theory approach (Anto et al., 2013). There are other studies that fall in the middle of the spectrum. This is where the majority of ethnographic research sits, led by broad research areas initially and a desire to explore the field, and where a specific theoretical framework does not inform the earlier stages of research design but is useful to iteratively develop the ongoing data collection and make sense of findings toward the analytical stage of the study. At the inductive extreme of the spectrum are studies that use theory to inform every aspect of research from the origin of the research question through to findings. An example is provided by the "socialisation of Mistansini Cree children" study (Delamont and Atkinson, 1980), which was based on social learning theory from inception through to completion or, similarly, Kooienga's ethnographic study of e-prescribing in rural communities (Kooienga and Singh, 2017) where the Ecological Transactional model was used to inform research design, data collection and analysis. These examples are listed to show the polar ends of difference between the wide ranges of ethnographic subcategories. In between is also a wide range of studies that demonstrate the enormously varying ways that theory can be applied to studies of ethnography in the process of both data collection and analysis. **Fig. 1** shows Winit-Watjana's diagram which visually maps this process (Winit-Watjana, 2016, p. 430).

One key advantage of ethnography as a tool is the need for the researcher to iteratively develop the focus of the research according to the findings as they emerge which requires a reflexive approach to the research. Anderson (1989) suggested that working with ethnographic data

> '. . . requires a reciprocal relationship between data and theory. Data must be allowed to generate propositions in a dialectical manner that permits use of a priori theoretical frameworks, but which keeps a particular framework from becoming the container into which the data must be poured' (Anderson, 1989, p. 267).

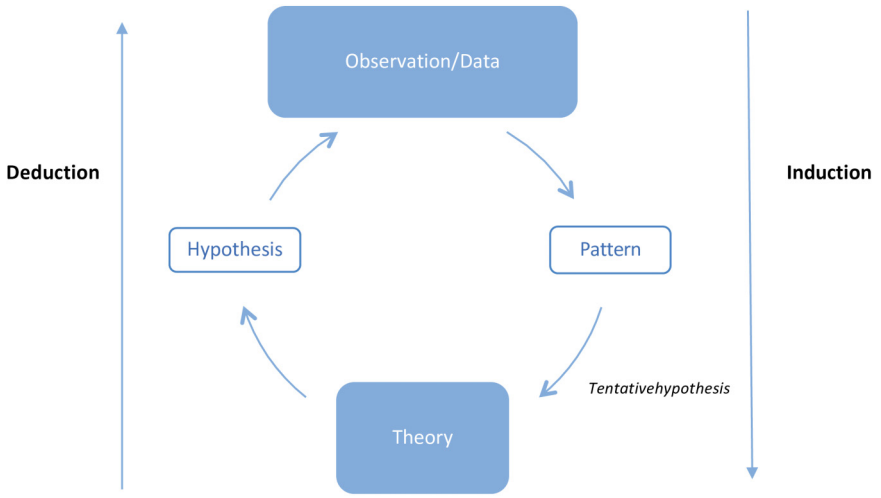

Figure 1 Research reasoning or logic of inquiry. *Source: Winit-Watjana, W. Research philosophy in pharmacy practice: necessity and relevance. Int. J. Pharm. Pract 24 (2016), 430.*

Ethnographic data analysis begins with coding data to identify areas of interest and overlap and their relationships. By applying labels to data through coding the researcher makes decisions about what the data collected represents and through arranging the coded data into categories can identify links between them. A range of tools can support this work. Software packages for analysis of qualitative data, such as NVivo, help the researcher to manage data and develop key themes. Some people prefer to use colored pens, stickers, electronic files or scissors and folders to organize data to aid in the identification of key themes and links. In an attempt to minimize subjective researcher impact, some studies use multiple coders to enhance (inter-coding) reliability (Denzin and Lincoln, 2011; Kooienga and Singh, 2017; Smith, 1998b).

By repeating the analysis at multiple time points through the research, as different sources of data are added, areas of interest can be iteratively developed. At each stage of coding, the researcher may revisit the literature, or iteratively develop more tools or methods for data collection. Coding and thematising data, in conjunction with reviewing the literature allowing emerging data to fit with emerging frameworks is a simultaneous, iterative process. The outcome is data that can simultaneously describe and analyze a context and culture through a vari-focal lens.

Rigor

Pharmacy has its' roots firmly in the Sciences, and as such can be reluctant to be open to Social Science which has many contradictions with traditional scientific approaches (Smith, 1998b). Some people suggest that because the health field has a strong tradition of biomedical research using conventional experimental and quantitative methods, qualitative research is often criticized for lacking scientific rigor (Mays and Pope, 1995). Early defenders of rigor in qualitative research (Lincoln and Guba, 1985; LeCompte and Goetz, 1982) identified that typical positivist measures of rigor used for scientific research were not transferable. More recent researchers suggest that the complex activity of ethnography and diverse epistemological positions and methods require different modes of evaluation from other methods more commonly employed in medical and healthcare research (Savage, 2000). Ethnography does not fit with traditional scientific methods of rigor and recent publications in qualitative research show that alternative methods of reflexivity, transparency and triangulation can be used as quality measures.

Reflexivity is a process where the researcher, actively and throughout their work, reflects on both the research process and their impact on it. Studies should clearly identify measures taken by the researcher to minimize impact on the conditions and participants of the research (Marshall et al., 2010). Barry et al. (1999) suggest that shared reflexivity significantly enhances the rigor of team based qualitative research. Hegelund (2005) discusses a range of ways for ethnographic researchers to distinguish between the problematic terms of subjectivity and objectivity. This paper suggests the ethnography can limit subjectivity through three key methods—firstly the study should correspond to the reality of the study (by including all relevant data, secondly methods of analysis should be objectively approached, and thirdly the perspective of the research and researcher should be transparent).

It is suggested that reliability in ethnographic studies is enhanced by transparent presentation of methods and analysis so that an audience can clearly understand the work undertaken, the context it is undertaken in and, through reflexivity, the impact of the researcher on each aspect of the research (Hegelund, 2005; Marshall et al., 2010; Murphy and Dingwall, 2003).

Data triangulation is a method inherent in the ethnographic approach used to minimize objectivity and achieve rigor in qualitative studies. Triangulation involves collecting and analyzing data from variations on one of the three types of data sources—time, space, and person (Denzin, 2013). The cyclical reflexive method of linking data to theory in **Fig. 1** (Winit-Watjana, 2016) demonstrates triangulation. For example a wide range studies use ethnographic interviewing as a technique to complement participant observation, ensuring a good in-depth fit between theory, data processing and researcher interpretation. Savage (Savage, 2000) argued that ethnography can be distinguished from other approaches by making the link between the micro and macrolevel of a context, with an interest in both individuals and their context and the interactions therein. Hirsch and Gellner (2001) provide an excellent visual representation of this approach as one with "one eye roving, the other focusing".

Ethnographic Writing

Since half of the etymology of the term "ethnography" relates to writing, it is important to emphasize ethnography as an approach to writing. Fetterman (2010) described ethnography as the art or science of describing a group. Harris and Johnson (2006) stated an ethnography is a written description of a particular culture, based on evidence and that this should include descriptions of the customs, beliefs, and behavior of the participants.

Ethnographic writing is often not just an output, but also a significant part of the analysis process, iterative and used as a method of enquiry to reorganize and refine ideas (Denzin and Lincoln, 2011). This approach to writing demonstrates progressive focusing (Strauss and Corbin, 1990); the writing occurs as a process of data analysis to focus the lens more specifically on areas of interest and significance.

Traditional ethnography sought to tell a story (Hammersley and Atkinson, 2007). Brown and Bellaby's (2002) article about community pharmacy is written in this true ethnographic style, using thick description and metaphor to invite the audience into the world of the community pharmacy from the perspective of the locum pharmacist. The imagery and creative prose generate strong understandings of what it means "to be" a community pharmacist: "Meticulous attention to clothing contributes to constructing the pharmacist's specific, respectable, trustworthy front" (p. 204). Through thick creative writing the reader is given insight into a range

of processes and perceptions that contribute to the pharmacist's professional identity. Brown and Bellaby (2002) used metaphors of dramatic performance allowing the reader to experience "what it means" to be a pharmacist in this context through the eyes of those who have experienced it, as the following extract demonstrates.

> 'Backstage: The pharmacist's performance is nearly finished for the day. He drinks strong coffee, in order to attempt to keep alert for the rush of prescriptions during the last 20 minutes, counts the pile of prescriptions, which is some quantification of the workload of converting drugs into medicines and returns the Controlled Drug key. He thanks his supporting cast, the assistant(s); they set the alarm and lower the roller blinds (stage curtain) in order to guard the stage props, especially medicines, overnight. In his car, the pharmacist relaxes, after his 12 hours of performance, by unbuttoning his shirt and loosening his tie.' (Brown and Bellaby, 2002, p. 210–211)

Many ethnographic works present data, full or partial findings, creatively as case studies or smaller vignettes for ease of reading (Oborn and Barrett, 2008). Reports of ethnography appear in a range of published press from full monographs to book chapters along with a wide range of peer reviewed journal papers and conference proceedings. Styles of writing are limited by the mode of delivery, with journal articles frequently focusing on one area of the ethnographic study rather than trying to report the full data of a study.

Ethnography in Health Services Research Pharmacy Practice and Policy Research

It is important to locate ethnography within the field of pharmacy practice for relevance.

Overview

Previous sections have outlined the reasons why ethnography is still a developing approach in pharmacy practice, a traditionally scientific and positivist environment.

There is, however, a wide range of colocated areas where ethnographic studies are more populous and interested readers and potential ethnographers are encouraged to explore literature in health services, medical and allied health qualitative research and education for a wider range of studies.

Literature Review

To understand and present a brief reflection of ways in which ethnography has been employed in pharmacy practice research, I undertook a small scoping literature review of two major peer reviewed journals focused on Pharmacy Practice research. The first, International Journal of Pharmacy Practice (IJPP) is the official journal of the Royal Pharmaceutical Society in the UK and published by Wiley; the second is Research in Social and Administrative Pharmacy (RSAP) a journal with international committee and audience, by Elsevier. It is acknowledged that this search is limited, but provides a useful introduction to the published research utilizing this approach. Further broader studies are recommended for a wider insights into the profession and its practices.

Both journals were searched for the terms "ethnography" and "ethnographic" from inception to April 2018. Initial searches returned a total of 83 papers; however, with duplications between findings from utilizing both terms removed, the total number of independent returns was 68.

Upon initial review a number of these papers (32) mentioned ethnography on a superficial level, or simply citing other ethnographic studies and these were withdrawn from further investigation (IJPP 15, RSAP 17). The total number of papers remaining for review after this initial skimming was 36.

Of these 36 papers, 9 (IJPP 6, RSAP 3) viewed ethnography as a method, usually within a wider view of qualitative research, or wider fields such as philosophy. While these were useful to review in the context of this chapter, they were excluded from further review.

The remaining 27 articles represented ethnographic studies (IJPP 13, RSAP 14) and these are presented below.

Lessons from Ethnographies of Pharmacy Practice

A small proportion of the papers reviewed described their work as taking an "ethnographic approach". Some of these studies could be categorized as clear ethnographic studies as they clearly fit the criteria outlined previously for ethnographic approaches to data collection and analysis. A number of studies that reported an "ethnographic approach" were reporting data collected by individual methods such as qualitative interviews, and this was justified as ethnographic in approach as they were conducted as part of a wider ethnographic study. Two authors had a different paper in each journal referencing the same ethnographic study but presenting findings from different themes or areas of the work.

The 27 ethnographic works reviewed can be broadly categorized into (1) Pharmacy Culture—the culture and role of the pharmacist and their profession broadly, or in specific locations such as community pharmacy or hospital pharmacy, (2) Patient–Pharmacy interaction culture, and (3) Global pharmacy culture (including the culture of pharmacists' relationships with others and pharmacy education).

Pharmacist Culture

Around half of the studies reviewed reflected on the role and identity of the pharmacist and the profession. These tended to be located in either the community or hospital pharmacy context.

Brown and Bellaby (2002) wrote creatively and used thick description about locum experiences in community pharmacy. This creative writing output from a period of immersive participant observation across a wide range of settings provides thick description about the experience of what it means broadly to work in a community pharmacy. This was a holistic, broad research study giving in-depth insights into the experiences of a community pharmacist and safety and responsibility emerged as two areas of key importance. Safety culture was a focus of other studies in community pharmacy. One study specifically focused on the safety culture in community pharmacy and explored strategies used by a range of pharmacists in this setting (Anto et al., 2013). Harvey et al.'s ethnographic study (2015) of safety in community pharmacy reviewed a wide range of factors that impact on safety within the community pharmacy dispensing culture and provided useful insight into the complexity of processes and relationships.

Other research in the community pharmacy setting was more specifically focused on understanding the experience of either unique settings, participants or Interventions. One study researched what it means to be a community pharmacist in one particular geographical and cultural area of the UK (Duckett, 2015). Another considered the role of the medicines counter assistant in community pharmacy, in particular in relation to the sale of deregulated medicines (Ward et al., 1998). Latif et al.'s (2013) study into the implementation of a new medicines review process took place in, and gave unique insight into, the community pharmacy context.

The remaining ethnographic studies relating to context provided insight into changing practices in hospital pharmacy culture. One study reported on the experience of automation implementation in hospital dispensary and showed the impact of the change on working culture (Oborn and Barrett, 2008). Another study explored the relationship between electronic prescribing in hospital and patient involvement with their medicines (Garfield et al., 2015).

Finally, some studies focus on interactions between pharmacists and others. One American-based study considers the relationship between pharmacists and industry (Saavedra et al., 2017).

Patient–Pharmacy Interaction Culture

A wide number of studies focused on interactions between pharmacists and patients, within the broadest culture of medication and health. Whilst those reported here featured in pharmacy practice publications, they are likely to be replicated on a much larger scale across broad health services research.

Studies took place in a wide range of contexts including studies of treatment culture in home settings (Norris, 2012) care homes (Shaw et al., 2013), the culture of patient-facing medication reviews in community pharmacy (Babalola and Erhun, 2001; Latif et al., 2013; Tulip et al., 2002) or the discharge process in hospital (Laugaland et al., 2014). Each of these offers a unique multifaceted insight into the cultures under examination. Kooienga and Singh (2017) ethnography of rural e-prescribing identified important points about relationships between patients and pharmacists and how different cultural areas respond to innovations differently.

Some studies focused on particular patient groups. Lau's (2014) ethnographic account of nonadherence to statins in 40–80-year-old men gives an interesting insight into the decision making process within this particular patient group. Norris (2012) study in New Zealand was a comprehensive ethnography of medicines use in the home that employed a wide range of techniques including participant diaries and mapping. This study gives useful insights into the way patients talk about medications, and their use of metaphor, in relation to medicines and, in particular, antibiotics. Ahiabu et al.'s (2018) ethnographic study of Ghanaian households' illness and medication use gives interesting insights into self-medication in this context that can usefully inform the development of health services.

> 'Medication use was for both treatment and illness prevention. Oppong (H4) believed he has had chronic typhoid fever for over 20 years and takes ciprofloxacin as often as every month; in his own words "anytime I sense the fever and headache. (Ahiabu et al., 2018, p. 5)

Whilst these studies could be categorized by their context of study (home, community) they are categorized here by their focus on patient's experiences. For example Latif et al.'s (2013) ethnographic study of medicines use reviews in community pharmacy were reported from the patient perspective.

Some studies focused more broadly on the patient experience. For example, one study focused on the culture of patient interaction with pharmacy practice research (Sutton and Weiss, 2008) and the work gives valuable insight into patients' understanding of the research process. Montagne's (2014) study of antidepressant use can be classified as a digital ethnography since all observations were online of activity conducted online. This was supplemented by online documents and online behavioral tracking statistics. The exploratory study by Traulsen et al. (2014) reported through conference proceedings was a groundwork scoping study focused on students and, through detailed fieldwork at two international sites, reported some of the reasons why students were taking "study drugs" and this identified a gap for further work.

Global Pharmacy Culture

As mentioned ethnography is useful for exploring unfamiliar landscapes and capturing cultural baseline data to inform future research in a wide range of studies both local and international.

One study, based in Malawi, resulted in two different publications, the first explored the involvement of practizing pharmacists in the development of education (Lim and Anderson, 2011) and the second investigated the notion of "drug pilferage" in the Malawi context (Lim et al., 2011). Several of the papers previously mentioned located their work in a specific culture (Ahiabu et al., 2018; Norris, 2012).

Discussion

What we learn about pharmacy practice from ethnographic accounts is invaluable. These published accounts give any audience a unique insight into the processes involved in pharmacy practice from the perspectives of those mostly deeply involved with them.

From the above reviews, we have interesting insights into community pharmacy, hospital pharmacy, and patient's interactions with their medicines.

The studies highlighted in this review are useful representations of what it means to be a pharmacy professional or work within the context of health and medicines. They also provide unique insights into what it means to be a user of medicines. They provide grounding data and identify gaps for further research.

Conclusion

This chapter has covered ethnography as both a broad methodology and a series of precise methods for data collection, analysis, and writing. A brief insight into ethnographies published in the UK about pharmacy practice provides an introduction to the field but also identifies gaps for further research about what it means to be a pharmacist or a patient in various cultures and contexts.

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Philosophical Perspectives and Theories Applied in Pharmacy Practice Research

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Philosophical Perspectives

Paradigms/Belief Systems

Four characteristics distinguish science from nonscience. Science is theory-based, uses systematic research techniques, is cumulative and predictive (Mount, 1989). All science is embedded in different belief systems also known as paradigms, world views or research types, not only in choices of method and theory that guide the investigator, but also in fundamental ways both ontologically (nature of being) and epistemologically (investigation of what distinguishes justified belief from opinion). One can identify four types of paradigms: positivist, post-positivist, interpretivist/critical theory, and constructivist (Guba and Lincoln, 1994).

These theoretical paradigms differ to such a degree that they are said to be inconsistent (Guba and Lincoln, 1994; Launsø, 1991). Research carried out within the positivist/post-positivist paradigm strives toward objectivity and neutrality, and typically employs quantitative studies with the focus on numbers, precision, and generalizability. These studies rarely have an explicit theoretical foundation and are characterized by distance between researchers and that being researched.

On the other hand, studies done under the interpretivist paradigm are most often qualitative studies focusing on understanding and grasping the wholeness of the study object. Often theoretically-based, these studies feature a closeness between researcher and that being researched. The constructivist paradigm and to some extend the interpretivist paradigm cover research (either quantitative or qualitative) whose focus is to criticize, suggest change, learn, and/or develop. These studies often have an emancipatory agenda for groups involved (might be all kind of groups, but would often be different types of vulnerable patient groups). Historically, there has been heavy emphasis on quantification in science, and thus research emanating from a positivist/positivist paradigm has traditionally been viewed as "hard", whereas research carried out under the other two paradigms is often referred to as "soft". See Sørensen et al. (2003) for a mapping of core questions, typical design, dominating method and quality criteria attached to each of the paradigms.

To illustrate the difference between research done in pharmacy practice under the first two paradigms, one might consider different theories of compliance/adherence or self-regulation. From a positivist point of view, a theory on how to make a drug user compliant by using different electronic or chemically marked methods would be useful. A researcher with an interpretivist view studying adherence would be more likely to employ theories that emphasize the patient's ideas, values and attitudes—most likely interpreting adherence as "self-regulation". Broadly speaking, the positivist researcher attempts to predict and control, whereas the interpretivist researcher focuses on understanding the patient's reflections in relation to medication behavior (Nørgaard et al., 2000).

History of Philosophical Perspectives and Theories in Pharmacy Practice Research

Underlying all belief systems are many different theories relating to specific topics. This is also true for PPR. The first decades of PPR were characterized by relatively few theoretical reflections and tended to be "hard" quantitative research carried out under the positivist paradigm. However, in recent decades a growing awareness of and interest in the critical paradigm has fostered efforts to

teach and conduct research using this tradition. The result has been an increase in the number of qualitative studies and studies with a specific theory base Bissell et al. (2001). Today, PPR is carried out under all three of the above-mentioned paradigms, and various theories have been developed under the umbrella of all three paradigms, as will be described below.

No one theoretical perspective is "better" than another. The methodologies and methods that follow the theories all serve different purposes. An example from PPR could be: If you want to map the number and types of drug-related problems in a population, an interpretative paradigm and qualitative methods will be of limited use. In contrast, if your aim of inquiry is to know more about individual patients' thoughts and ideas in relation to medicine use, using a positivist approach and quantitative methods will not make much sense.

The Why and How of Theory Base in Pharmacy Practice Research

The explicit use of theories serves various purposes ranging from explanation and prediction in the positivist research tradition to understanding, sense making and critiquing in the interpretivist, and critical theoretical research traditions (Buchanan, 1998). There are many definitions of theory, but suffice it to say that a theory is an account of the world that goes beyond what we can see and measure. Theory embraces a set of interrelated definitions and relationships that organize our concepts and understanding of the empirical world in a systematic way (Marshall, 1998). The above definition suggests that theories are bodies of knowledge that allow a more elaborate/complex or sophisticated framework for understanding the world. Theories can thus range from explicit hypotheses to working models and frameworks of thinking about and studying reality. A theory constitutes a classification system, a taxonomy, consisting of categories that organize and summarize empirical observations, thus providing the researcher with a framework for understanding and organizing empirical findings.

Decades ago, it appeared that while research in nursing practice was acknowledging the benefits of theory-based research, this was not the case in PPR (Nørgaard et al., 2000). Some researchers argued for theory-based PPR, because, as they pointed out, there was an overwhelming tendency to focus on descriptive studies, addressing the "what" or "how many" questions, but rarely addressing the "why" questions. Although this is still true to some extent (Lau and Traulsen, 2017), it is fair to say that PPR has moved on, and it is no longer rare to find theory-based studies in peer-reviewed journals, which will also be seen in the rest of this chapter.

Much if not all of PPR deals with human beings. People go to a pharmacy with their personal problems related to illness, health, and drugs. Although not obvious on the surface, these "personal problems" are often interconnected with or reflections of political and administrative constraints found in societal structures, including the cultural and social environment: questions of access, affordability, beliefs about health and illness and the effects of poverty, to name a few. Given the acceptance that social factors play a key role in the determination of health and illness, there is a need for those involved in pharmacy practice to understand the nature and effects of those factors, and hence the need for social theories grounded in sociological knowledge.

Researchers use theories and think theoretically, even if they do not make it explicit. In research all observations and interpretations have some theoretical assumptions. No study of reality is presented independent of the preconceptions one has about them. Consciously or unconsciously, researchers include their own expectations and theoretical basis as the starting point of their work, which influences the method and strategies as well as the results of the project. The manner in which observations are organized, analyzed and interpreted determines what is "found". Thus, clarifying the theoretical background for one's research enables others to assess the validity of the research and judge the relevance of the theories in relation to the specific research area. Using a specific theoretical background also allows researchers to assess the relevance of their research findings to the available literature.

Existing social science theories can assist the pharmacy practice researcher in identifying questions and topics that need to be addressed. Instead of being stuck with a "trial-and-error" approach, social science can provide the researcher with an explanatory framework for interpreting questions and answers (Mount, 1989). On the one hand, researchers should consider the theoretical basis at the outset of planning a study. Conversely, the application of theory in research can be confusing, with a multitude of terms and definitions and many approaches described. Theories can be applied at many stages of quantitative and qualitative (and mixed) research processes and for many reasons: for example, providing rationale for the study, defining the aim and research questions, considering the methodological stance, developing data collection and generation tools, providing a framework for data analysis, and interpretation (Stewart and Klein, 2016).

It is clear that working with models has been more accessible and easier to apply to PPR than hardcore sociological and psychological theory. Although they both share common elements, the distinction between theories and models is as follows. A theory is a set of statements developed through a process of continued abstractions. Where a theory is often a generalized statement aimed at explaining a phenomenon, models are purposeful representations of reality, often stylized, graphic drawings. Although both share common elements in their definitions, a model is often used to describe and simplify an application of a theory, and its aim is to provide a tool for understanding specific phenomena (modeling).

Main Theories and Models Applied in Pharmacy Practice Research

An exhaustive description of how PPR researchers have worked theoretically is not within the limits of this chapter. However, a description of the main areas in which PPR has used theory follows. Each section concludes with one or two concrete examples of the theory used in PPR. Focus is on social science theories, which include political science, demography, epidemiology,

economics, management, and organization. Theories from the humanities (anthropology, ethnology, ethnography, pedagogy, psychology, linguistics/language, law, and politics) are also presented, as they are often used for understanding pharmacist's communicative, interdisciplinary and interactive tasks. For a more thorough description of sociological theories used in PPR, see the chapter "Sociology for Pharmacists" by Traulsen, Bissell and Ryan in this encyclopedia. The chapter presents theories of beliefs about health and illness, risk theories, theories of pharmaceutical policy, and theories of the professions. Other sociological theories, such as feminist theories, theories of ethnic minorities, materialist/structuralist theories, and interactionist theories are covered in an article series and a handbook, both of which deal with sociological theory and PPR (Bissell and Traulsen, 2005; Bissell et al., 2001).

Grounded Theory

Grounded theory was developed by Glaser and Strauss (1967). It is an investigative research approach with no preconceived hypothesis or theoretical approach. A study in this tradition presupposes that a theory will "emerge" from the empirical data. The goal of such a study is to generate a theory that explains how some aspect of the social world works. Grounded theory is criticized because it is often used—and has become popularized—by people with no prior knowledge or experience with theory, since it does not require a time-consuming and in-depth argument for a specific theory prior to or during the research process (Lau and Traulsen, 2017). In addition, the analysis and results in grounded theory studies often suffer from an all too obvious naiveté and ignorance of prevailing knowledge in the field (Sandelowski, 1993). PPR has used grounded theory extensively, see for instance Cunningham et al. (2016) who used a grounded theoretical approach for describing GPs and pharmacists perception and experiences of learning together in an interprofessional project.

Behavioral Change Theories and Models

Some of the first explicit theories and pharmacy-based patient adherence studies were carried out in the late 1970s/early 1980s in Denmark and Wisconsin, USA (Svarstad, 1979; Larsen and Hansen, 1985). The Danish contributions in particular spotlighted the development of a user perspective in medicine use, with focus on patient autonomy and self-regulation. In more recent times, the scientific literature on how pharmacy staff can come to understand and thereby help the individual person/patient change behavior (also in terms of medication intake) has exploded with theory-based PPR studies.

Understanding socio-behavioral aspects of patients in the medication use process is paramount to achieving optimal clinical and humanistic outcomes from therapy. Many PPR studies have undertaken the task of trying to understand the extent to which patients' medication-taking behavior is consistent with the recommendations of health care providers. A variety of theoretical underpinnings have been used in PPR regarding studies of pharmacy-based advice and counseling on medication adherence/compliance and concordance. A recent meta-review including almost 20,000 patients by Conn et al. (2016) on theory use in medication adherence intervention studies showed that the most frequently used theories and models were motivational interviewing (34 studies), social cognitive theory (31 studies), health belief model (15 studies), trans-theoretical model (14 studies), and self-regulation/common sense model (11 studies). These theories/models all originate from the health psychology area. The review concludes that theory- and model-linked interventions have a significant but modest effect on medication adherence outcomes. A concrete example of theory-based PPR research in the field was conducted by Alatawi et al. (2016), who successfully created new multidimensional adherence measures by taking patient preferences into account and combining models, such as the trans-theoretical model in combination with the health belief model (Alatawi et al., 2016). Another example is the safe and effective medicine use model (SEM-model) by Henriksen et al. (2008), which combines different types of compliance with motivational interviewing, self-efficacy, a WHO-model of adherence, stages of changes theory, coaching techniques, and narratives.

A long list of PPR studies includes in particular social cognition models/theories such as the Theory of Reasoned Action (Ajzen and Fishbein, 1980), Common Sense Model of Self-regulation (CSM) (Leventhal et al., 1997) and Bandura's concept of self-efficacy (1977). In fact, the social cognitive theory and theory of planned behavior are the most frequently used frameworks in driving change within health care practices (Durks et al., 2017). According to Bandura, the reproduction of an observed behavior is influenced by the interaction of three determinants: personal, behavioral, and environmental. Perceived self-efficacy is a pivotal concept in social cognitive theory. It refers to beliefs in one's abilities to organize and execute the courses of action required to manage prospective situations, and has had an impact on several adherence counseling programs and models used in pharmacy practice research. The key construct of the CSM is the idea of illness representations or "lay" beliefs about illness. The representations integrate with existing schemata, the normative guidelines that people hold, enabling them to make sense of their symptoms and guide any coping actions. Leventhal et al. (1997) describe five components of these illness representations: identity, cause, timeline, consequences, and curability/controllability. While these theories can and do provide some explanation for intentional nonadherence, they do not address the widespread, unintentional nonadherence in relation to medicine intake.

For decades, community pharmacy has contributed to public health in terms of medicine use and other health interventions (Anderson et al., 2003), such as smoking cessation, obesity and weight reduction, skin cancer prevention, nutrition, and physical activity. In particular, the Trans-theoretical Model (TTM), also known as the Changes of Stage Model, has been used for pharmacy-based smoking cessation and has been described extensively in the literature (Greenhalgh et al., 2016). The TTM (Prochaska et al., 1992) is an integrative, bio-psychosocial model used to conceptualize the process of intentional behavior changes based on the six phases: precontemplation, contemplation, preparation, action, maintenance, and relapse. Whereas other models of

behavioral change focus exclusively on certain dimensions of change (e.g. theories focusing mainly on social or biological influences), the TTM seeks to include and integrate key constructs from other theories into a comprehensive theory of change that can be applied to a variety of behaviors, populations, and settings.

Other examples of behavioral theoretical models used in medication adherence programs are the Health Belief Model (Yue et al., 2015), Theory of Planned Behaviour (Bane et al., 2006), and locus of control theory (Rickles, 2010).

A recent review of 47 papers based on theories of planned behavior and pharmacists' personality traits revealed how pharmacists' attributes and attitudes favor the implementation of cognitive and patient-focused health care services and should not be regarded as major barriers to the uptake of extended pharmacy practice roles (Luetsch, 2017).

Patient Safety Theory and Models

Medical error is estimated to be the eighth leading cause of death in the USA (Kohn et al., 1999). Patient safety is a growing major public health issue, since the knowledge, skills and experience of health professionals, including pharmacists, are very much essential for improving patient safety. Patient safety is the reduction of risks of unnecessary harm associated with health care to an acceptable minimum (World Health Organization, 2009).

Since the landmark publication *To Err is Human* (Kohn et al., 1999) by the Institute of Medicine, improving patient safety and reducing medical errors has been a priority for health care researchers around the globe, including PPR.

A systems model often used to study patient safety issues in the pharmacy practice area is the Swiss Cheese Model (SCM) by Reason (1990). The original intention for the model was to provide an essentially cognitive psychological account of the nature, varieties and mental sources of human error. The underlying question is: What can the appearance of relatively nonrandom forms of error tell us about the largely hidden processes that govern our thoughts and actions? The model is used in many fields for risk analysis and risk management, including health care. It likens human systems to multiple slices of Swiss cheese, stacked side by side, in which the risk of a threat becoming a reality is mitigated by the differing layers and types of defenses "layered" behind each other. Therefore, in theory, lapses and weaknesses in one defense do not allow a risk to materialize, since other defenses also exist to prevent a single point of failure. The model thus focuses on the necessity for systems to change and learn.

A series of health care tools have been developed based on the SCM to facilitate the investigation of incidents in clinical practice and to identify educational opportunities at a systems level, also in relation to medicines. For instance, it has been used for the creation of the human error theory (Barber, 2002; Franklin, 2001). Both authors argue that much can be gained in terms of insight into noncompliance, if theories developed to explain human error in organizations are also applied in patient safety studies. The resultant framework encompasses intentional and unintentional noncompliance, shifts blame from the patient, and recognizes the influence of other factors, including organizational ones. There are also consequences for the measurement of compliance and new strategies to improve it.

Learning Theories

Basically, learning is the foundation of what it means to be human. Pharmacists are currently developing so many new roles in both primary and secondary health sectors, developing skills as care providers, prescribers, coaches, and discussion partners, that a strong theoretical focus on pharmacists' learning ability is pivotal for this field of research. Several theories and models of learning styles have underpinned much PPR. Learning styles are considered by many to be one factor of success in higher education. A benchmark definition of "learning styles" is "characteristic cognitive, effective, and psychosocial behaviors that serve as relatively stable indicators of how learners perceive, interact with, and respond to the learning environment" (Romanelli et al., 2009).

Several models and measures of learning styles have been described in the literature. Kolb proposed a model involving a four-stage cyclic structure that begins with a concrete experience leading to a reflective observation and subsequently an abstract conceptualization that allows for active experimentation (Kolb, 1985). Kolb's model is associated with the so-called Learning Style Inventory Instrument (LSI). The LSI focuses on learners' preferences in terms of concrete versus abstract and action versus reflection. Learners are subsequently described as divergers, convergers, assimilators, or accommodators. Primarily adapting aspects of the Kolb LSI, Austin developed and validated the first pharmacy-specific instrument to assess pharmacists' learning styles, entitled the Pharmacists' Inventory of Learning Styles (PILS), to measure dominant and secondary learning styles (Austin, 2004). PPR conducted with both the LSI and the PILS recommended that educators take into consideration the learning style preferences of future pharmacists (Wallman, 2010).

How to educate the next generation of pharmacists in the most appropriate way has long interested pharmacy practice teachers and researchers, with learning during the pharmacy internship in particular drawing academic attention. Learning as such can be categorized according to one of the following three theoretical perspectives: learning as acquisition, learning as participation, or a combination of the two (Wallman, 2010). Learning as acquisition implies that the individual possesses and is aware of the activity, whereas learning as participation implies an ongoing process that is produced and constantly reconstructed through relationships and interactions. Hence, from a participatory point of view, knowledge is not something individually "possessed", but rather a social construction. One of the leading educational researchers Etienne Wenger states that, in practice, learning is a combination of the following four subtypes: learning as doing (practice, i.e., what are we doing?); learning as belonging (community, i.e., where do we belong?); learning as becoming (identity, i.e., who are we becoming?); learning as experience (meaning, i.e., what is our experience?) (Vestergaard et al., 2017).

Theories on the reflexive practitioner and single/double-loop learning by Donald Schön (1983) and Argyris and Schön (1978), among others, have also been used in PPR studies on learning by pharmacists and pharmacy interns (Droege, 2003; Kansanaho et al., 2015; Schumann et al., 2004; Sørensen et al., 2005; Wallman, 2010). Schön (1983) states that reflection is the means by which the complex epistemology of practice may be uncovered.

Patient–Pharmacist Interaction Theories

Although patient-centered communication is extensively described and studied among doctors and nurses, it is not well defined for pharmacists. This is the case even though since the 1960s, community pharmacies have been recognized as being ideally located within the community to provide health education (inspired by Gatherer, 1966). However, patient–pharmacist interactions at the pharmacy in particular have been studied, and several theories have been used to describe interactions, including PRECEDE-PROCEED theory (Paluck et al., 2003; Aslani et al., 2006), interpersonal perception theory (Assa and Shepherd, 2000), patient satisfaction models (Ried et al., 1999; Larson and MacKeigan, 1994), health communications model (Svarstad et al., 1986), and role theory (Guirguis and Chewning, 2005).

Only role theory applied in PPR will be described here, because the theory has been widely used in pharmacy, and because it allows us to account for both actors in an interaction (in contrast to the other theories). In a review by Guirguis and Chewning (2005), the two authors identified no fewer than 30 PPR papers in which four out of five perspectives of role theory (functionalist, symbolic interactionist, organizational, and cognitive) had been applied. Role theory concerns itself with *"a triad of concepts: patterned and characteristic social behaviors, parts or identities that are assumed by social participants and scripts or expectations for behaviors that are understood by all and adhered to by the performer"* (Biddle, 1986).

Among other things, role theory has been used to investigate the pharmacist's role (business, clinical, and professional) (Quinney, 1964), to describe the patient's role in counseling (Schommer et al., 1995), for job satisfaction descriptions (Ralph and Langenbach, 1987), and to examine perceptions of health care providers other than pharmacists (Nørgaard et al., 2001).

Theories of GP–Pharmacist Collaboration

Much has been written about the need for greater cooperation and collaboration in the primary sector, specifically between general practitioners (GPs) and community pharmacists. The advantages of better and increased collaboration for the health care sector include improving patient care, continuity of care, and consistency in the information to patients, as well as optimizing pharmacotherapy. All of these improvements contribute to increased visibility of the pharmacy profession (General Pharmaceutical Council of Spain, 2015). This chapter only covers the main theories on the pharmacist's collaboration with GPs, since the GP is the most important and common cooperation partner for community pharmacists. It is on this collaborative relationship that the majority of theoretically informed papers are written. However, one must bear in mind that pharmacists cooperate to an increasing degree with a variety of other health care practitioners such as nurses, dieticians, and physiotherapists.

Several conceptual models have been developed as a tool to describe and aid understanding of the stages and characteristics of collaboration and integration between health and/or social care professionals and services (Bradley et al., 2012). Relatively little theoretical attention has been given; however, to understanding how these concepts and their characteristics relate to the community pharmacy and general practice relationship. A popular topic of study in PPR on GP/pharmacist collaboration has been the facilitators and barriers to collaboration (e.g. Hughes and McCann, 2003). The most developed theoretical model on GP–pharmacist collaboration is McDonough and Doucette's (2001) collaborative relationship model for pharmacists and physicians. This model was synthesized from previous models of interpersonal relationships, including theories of social exchange, business relationships such as the buyer–seller relationship and organizational behavior, and collaborative care models primarily relating to nurses and physicians. The model attempts to demonstrate factors that influence the level of collaboration, including participant characteristics (level of education, training experience, age), context characteristics (practice environment, type and size) and exchange characteristics (trustworthiness, relationship initiation, and role specification).

In 2012, Bradley et al. further developed the McDonough and Doucette model (2001), and the result was a conceptual model with three main stages of collaboration between GPs and community pharmacists, with level 1 being "isolation", level 2 "communication" and level 3 "collaboration". The model also describes how the three stages of collaboration are characterized by a number of factors, such as locality, service provision, trust, "knowing each other", professional roles, communication, and professional respect. Examples of PPR based on the model can be found in Doucette et al. (2005) and Zillich et al. (2004).

Organizational Theories

Although there is no consensus on whether pharmaceutical care (also called "medicines management" or "medication therapy management" in the USA and UK) is a theory, a model or a practice, there is no denying that studies of pharmaceutical care have had a tremendous impact on PPR and inspired an entire generation of pharmacists to re-evaluate and re-orientate their profession. According to Cipolle et al. (1998), pharmaceutical care (PC) is a professional model of practice that provides medication management services to patients. Cognitive pharmaceutical services, clinical pharmaceutical services, and medication review involving identifying, solving and preventing medication/drug therapy problems are concepts identical to or closely related to PC.

PC was supposed to revolutionize the way pharmacy staff deal with and counsel their patients. Three decades later, one might question whether this has now come to pass (Costa et al., 2017). Pharmaceutical care models and practices differ from country to country. For example, reimbursement for cognitive services varies across countries in Europe, Asia and the Americas. Practice-based research has blossomed in many countries, but with different emphases and challenges. Each country has perspectives of pharmaceutical care and pharmacy practice that impact the implementation and practice model of pharmaceutical care (Farris et al., 2005).

There is one aspect/issue, however, that binds all pharmaceutical care initiatives together throughout the world, namely how to implement and maintain PC in pharmacies on an organizational level. Many studies have been conducted on the facilitators and barriers involved in implementing PC in pharmacies, but there is far less literature on the explicit use of theories for implementing PC and other cognitive services. Roberts et al. (2006) investigated models and frameworks for the implementation of cognitive pharmaceutical services (CPS) in community pharmacy, and divided them into theories dealing with the individual, the internal pharmacy environment, the external pharmacy environment and business-related/financial components. The process of implementation was the focus of just half the models identified, with others focusing on specific services and often seeming to overlook the importance and complexity of the implementation process. Many relied on behavioral theories, with an assumption that changing pharmacists' knowledge, skills or attitude will automatically result in successful change, often ignoring organizational aspects of change (Roberts et al., 2006). However, since 2006 several of these broad frameworks have been utilized. One example is the Active Implementation Frameworks (AIFs), an evidence-based set of frameworks to use when attempting to put into practice any innovation of known dimensions. It consists of five core components: a usable innovation, implementation drivers, implementation stages, improvement cycles, and implementation teams (Blanchard et al., 2017). Another example is Moullin et al. (2016), which described and used the so-called Generic Implementation Framework (GIF). The GIF is an overarching, broad framework that collates and illustrates the core implementation concepts and is suitable across disciplines. It has a skeletal structure into which specific, detailed meta-frameworks, models or theories should be chosen for each concept: innovation, process, contextual, domains, factors, strategies, and evaluations.

Certainly pharmacists work within quickly changing organizations, whether they are embedded in hospital pharmacies, community pharmacies, the pharmaceutical industry, government or nongovernment organizations, or within general practices. Organizational theories (meso-level theories) are thus relevant for framing and analyzing research in this field (Scahill, 2015). As shown below, theories on organizational effectiveness, organizational change, leadership style and entrepreneurial orientation have been applied in PPR. Pharmacy practice researchers have not yet capitalized on the application of management/organizational theories to the extent they could (Scahill, 2015). In PPR especially, the theories resource-basing, double-loop-learning, organizational cognition and managing organizational knowledge could fruitfully be applied (Smith and Hitt, 2005).

With regard to organizational effectiveness theories, the Donabedian model of quality of care in particular has dominated the PPR literature (Jackson et al., 1975; Panyawuthikrai et al., 2005; Rai and Wood, 2018). This model focuses on quality of care as one indicator of high performance, with the impetus on the structures and processes shaping health services delivery and outcomes achieved.

Organizational theories have been used as the basis for describing, understanding and changing community pharmacies, but only to a minor extent. A consistent finding in articles on quality improvement in health care is that change is difficult to achieve (Grol et al., 2007), a conclusion that has also been put forward in several PPR projects, such as Sørensen and Haugbølle (2008). According to the research literature, the majority of interventions are targeted at health care professionals. However, success in achieving change may be influenced by factors other than those relating to individual professionals, and theories may help explain whether change is possible.

A Danish-Australian research cooperation resulted in several theory-based studies describing community pharmacy leadership using Borum's Theory of Organizational Change, which categorizes change strategies as rational, natural, political or open, and Social Network Theory, which helps identify and explain the relationships between key people involved in the change process (Roberts et al., 2003). The transition of a pharmacy practice from focus on dispensing to one that embraces pharmacy service delivery requires the rearrangement of resources and organizational changes. American researchers have used theories of entrepreneurial orientation (EO) and resource adequacy to describe this transition (Doucette et al., 2012). EO consists of elements such as "proactiveness," "autonomy" (decentralization), and "innovativeness". Another theoretical framework, organizational flexibility, has also been used to assess the capacity of community pharmacy to implement change programs and guide capacity-building initiatives (Feletto et al., 2011).

Leadership style theory by Bolman and Deal (2003) has also been applied in a study on the implementation of a new inhaler service in pharmacy (Kaae et al., 2011). Bolman and Deal (2003) distinguish between four mental frames when defining how leaders perceive organizations and their resulting actions. The four frames are defined as structural, human resource, political and symbolic.

Behavioral change is key to increasing the uptake of evidence into health care practice. Designing behavioral-change interventions first requires problem analysis, ideally informed by theory. Yet the large number of partly overlapping theories of behavior makes it difficult to select the most appropriate theory.

A range of theories, models, and frameworks has been proposed to understand the complexity surrounding implementation in different health-care settings, including pharmacy (Garcia-Cardenas et al., 2017). The development of health interventions is receiving increasing attention within scientific literature. In the past, interventions were often based on the ISLAGIATT principle: that is, "It seemed like a good idea at the time" (Hughes et al., 2016). However, the large number of partially overlapping theories makes it difficult to select the most appropriate and utilized theory in PPR. The need for an overarching theoretical framework of behavioral change was actually addressed in a research project in which 128 explanatory constructs from 33 theories of behavior

were identified and grouped. The resulting Theoretical Domains Framework (TDF) appears to be a helpful basis for investigating implementation problems (Francis et al., 2012). The TDF is a theoretical framework rather than a theory. It does not propose testable relationships between elements, but provides a theoretical lens through which to view the cognitive, affective, social and environmental influences on behavior. The TDF was initially developed for implementation research to identify influences on health professional behavior related to implementation of evidence-based recommendations, and has been cited in over 800 peer-reviewed publications (Atkins et al., 2017). For example, in PPR the TDF has been used to identify the relationship between barriers and facilitators to pharmacist prescribing and self-reported prescribing (Isenor et al., 2017), to investigate prescribing errors (Duncan et al., 2012), and to create a model for use in patient-centered, pharmacist-led interactions to improve medication adherence (Wiener et al., 2015).

Technology Theories

The number of services and goods for consumers in community pharmacies has grown concurrently with technological advances, resulting in an interest in research dealing with new and innovative technologies in PPR. These studies have dealt with topics ranging from what happens when a new product/therapy/service enters the pharmacy to how new organizational models are introduced in the pharmacy and their effects. The theoretical basis for these studies can be found in the field of social studies of science and health care technology assessment.

One theory that has caught the imagination of PPR has been the diffusion of innovation theory developed by Rogers (1995). The theory attempts to explain how over time, a product or an idea gains momentum and diffuses (or spreads) through a specific population or social system. This theory can be classified as a "behavioral change model" in that the end result of this diffusion is that people, as part of a particular social/organizational system, adopt a new idea, behavior, or product and thereby do something differently than previously (i.e., purchase or use a new product, acquire and perform a new behavior). The core of this adoption is that the person perceives the idea, behavior, or product as new or innovative, and in this way make diffusion possible.

According to this theory, if the organization has a positive assessment of a new innovation, it is likely to adopt it, and conversely, if the organization has a negative assessment of a new innovation, it is likely to reject it (Pronk et al., 2002).

Rogers' Diffusion of Innovations model has been used in a variety of PPR studies, such as an American study that used it to identify the associations between perceived characteristics of immunization services and backward/forward transitions in pharmacy-based immunization services (Westrick, 2009). This theory was widely used in PPR in Holland. One Dutch study used it to explore the perception of an innovation aimed at implementing patient education and the preconditions for implementing this innovation among Dutch pharmacists (Pronk et al., 2002).

Health Technology Assessment (HTA) is the comprehensive form of policy research that examines the technical, economic and social consequences of technological application. HTA is especially concerned with unintended, indirect or delayed social impacts of technology (Traulsen and Klinke, 2004). HTA has developed an arsenal of tools/methods for evaluating the pros and cons of new therapies including pharmaceuticals. Becoming aware of and subsequently using these tools in PPR can contribute to the acceptance and thereby implementation of improvements and innovation in pharmacy services (e.g. pharmaceutical care) by creating the evidence and documentation necessary to make the advantages of these services visible to a wider audience, including politicians and policymakers (Traulsen and Klinke, 2004; Simoens and Laekeman, 2005; Manfrin et al., 2018). Whereas researchers in 2004 suggested using technology assessment to put pharmaceutical care on the political agenda, almost 15 years later Manfrin et al. (2018) continue to point out the lack of HTA tools in pharmacy practice and in the collection of real world evidence in community pharmacy.

Political Science Theories

The importance of evidence derived from clinical pharmacy on high-level decision-making about pharmaceuticals has made it necessary for PPR to engage in and become more active in the policy arena using its clinical and practice-oriented knowledge base. A necessary precursor to this increased political activity is a thorough understanding of what issues are important in pharmaceutical policy, how they have been dealt with in the past, and how they can be tackled in future (Traulsen and Almarsdóttir, 2005). This requires becoming familiar with and using theories from the political sciences.

One example is the Advocacy Coalition Framework (ACF) Theory. Sabatier and Jenkins-Smith (1999) developed the ACF to describe and explain an otherwise complicated policymaking environment. One of ACF's key terms is belief systems, that is, people engage in politics to translate their beliefs into action.

According to ACF, coalitions are formed and learn from policy implementation. ACF was used in the PPR arena to design a study to analyze some of the mechanisms involved in the political process of deregulating the sale of OTC medicines in the Danish pharmacy sector. The conclusion of this study was that ACF produced results that were detailed, although not clear-cut, generating new insights about policy formation within the pharmacy sector in Denmark. The study showed that both policy ideas and technical information are independent variables that partly explain the course and outcome of the reform process (Larsen et al., 2006).

Another theory, which originates from economics and is used by sociologists, political scientists and recently in PPR, is the theory of regulatory capture. This takes place when a regulatory agency, formed to act in the public's interest, eventually acts in ways that

benefit the industry it is supposed to be regulating rather than the public. This theory has been used to look at how and to what extent this happens in the interactions between regulatory agencies such as the FDA and the EMA and the pharmaceutical industry (Abraham, 2002; Carpenter and Moss, 2014; Borup and Traulsen, 2016).

Ethics

The field of ethics (or moral philosophy) involves systematizing, defending, and recommending concepts of right and wrong behavior. Ethics deals with questions of what should be done and how we should do it. It is about making the best decisions or choices in difficult situations (Sporrong et al., 2005). In general, ethical theories are used to guide decision making and emphasize various aspects of an ethical dilemma. Guidelines are normally used in the search for the most ethically correct solution. These guidelines are based on four broad categories of ethical theory: deontology, utilitarianism, rights, and virtues.

Pharmacists are health professionals who help individuals make the best use of medications. Ethical codes, prepared and supported by pharmacists, are intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society.

Ethical guidelines for pharmacists are associated with several factors. Ethical codes in health care are formulated to protect the patient and the reputation of the profession as a whole, and to be attuned to the growing consciousness of professionalism among various categories of professionals (Sporrong et al., 2005).

An Australian study developed and validated a psychometric measure of cognitive moral development in professional ethics in pharmacy (the psychometric instrument Professional Ethics in Pharmacy). The theoretical foundation of the instrument was based on a hypothesized theory of cognitive moral development in professional ethics, which was integrated into a selection of scenarios pharmacists experienced in practice (Chaar, 2009).

The Future

PPR has been criticized for failing to look outward and thereby concerning itself with narrowly focused evaluations of specific pharmacy services (Almarsdóttir et al., 2014). The added challenge of diminished funding for research and the pressures on researchers to publish results has forced this field of research into "answering questions" and "finding solutions" rather than being free to do basic PPR (i.e. theory and methods development). One sure way to weaken the field is to resort to "writing reports" rather than pursuing scientific research.

Given that pharmacy practice is constantly changing and facing new external challenges, it stands to reason that research in the field must move beyond traditional pharmacy-specific problems by placing them in a context broader than how to use medicines. Some examples are: what are the current trends in pharmaceuticals, organization of work, health care sector services and effective communication with patients/clients. A broader context can be achieved by widening the scope of the research and including a societal perspective to a larger extent than today: for example, including the analysis of other health care professionals and the effects of the continuous expansion of patient power. Widening the scope of the research means simultaneously being aware of and open to adapting new theoretical approaches, which can be found in the scientific literature on public health, health services and societal and economic challenges.

It goes without saying that when considering the future of PPR, it is important to reflect about the future of pharmacy practice itself, more specifically, the community pharmacy. The following is one likely scenario based on current trends. Research conducted on each of these issues would benefit from a theory. The pharmacy of the future will offer even more patient and individual-based services other than medicine than it already does: for example, point of care testing (POCT) (measuring cholesterol, hepatitis, glucose, vitamin D, etc.), vaccination services (already provided by more than 320,000 trained pharmacists in the USA today) and the like. Another service that will expand in future and is already available in some countries is prescription renewal and the prescribing role of the pharmacist. Theories on the pharmacist's clinical judgments and decision making will be beneficial in studying the pharmacist's point-of-care testing and prescribing activities. Previous theoretical models of GP's clinical judgments and prescribing decisions have been described in a review by Murshid and Mohaidin (2017). The review includes a suggestion for a value conceptual model that explains the theoretical linkages existing between marketing efforts, patient and pharmacist, and the physician's decision to prescribe the drugs. More specifically, the review identifies and uses several valuable perspectives such as the "persuasion theory—elaboration likelihood model", "stimuli–response marketing model", "agency theory", "theory of planned behavior", and "social power theory", in developing an innovative conceptual paradigm (Murshid and Mohaidin, 2017). Theories on (and training in) clinical decision making is needed (Duffull et al., 2018).

A closer inter-professional collaboration will increasingly be necessary to coordinate transitional care for patients transitioning from hospital to primary care. This requires pharmacy staff to work even closer with other health care professionals. A meta-analysis of pharmacists located in general practice has favored pharmacist intervention, with significant improvements in patients' blood pressure, glycosylated hemoglobin, cholesterol, etc. in intervention patients compared to control patients. Thus pharmacists located in general practice clinics deliver a range of interventions with favorable results in various areas of chronic disease management and quality use of medicines (Tan et al., 2014). Theories on inter-professional cooperation will increase the quality of research carried out in this area in future.

The ways in which medications are prescribed, dispensed and administered are rapidly changing in pharmacies. Health information technology is central to this transformation and includes a broad array of tools used in managing and sharing patient information electronically, replacing paper records and traditional phone and fax methods. Theories are needed on how to interpret, share and inform about data from apps etc.—and to whom.

New advances in medicine production technology are contributing to a whole new age of therapies, such as 3D printing of medicines and cell therapies. This could mean that medications/treatments will no longer depend on large batch productions from industry, but will provide a niche for individualized treatment originating once again from the local pharmacy. Last but not least, the pharmacy of the future will be green and sustainable through the reduction of plastic and medicine waste, and new methods of protecting the environment from pharmaceutical waste (Nørgaard, 2018). Theories and methods can and should be adapted from the vast literature produced in recent years dealing with environmental issues.

In 1968, Garrett Hardin authored a paper entitled "The Tragedy of the Commons", an economic theory describing how people often use natural resources to their advantage without considering the good of a group or society as a whole (Kümmerer, 2010). When a number of individuals consider only their own welfare in this manner, it leads to negative outcomes for everyone, as the natural resource becomes depleted. This theory can be applied in future research concerned with how we can solve the huge problems associated with the growing antimicrobial resistance in the world, as well as being useful for research on how pharmacies in the future can act responsibly in an effort to reduce the environmental impact of the life cycle of a pharmaceutical in society.

One thing that is certain is the enormous impact on pharmacy practice of the unprecedented rapid increase in technology and automation often referred to as the Fourth Revolution. According to a recent World Economic Forum report (WEF, 2016), more than one-third (35%) of the skills considered important in today's workforce will change. By the year 2020 the Fourth Revolution will have introduced more advanced artificial intelligence, biotechnology and genomics, all of which will transform the pharmaceutical industry, and pharmacy practice including the work and careers of pharmacists. The skills that are foreseen as being important include complex problem-solving, critical thinking, people management and the ability to coordinate others (WEF, 2016). The report also points out that negotiation skills and flexibility, skills high on the list in 2015, will be taken over by machines capable of processing masses of data. Pharmacy practice research must be proactive if it is to stay abreast of these scientific, societal, technological, and organizational trends. If PPR hopes to steer practice and avoid the potential negative effects of these developments, it needs a strategy, preferably one based on specific theoretical grounds. Some of the key drivers of change that will influence the future of pharmacy practice include population demographics, technology (informatics and health/pharmaceutical/device technologies), pharmacy as both institution and profession, consumers of health care services and new research capabilities building on technological changes (Babar and Almarsdóttir, 2015).

eHealth innovations have been identified as enablers of transition from traditional institutional-centered health care to a more patient-centered approach. To enhance the contribution of community pharmacies to the effectiveness and efficiency of health systems, community pharmacy should be ready to play an even more active role in primary health care teams in future. Therefore the use of eHealth solutions in the community pharmacy should be supported, and national medicine management eHealth services and systems can act as a catalyst for the redesign of traditional health services and facilitate the implementation and development of innovative dispensing practices, pharmaceutical care and new pharmacy services. Theories on how to use e-health solutions for patient care are thus needed.

In conclusion, continually renewing PPR requires the willingness to collaborate with social scientists as well as to engage in and become familiar with theories from the social and behavioral sciences. Be bold. Dare to use theories that criticize and challenge the status quo. The problem-solving approach to research is fine for making adjustments in the daily running of pharmacies, but research that strives to innovate requires studies of pharmaceuticals, pharmacies and pharmacists in a broader societal context. A more systematic use of existing theories, particularly for planning and evaluating clinical practice, also within pharmacy, will provide a very useful knowledge base for developing strategies for the future of pharmacy (Grol et al., 2007). Theories will provide a framework for understanding the current and future trends and drivers of change, which in turn will ultimately provide a basis for new and innovative strategies for the future of pharmacy practice and the pharmacy profession.

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Principles, Paradigms, and Application of Qualitative Research in Pharmacy Practice

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Learning Objectives

Upon completing the chapter, the reader should be able to:

1. Discuss the value of qualitative research in deeply explaining investigated phenomena in pharmacy practice.
2. Describe the interpretative frameworks and the philosophical assumptions in conducting qualitative research.
3. Discuss the classification of qualitative research based on the research question and the investigated phenomenon.
4. Describe the most common data collection and data analysis methods used in conducting qualitative research.
5. Discuss the trustworthiness criteria and measures used in qualitative research to ensure quality and rigor.

Qualitative Research Designs in Pharmacy Practice and the Limit of the Evidence

The use of qualitative research methods in health services research in general and pharmacy practice research in particular has been increasing over the past years (Rosenthal, 2016; Tonna and Edwards, 2013). The place and immense value of this approach in pharmacy practice research cannot be overemphasized (Austin and Sutton, 2014). A quick search into the published pharmacy practice literature will confirm that there are several published studies utilizing qualitative methods. These studies have undoubtedly added to the existing body of evidence globally and several might have ultimately informed policy and practice changes in certain countries (Tonna and Edwards, 2013).

In a letter to the editor, Gardner described the immense value of qualitative research to pharmacy practice (Gardner, 2016). The commentator felt that a recent qualitative investigation conducted by Gregory et al. on how community pharmacists make decisions represented an exceptional scholarship in the research question, methods, analysis, and writing (Gregory et al., 2016). Gardner believed that the article has inspired him as a researcher, advanced his knowledge, and would influence his teaching and contributions as a researcher and educator. Therefore, these type of studies may create strong impressions and enthusiasm in other pharmacy practice scholars within the profession. Nevertheless, an examination of a sample of these studies would clearly show that many pharmacy practice researchers utilizing qualitative methods do not report important aspects of the methodology that should have been reported (Lau and Traulsen, 2017) and might have even misunderstood some important methodological aspects. For instance, many researchers have described "interviews" and "focus groups" as their methodology or approach to inquiry in qualitative research. Here, we are not referring to the guidelines for reporting and evaluating qualitative research, but certain fundamental methodological issues that should be known by all qualitative researchers.

Furthermore, several articles in the published pharmacy literature and book chapters have given some overview about qualitative research method in pharmacy practice (Austin and Sutton, 2014; Kaae and Traulsen, 2015). In recent years, pharmacy practice journals such as the International Journal of Clinical Pharmacy (Chen and Hughes, 2016), Currents in Pharmacy Teaching and Learning (Rosenthal, 2016), Research in Social and Administrative Pharmacy (Lau and Traulsen, 2017), and the Canadian Pharmacy Journal (Austin and Sutton, 2014) have published series, special issues, or a part of these, to promote knowledge and utility of qualitative methods in pharmacy research and education. Some of these important resources are comprehensive in nature and cover most important components related to qualitative research that a scholar should know.

However, there are several that are lacking in terms of their inclusivity, and omit important aspects such as interpretative frameworks and philosophical assumptions underpinning qualitative research. Furthermore, attempts have been made by scholars to provide novice and experienced researchers with the nitty gritty of conducting pharmacy practice research using qualitative approach through training workshops or professional development seminars. Our personal experiences and those of colleagues have proven that many teachers of this important methodology do not comprehensively cover several important aspects, even in advance qualitative research methodology courses. In an effort to bridge these gaps, this chapter is primarily intended to provide an overview of philosophical paradigms, approaches to inquiry, quality perspectives, and other fundamental elements of qualitative research as it applies to pharmacy practice research. We made every effort to minimize duplication with other related chapters and ensure that the content would be complementary.

Qualitative research has its origin in the social science disciplines such as sociology, psychology, and anthropology, and has struggled to gain credibility in the health science disciplines, often because of concerns about its robustness and perceived differences in structure for presenting the results (Tonna and Edwards, 2013). For example, the viewpoint, methods, and presentation of findings may vary among a sociologist, an anthropologist, a psychologist, and a pharmacists for a similar research question that requires a qualitative study design. Qualitative research within the health science disciplines has developed as a means to gain an in-depth understanding of human behavior (e.g., patients' needs and preferences), as well as to discover the underlying reasons, attitudes, and motivations that govern such behavior (Kaae and Traulsen, 2015). It provides a deep explanation of the investigated phenomena, settings and procedures that clarify the link between all factors, by revealing unexpected information (Ping, 2008). This description cannot be attained through quantitative research approaches, as they describe phenomena in discrete means (Bryman, 2015; Sofaer, 1999) that might not be appropriate for the research questions and investigated problem (Silverman, 2013).

In pharmacy practice research, qualitative research is used to identify and improve current practices and beliefs by understanding patients' and health-care providers' perspectives about medicine and treatment, which ultimately strengthen the research impact (Kaae and Traulsen, 2015; McLaughlin et al., 2016). However, pharmacy academics, researchers, and practitioners need to develop a certain level of expertise and confidence in conducting qualitative research, which can be achieved by carefully planning and implementing appropriate professional development opportunities related to qualitative research methodology (Behar-Horenstein et al., 2018). Most pharmacy practice textbooks and published studies do not present important philosophical paradigms, approaches to inquiry (methodologies), and quality perspectives related to qualitative research. In fact, most published research studies and textbooks in pharmacy practice assume that the methods of data collection (e.g., focus group discussions or one-on-one interviews) are synonymous with the qualitative research designs or research methodologies. Companion chapters related to qualitative research in this Encyclopedia have extensively discussed topics related to data collection methods, sampling and recruitment of participants, conducting data collection sessions, data analysis methods, ethical issues, and reporting and writing qualitative research. Furthermore, there are chapters exclusively dedicated to some of the approaches to enquiry such as ethnography and phenomenology.

This chapter discusses significant foundational elements for conducting high-quality qualitative research in pharmacy practice. It is structured in six sections. In Section Qualitative Research Designs in Pharmacy Practice and the Limit of the Evidence, the significance of qualitative research in pharmacy practice and some contentious issues surrounding its application in pharmacy are discussed. In Section Interpretative Frameworks and Philosophical Assumptions, the interpretative frameworks and philosophical assumptions underpinning qualitative research are described, so that the qualitative researcher can justify the research methodology and research methods selected. In Section Approaches to Inquiry (Methodology) and Case Applications, the five approaches to inquiry (methodology) are explained, giving practical case examples and applications from the pharmacy practice literature.

In Section Methods in Qualitative Research, a brief overview of the most commonly used data collection and data analysis methods used in health science research in general and in pharmacy practice research in particular is provided. Detailed information

about data collection methods (e.g., observations, documents, individual and group interviews, and Delphi technique), sampling and recruitment of participants, conducting data collection sessions, and data analysis methods (e.g., content analysis, thematic analysis, framework analysis, discourse analysis, and interpretative phenomenological analysis) are discussed in the companion chapter. In Section Quality Perspectives in Qualitative Research, the importance of ensuring rigor in conducting qualitative research is stressed, indicating various measures to ensure quality and to achieve trustworthiness criteria in qualitative research. Finally, in Section Conclusion and Take-home Messages, key conclusion remarks and take-home messages are provided.

Interpretative Frameworks and Philosophical Assumptions

Discussions on research philosophical orientations are usually found in the social science literature, in which the research questions are linked first with a pertinent research philosophy and methodology, before selecting a research method. Nursing and health sciences disciplines have also considered philosophical issues underpinning research because scientific philosophy cannot fully examine human perceptions and behaviors (Winit-Watjana, 2016). However, this research philosophy has not been well developed and expressed in pharmacy practice research (Gray et al., 1999; Winit-Watjana, 2016). This section discusses various philosophical orientations and guiding principles of qualitative research in pharmacy practice because they are the first few decisions and steps in conducting qualitative research.

Interpretative Frameworks

Qualitative research should start with the choice of a problem to be studied, an interpretative framework that guides the study, and a suitable approach to enquiry for the research question(s) (Creswell, 2013).

Interpretative frameworks are the conceptual structures for the researcher's comprehension, which form the researcher's reasoning and views of truth and knowledge (Babbie, 2015). Cohen et al. (2013) defined these frameworks as research traditions, selected according to the research purpose. Interpretative frameworks have also been referred to as social research strategies (Bryman, 2015).

Different scholars, researchers, and academics have categorized qualitative research paradigms or interpretative frameworks differently (Winit-Watjana, 2016). For example, Creswell categorized interpretative frameworks as social constructivism, postpositivism, transformative, feminist, critical frameworks and disabilities theories, postmodern, and pragmatism frameworks (Creswell, 2013). On the other hand, Cohen et al. called interpretative frameworks research traditions and categorized them into positivism, interpretive, critical theory, complexity theory, and feminist research (Cohen et al., 2013). Furthermore, Bryman categorized them either as ontological considerations, which comprise objectivism, and constructionism, or as epistemological considerations, which comprise positivism, realism, and interpretivism (Bryman, 2015). Finally, Silverman suggested that interpretative frameworks represent either naturalism or constructionism (Silverman, 2013).

The following are examples of interpretative framework categories that are used in health services and pharmacy practice research based on the categorizations of Creswell (2013) and Winit-Watjana (2016). Case applications about the use of these interpretative frameworks in pharmacy practice research are provided in **Box 1**, the majority of which are adopted from the work of Winit-Watjana (2016).

Box 1 Case applications about the use of interpretative frameworks in pharmacy practice research

The postpositivism framework was used in pharmacy practice research to:

1. assess patients' experiences in receiving their influenza vaccination in a community pharmacy by conducting a survey with telephone interviews (Poulose et al., 2015).
2. describe the doses and routes of administration of the most frequently used drugs at admission and at day of death in a palliative care center by conducting quantitative content analysis (Masman et al., 2015).

The social constructivism framework was used in pharmacy practice research to:

1. determine the issues that patients taking long-term medicines consider affect their day-to-day lives, including quality of life, by conducting face-to-face interviews (Krska et al., 2013).
2. examine how elderly patients are defined and considered within Australian clinical guidelines for the use of pharmacotherapy by conducting integrative reviews (Singh and Bajorek, 2014).
3. examine the process of adherence to oral chemotherapy in Hispanic and Caucasian children and adolescents with acute lymphoblastic leukemia by conducting semi-structured interviews with patients, parents, and caregivers (Landier et al., 2011).

The pragmatism framework was used in pharmacy practice research to:

1. develop Patient-Reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life (PROMPT-QoL) and evaluate its content validity and preliminary psychometrics by conducting a mixed methods study (Sakthong et al., 2015).
2. determine communication strategies associated with smoking cessation in the National Health Service community pharmacy Stop Smoking program, by conducting a mixed methods study (Rivas et al., 2017).

1. *The positivism (or empiricism) framework* focuses on exploring the objective reality, which is controlled by the researcher, by conducting theory-based research.
2. *The postpositivism (or realism, postempiricism) framework* employs a scientific approach to research, with cause and effect and a priori theories orientation.
3. *The social constructivism (or interpretivism, relativism) framework* opposes the postpositivism framework and focuses on examining and describing the meanings of the world in a complex and subjective manner, emphasizing processes and social and historical contexts, while recognizing the effect of researchers' values and experiences on the research conduction.
4. *The pragmatism framework* accepts multiple realities and focuses on offering practical solutions to the investigated problem.
5. *Transformative, feminist, critical frameworks, and disabilities theories* focus on developing societies or investigating marginalized clusters or examining social patterns, liberty and control, for the purpose of modifying and minimizing these phenomena and associated problems.
6. *The postmodern framework* focuses on the race, class, or gender of participants, while highlighting the influence of variable discourses.

Philosophical Assumptions

Philosophical assumptions are theories and perspectives about ontology, epistemology, axiology and methodology that underpin the interpretative frameworks selected by a qualitative researcher. These philosophical assumptions facilitate the comprehension of the universe, which is enlightened through perspectives and interpretations (Cohen et al., 2013). Some literature refers to these assumptions as **paradigms**, broadly conceived research methodologies, epistemologies, ontologies, and alternative knowledge claims. The choice of philosophical assumptions is important for numerous reasons. First, they influence the selection of the interpretative framework or theories that lead a research process. Second, those assumptions are informed by the researcher's experiences and background and are strengthened by the research activities that researcher conducts. Lastly, the researcher's philosophical assumptions and interpretative frameworks should be clear to the research reviewers, which enables transparency and helps in resolving differences related to diverse interpretative frameworks.

There are numerous means to explain and categorize the philosophical assumptions that are folded within the interpretative framework. For example, Bryman (2015) categorized them as epistemological considerations and ontological considerations, while Cohen et al. (2013) indicated that ontological, epistemological, and methodological considerations influence each other. However, Creswell and Winit-Watjana categorized philosophical assumptions as ontological, epistemological, axiological, and methodological assumptions (Creswell, 2013; Winit-Watjana, 2016) as follows:

1. *Ontological assumptions:* Define the nature of reality, being or existence.
2. *Epistemological assumptions:* Clarify the knowledge of reality, that is, what comprises an acceptable knowledge.
3. *Axiological assumptions:* Explain the role and influence of the researcher's values on knowledge.
4. *Methodological assumptions:* Identify approaches to inquiry strategy or plan of action use to know the reality based on the researcher's reasoning.

Table 1 provides a clarification of how positivism, postpositivism, social constructivism, and pragmatic interpretative frameworks are distinguished because of their underpinning philosophical assumptions. The table is adapted and modified from the

Table 1 Interpretative frameworks and their underpinning philosophical assumptions

Philosophical assumptions	*Interpretative framework*			
	Positivism	*Postpositivism*	*Social constructivism*	*Pragmatism*
Ontological assumptions	A single, objective and external reality exists with universal laws used to describe it	A single reality exists beyond ourselves, but it is known only imperfectly and probabilistically	Multiple realities are constructed through experiences and interactions	Reality is what is useful, practical and works well
Epistemological assumptions	Reality in the form of facts can be measured using reliable and valid tools	Reality can only be approximated through research and statistics	Reality is constructed between researchers and participants	Reality is known through objective and subjective evidence
Axiological assumptions	Researchers are independent of the data with an objective stance and distance	Researchers' biases need to be controlled and not expressed	Individuals' values are honored and negotiated	Values are discussed reflecting knowledge obtained from researchers and participants
Methodological assumptions	Quantitative or scientific and predetermined methods, followed by scientific style of writing	Use deductive methods, followed by scientific style of writing	Use inductive methods, followed by literary style of writing	Use qualitative and quantitative approaches to data collection and analysis

works of Creswell (2013) and Winit-Watjana (2016), and it does not include transformative, feminist, critical frameworks, and disabilities theories or postmodern frameworks because they are not usually utilized in pharmacy practice research (Gray et al., 1999; Winit-Watjana, 2016).

Approaches to Inquiry (Methodology) and Case Applications

In qualitative research, it is important to select an approach to inquiry to attain methodological congruence. Methodological congruence implies that research questions, aims, objectives, and methods are coherent and compatible (Creswell, 2013). The five approaches to qualitative research inquiry as identified by Creswell (2013) are described below:

Narrative Research

Narrative research describes participants' written and spoken stories about their experiences with a phenomenon being investigated. Narrative research considers the phenomenon's series of events and actions that are chronologically connected, highlighting turning points in the story, as it develops through interaction and collaboration between the researchers and the participants. The narrative could be a life story of an individual, or a story of an illness, or a story of a specific phenomenon (Anderson and Kirkpatrick, 2016; Creswell, 2013; Czarniawska, 2004). Case applications about the use of narrative research in pharmacy practice are provided in **Box 2**.

Phenomenological Research

Phenomenological research describes the essence of participants' common experiences of a phenomenon so that the description is a universal essence rather than an individual experience. This description focuses on what participants experienced and how they experienced it, while bracketing the researcher out of the research, by having him/her disclosing his/her personal experience with the examined phenomenon. The described phenomenon could be a feeling, such as anger, or an experience, such as undergoing a surgery (Creswell, 2013; Giorgi, 1997; Moustakas, 1994). **Box 3** provides some case applications about the use of phenomenological research in pharmacy practice.

Grounded Theory Research

Grounded theory research aims to generate or discover a theory grounded in participants' data that conceptually explains a social phenomenon, such as human motivation or patterns of behavior, through a systematic methodology, rather than only describes the social phenomenon. Grounded theory has been developed from being too structured to becoming more constructivist-driven by identifying key explanatory constructs of the phenomenon and the relationships between those constructs (Creswell, 2013; Strauss and Corbin, 1990; Woods et al., 2016). Human phenomena could involve social processes or actions or interactions, such as dealing with death or quality of care or chronic illness. Case applications about the use of grounded theory research in pharmacy practice are provided in **Box 4**.

Box 2 Case applications about narrative research

1. Narrative research was used to examine patients' experiences of taking antidepressants by placing the meanings that patients assign to their stories at the heart of the study process (Anderson and Kirkpatrick, 2016).
2. Researchers made a thematic overview of moral dilemmas experienced by community pharmacists in daily pharmacy practice. The participants wrote a narrative about a moral dilemma they had experienced in clinical practice (Kruijtbosch et al., 2018).

Box 3 Case applications about phenomenological research

1. The phenomenological approach to enquiry has been selected to explore the essence of experiences of African American type 2 diabetes patients with adherence to diabetes medications and their perceived solutions to nonadherence based on these experiences (Shiyanbola et al., 2018).
2. Todd et al. utilized the phenomenological approach to explore the lived experience of patients, caregivers, and health-care professionals in the context of medication use in life-limiting illness (Todd et al., 2016).
3. Shoemaker et al. evaluated patients' medication experiences using unstructured interviews through a phenomenological approach (Shoemaker and De Oliveira, 2008).

Box 4 Case applications about grounded theory research

1. Grounded theory research was used to create a theoretical framework model for the process of adherence to oral chemotherapy in children with acute lymphoblastic leukemia (Landier et al., 2011). However, Woods et al. (2016) argued that there is generally limited literature engaging with theories based on grounded theory in pharmacy practice.
2. Jonsson et al. explored how individuals with medication overuse headache use medications and other strategies to manage headaches in their daily lives and their thoughts about their own use of acute medications. In this study, the data collection and analysis were conducted according to grounded theory methodology (Jonsson et al., 2013).

Box 5 Case applications about ethnographic research

1. Ethnographic research was used to examine interdisciplinary medication decision-making by pharmacists in pediatric hospital settings (Rosenfeld et al., 2017).
2. Rivas et al. (2017) used the focused ethnography approach to explore counseling strategies used in consultations between pharmacy Stop Smoking advisers and smokers. Their aim was to use the findings to develop an intervention intended to improve both service uptake and quit rates in the community pharmacy Stop Smoking program (Rivas et al., 2017).

Box 6 Case applications about case study research

1. Case study research has been used to explore the perceptions of health-care professionals about the provision of clinical pharmacy services in the public health sector in Mexico (de León-Castañeda et al., 2018).
2. Case study research has been used to examine the disconnect between the communities of practice (CoP) learning theory and the educational practices in the Doctor of Pharmacy program at Qatar University (Mukhalalati, 2016).
3. Ryan et al. (2018) provided a descriptive report of stakeholders' experiences and outline their views on the practicalities of setting up and maintaining pharmacy services in general practice in the UK (Ryan et al., 2018).

Ethnographic Research

Ethnographic research involves describing and interpreting the culture of a group by describing the shared patterns of values, behaviors, and beliefs of culture-sharing participants who are located in the same place or who interact frequently. An ethnographic approach is usually conducted in a natural setting through extensive fieldwork and participant observations so that the researcher is immersed in close interactions with the culture of the participant. This immersion enhances a deeper understanding of participants' perspectives, behaviors and actions (Creswell, 2013; Harris, 1968; Rosenfeld et al., 2017). Ethnographic research could focus on participants who share a primitive culture or on participants who have common theoretical orientations, such as marginalized ethnic groups. **Box 5** provides case applications about the use of ethnographic research in pharmacy practice.

Case Study Research

Case study research provides an in-depth examination and understanding of a real-life contemporary bounded system or a particular phenomenon that researchers cannot change over time, to illustrate the significance of another general topic. Case study research most commonly aims to answer why, what, and how research questions, which are explanatory and descriptive rather than exploratory, through multiple data collection methods. Case study research usually ends with the development of a case study-developed theory, which facilitates the understanding of complex interrelated factors that influence the investigated phenomenon. The development of a theory is specifically significant to research in health science because it enhances its rigor. Based on the research question, examined phenomena, and context, the researcher could decide whether it is better to conduct a single case study to understand a phenomenon or multiple case studies (Baker, 2011; Baxter and Jack, 2008; Creswell, 2013; de León-Castañeda et al., 2018; Nisbet and Watt, 1984; Yin, 2014). Case applications about the use of case study research in pharmacy practice and pharmacy education are provided in **Box 6**.

Table 2 summarizes the differences between the characteristics of the five qualitative approaches to inquiry in terms of focus, unit of analysis, and data collection and analysis tools. The table is adapted and modified from the work of Creswell (2013).

Methods in Qualitative Research

Data Collection Methods

Data collection methods can be categorized into five categories: (1) observation, (2) documents, (3) individual interviews, (4) focus groups, (5) audio visual materials, and (6) emails, chat rooms, weblogs, life journals and instant messaging

Table 2 Characteristics of the five qualitative approaches to inquiry

Qualitative approach	*Characteristic*			
	Focus	*Unit of analysis*	*Data collection tools*	*Data analysis tools*
Narrative research	Explores the stories of individuals about their experiences	One or more individual	Primarily interviews and documents	Retelling stories and developing themes using chronology
Phenomenology	Understands the essence of the experience with a phenomenon	Several individuals who have shared the experience	Primarily interviews, but documents and observation are also used	Analyzing data of significant statements about the description of the "essence"
Grounded theory	Develops a theory grounded in data from participants	A process, an action, or an interaction involving many individuals	Primarily interviews with more than 20 participants	Analyzing data through open, axial and selective coding
Ethnography	Describes and interprets a culture-sharing group	Several individuals who share the same culture and values	Primarily observations, interviews and extended fieldwork	Analyzing data by describing themes about a culture-sharing group
Case study	Develops an in-depth description of a case or of multiple cases	An event, a program, an activity or more than one individual	Multiple: interviews, observations and documents	Analyzing data by describing themes of the case and cross-case

(Creswell, 2013). The most commonly used data collection methods in health science research, including pharmacy practice, are discussed below.

Documents

Documents support, tap, and offer explanations of the argument developed from other data collection tools (Hanson et al., 2011; Yin, 2014).

Individual Interviews

Semistructured individual interviews are focused, guided, open-ended, and flexible discussions (Cohen et al., 2013; Crabtree and Miller, 1999; Nunkoosing, 2005; Sofaer, 1999).

Focus Groups

A focus group is an organized discussion about a research topic with a group of participants to gain their joint perspectives (Gibbs, 2012; Hanson et al., 2011; Morgan, 1997).

Data Analysis Methods

Data analysis comprises several fundamental steps that involve continuous revisions, such as reading the transcribed text, arranging and preparing data, coding, summarizing the codes into themes, and presenting the analyzed data as results (Cohen et al., 2013), as illustrated in **Fig. 1**. The most commonly used data analysis methods in health science research, including pharmacy practice, are discussed below.

Thematic Analysis

Thematic analysis is the primary data analysis method that researchers should apply because of its flexibility and compatibility with various interpretative frameworks (Braun and Clarke, 2006; Castleberry and Nolen, 2018).

Content Analysis

Content analysis is a research method that comprises systematic coding followed by quantification of the analyzed data in a logical and unbiased way (Berelson, 1952; Vaismoradi et al., 2013).

Discourse Analysis

Discourse analysis emphasizes the core format and the structure of texts or meanings to examine the assumptions, rules, and concealed aspirations (Brown and Yule, 1983; Gee, 2004).

Quality Perspectives in Qualitative Research

Qualitative research validation helps researchers to conduct quality research. This involves ensuring the rigor of the data collection, management, and analysis methods, by utilizing validation approaches. Approaches to ensuring the quality of qualitative research

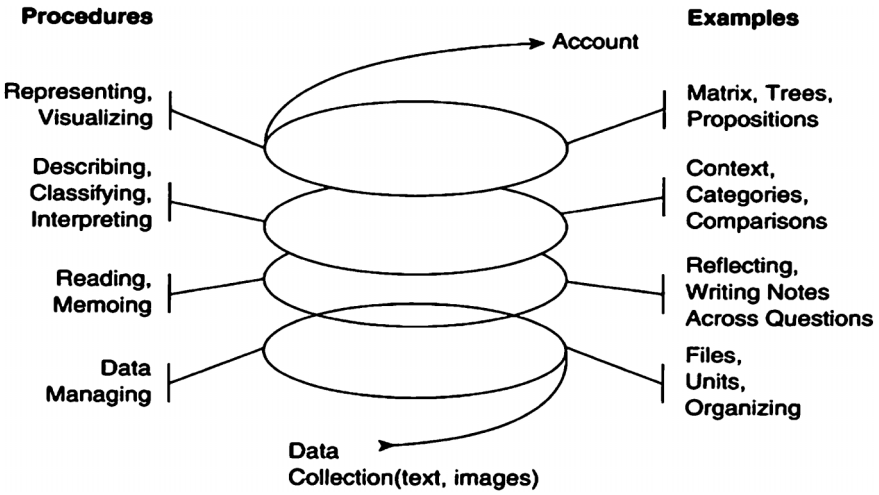

Figure 1 Data analysis spiral. *Source: Creswell, J.W., 2013. Qualitative Inquiry and Research Design: Choosing Among Five Approaches. Sage., p. 183*

are either the same as approaches usually used to ensure the quality of experimental or experiential research, such as internal, external, and construct validity, and reliability (Yin, 2014), or internal validity, external validity, reliability and objectivity (LeCompte and Goetz, 1982), or they are different from approaches used in experimental or experiential research by using qualitative terms such as the trustworthiness criteria, including credibility, conformability, transferability, and dependability (Lincoln and Guba, 1985), or the structural corroboration, consensual validation, referential adequacy, and ironic validity (Eisner, 2017).

In healthcare-related qualitative research, the use of reliability, validity, and generalizability to assess quality should be operationalized carefully because of differences in the methods and in the nature of knowledge produced by conducting qualitative research (Pope et al., 2000). However, while maintaining the efforts for identifying specific operational quality criteria for judging qualitative research in health sciences, it is important to avoid rigidity in defining these criteria and to give the researcher the flexibility in selecting the suitable criteria, based on the research field, goals, and specification (Santiago-Delefosse et al., 2016).

In pharmacy practice research, Hadi and Closs argued that the "quality in qualitative research" topic has not been discussed extensively in the literature compared to other health care disciplines (Hadi and Closs, 2016), and therefore, suggested using at least two trustworthiness strategies to ensure the quality and rigor of qualitative study in the clinical pharmacy discipline. These strategies are categorized under (Lincoln and Guba, 1985) trustworthiness criteria for ensuring quality in qualitative research, which are explained in the following sections.

Trustworthiness Criteria for Ensuring Quality in Qualitative Research

The approach of Lincoln and Guba (1985) to evaluate the quality of qualitative research follows a naturalistic perspective, which is equal to that used in social sciences and quantitative research and includes internal and external validation, reliability and objectivity. The naturalistic perspective to quality proposes the following trustworthiness criteria and approaches (Lincoln and Guba, 1985).

Credibility

This criterion resembles internal and construct validity in social sciences and quantitative research. Applying credibility measures aims to ensure that the results are true and increases the possibility that the conclusions are credible (Cohen and Crabtree, 2008). Credibility can be ensured by applying several measures, including (1) triangulation of data types and sources so that the phenomena is studied from several views, (2) peer review process by other researchers, (3) member checking step, which allows sharing the transcripts and or results with research participants to check that they reflect their actual views, (4) implementation of appropriate data analysis methods, and (5) conduction of reflexivity analysis in order to disclose the researcher's biases and influences in research methods and findings (Lincoln and Guba, 1985).

Dependability

This criterion resembles reliability in social sciences and quantitative research. Applying dependability measures aims to indicate that the research results are repeatable and consistent (Cohen and Crabtree, 2008) and to ensure that the conceptualization of the research, the collection and analysis of data, and the interpretation and reporting of the results are correct (Krefting, 1991). The dependability criterion is achieved by applying several measures, such as (1) collecting data with more than one method so that limitations in one method are balanced by the strengths of other methods, (2) fully describing the research methodology, (3) conducting peer review, (4) maintaining a database of the research that is comprised of all research records and procedures and that

acts as an "audit trail, and (5) conducting intracoder and intercoder reliability testing, which involves independent coding, analysis, and interpretation of the data by the same researcher (intra) or by another researcher (inter) and then comparing the results (Lincoln and Guba, 1985).

Confirmability

The confirmability criterion is similar to the objectivity in social sciences and quantitative research. It aims to confirm the neutrality in interpretation by ensuring that the perspectives of participants, rather than the bias of researchers, influence the results, which allows the findings and conclusions to be supported by other researchers. This criterion can be established by applying the following measures: (1) audit strategy, which requires the researcher to record and maintain all research-related activities and documents, so that an independent researcher can examine the evidence of the results in order to reach similar findings, given the same research context (Krefting, 1991), (2) data triangulation, so that more than one set of evidence is available to support the research findings, (3) oversight of the research activities by senior or peer researchers, (4) describing the research procedures and methods so that they can be followed by other researchers, and (5) conducting a reflexivity analysis (Lincoln and Guba, 1985).

Transferability

This criterion resembles external validity in the social sciences and quantitative research. Transferability involves identifying the contexts and fields to which the study results can be generalized (Yin, 2014) and indicating whether the study conclusions can be applied in similar settings and contexts (Lincoln and Guba, 1985). Hence, comprehensive and rich descriptions of the research context and participants, as well as credible interpretation of the data should be provided. The transferability criterion can be achieved by applying several measures, such as (1) recording and maintaining research-related information and activities, (2) member checking, (3) comprehensive presentation of data interpretation and discussion, and (4) writing up the research (Krefting, 1991; Tuckett, 2005).

Reflexivity in Qualitative Research

In qualitative research, researchers have two roles, as investigators and as participants. Hence, researchers have to position themselves correctly during all research phases and to reveal, evaluate, and reflect about the influences and biases that they can possibly bring to the research process (Creswell, 2013). Researcher influence can be due several factors, such as: gender, class, socioeconomic status, history, perspectives, and experiences (Yin, 2014). Reflexivity can be achieved by applying several measures, such as (1) keeping a research diary, which includes three kinds of information: (a) day-to-day activities and schedules, (b) issues associated with data collection and analysis, and (c) ideas, insights and views generated by interaction with respondents and during results interpretation (Krefting, 1991; Lincoln and Guba, 1985); (2) explaining the researcher's opinion, feelings, and experience with the phenomenon in question; and (3) explaining the influence of this experience on data collection and analysis, on findings interpretation, and on writing up the research (Creswell, 2013).

Conclusion and Take-Home Messages

Qualitative research methodologies have become increasingly recognized and popular in pharmacy practice research. The approach is now frequently used to investigate medication use behaviors of patients, health-care professionals, and caregivers. Qualitative research aims to answer the "why" and "how" questions and to identify and develop current practices by providing a complete and detailed description of the attitudes, values, and perceptions underlying these practices. For the potential of qualitative research to be fully realized and appropriately utilized in pharmacy practice, appropriate considerations of important methodological issues surrounding qualitative research are warranted. With that in mind, qualitative researchers should be well-oriented and well-trained on qualitative research paradigms, philosophical assumptions, methods, and approaches to ensure rigor before conducting qualitative research. This training will ensure that researchers conduct high quality qualitative pharmacy research, while avoiding researcher's personal biases and idiosyncrasies, leading to valuable improvements in pharmacy practice.

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Medicines Management: The Core of Pharmacy Practice

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Introduction

The term "responsible use of medicines" has been used to describe how medicines ought to be used and implies that the "activities, capabilities, and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them" (IMS Institute for Healthcare Informatics, 2012, p. 12). However, despite their benefits, a significant body of evidence suggests medicines are failing to reach their full potential and that the gains are not always capitalized upon. In the United Kingdom (UK), as well as internationally, the profession of pharmacy is increasingly being called upon to better manage medicines. Services are being reappraised and reconfigured to support patients' medicine-taking and to make better use of the pharmacist's skills.

This chapter is divided into four sections. The first considers the broad question "*what is medicines management*?" Following some examples of definitions used to describe the term, we briefly look at where the philosophy of medicines management had emerged from, the synonymous terms used in other countries and the scope of activities that fall within medicines management. In Section 2, we explore the reasons underpinning the medicines management agenda and why this is increasingly being perceived as an important part of healthcare. We draw attention to three "drivers," namely a changing demographic, policy motivations, and lastly pharmacy's professional ambitions to and role extension. In Section 3, we touch on a broad range of pharmacists' medicine management activities within the different sectors of the profession and in the last section we comment on future medicines management opportunities and draw some overall conclusions.

What Is Medicines Management?

In this section we start by reviewing the more common definitions of medicines management. We outline and discuss associated terms and finally outline the scope of activities that falls within medicines management.

Common Definitions

Medicines management is a complex process involving patients and professionals and encompasses the entire way medicines are used. Effective medicines management ensures patients receive the best from their pharmacotherapy, underpinned by the cost-effectiveness of treatment for the best possible outcomes. The process incorporates the ways medicines are selected, procured, delivered, prescribed, administered, and reviewed. In the literature, multiple definitions exist to describe "medicines management." Earlier definitions sought to describe the broad range of activities that encompass medicines management, for example:

> Medicines management . . . encompasses the entire way that medicines are selected, procured, delivered, prescribed, administered and reviewed to optimise the contribution that medicines make to producing informed and desired outcomes of patient care.
>
> Audit Commission, 2001

Other definitions of the term focused more on individual patient care activities:

> Medicines management encompasses a range of activities intended to improve the way that medicines are used, both by patients and by the NHS. Medicines management services are processes based on patient need that are used to design, implement, deliver and monitor patient-focused care. They can include all aspects of the supply and use of medicines, from an individual medication review to a health promotion programme.
>
> MeReC Bulletin, 2002

> [Medicines management is] the systematic provision of medicines therapy through a partnership of effort between patients and professionals to deliver best patient outcome at minimised cost.
>
> Tweedie and Jones, 2001

Later attempts also sought to focus on the broad range of services, the cost-effectiveness of care and safety:

> Medicines management (MM) includes the clinical, cost-effective and safe use of medicines to ensure that patients get the maximum benefit from the medicines they need, while at the same time minimising potential harm.
>
> DH, 2004

Associated Terms

The concept of medicines management appears to have originated from an organization perspective where medicines were paid for and therefore the desire to "manage" them (Barber, 2001). This movement to manage medicines differs from a more patient focused concept of "pharmaceutical care." Whereas medicines management has its origins in policy and organizations seeking to manage medicines, the philosophy of "*pharmaceutical care*" has been conceptualized as a patient-oriented practice (Hepler and Strand, 1990). Emerging from the United States in the 1990s, this concept significantly differed from the traditional "pharmacist as supplier" model that had persisted in the pharmacy profession since the creation of the NHS in 1948. Pharmaceutical care is defined by Helpler and Strand as the "responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Strand, 1990).

It has been suggested that whereas pharmaceutical care focuses on the individual, when provided as an organized service, this is experienced, documented, evaluated, and paid for as a medication management service. The term "medication management service" is therefore seen as "those identifiable events in practice surrounding the professional responsibility of managing a patient's medications" (Cipolle et al., 2012). Whereas pharmaceutical care may be more commonly perceived as pharmacist led, medicines management has been suggested as the joint responsibility of all those involved in initiating or reviewing medications (Blenkinsopp and Bond, 2008). Today, pharmaceutical care in the United States has largely been substituted for the term "*medication therapy management*" (MTM). MTM describes the broad range of professional activities and responsibilities within the licensed pharmacist's, or other qualified health care provider's, scope of practice. It is defined as "a distinct service or group of services that optimize therapeutic outcomes for individual patients [that] are independent of, but can occur in conjunction with, the provision of a drug product" (Bluml, 2005).

In the Australian context, "*cognitive pharmaceutical services*" is a commonly used term in the literature. Having its roots in the concept of pharmaceutical care, this strategy also aims to enhance public health and the quality of drug therapy. It has been defined as "professional services provided by pharmacists, who use their skills and knowledge to take an active role in patient health, through effective interaction with both patients and other health professionals" (Roberts et al., 2006). In the United Kingdom, the concept of "*medicines optimization*" (RPS, 2013) has been developed. Medicines management (the safe and efficient process of issuing medication)

is described as a cornerstone of "medicines optimization" (supporting the best outcomes for patients) (RPS, 2013). Being patient-focused, this newer concept contrasts with medicines management to encompass all aspects of a patient's medicines' journey from prescribing through to ongoing review and support. It therefore shares similarities with the concepts of pharmaceutical care and clinical pharmacy. Medicines optimization is based around the following four key areas:

1. To understand the patient's experience
2. Ensure evidence-based choice of medicines
3. Embed medicines optimization as part of routine practice
4. Ensure medicines use is as safe as possible (RPS, 2013).

Although it may appear synonymous terms for medicines management exist, the proliferation of these concepts reflects the pharmacy professions vibrant thinking and inclusiveness in this area. In the following section we further explore what is meant by medicine management by detailing its scope.

The Scope of Medicines Management

There are many steps involved that eventually enable the patient to take their medicines. This process has been conceptualized as a medicines management "pathway" (Stowasser et al., 2004). Stowasser and colleagues have identified nine steps (cognitive and physical) that describe this process. These are namely: (1) decision to treat and prescribe, (2) record medicine order, (3) review of medicine order, (4) issue of medicine, (5) provision of medicine information, (to the patient) (6) distribution and storage of medicine, (7) administration of medicine, (8) monitor for response, and lastly (9) transfer of verified information. Three background processes are also acknowledged 1. Medicines Procurement and Materials Management; 2. Reporting and Quality Safety Audit Review and 3. Communication (both interprofessional and patient directed). This medicines management framework provides opportunities to identify weak or error-prone processes and so allowing improvements to services to occur (Bajorek, 2011).

To support implementation, the UK Department of Health has produced a summary of the components of medicines' management (**Box 1**).

It is evident that medicines management encompasses a broad range of variegated activities that may have different interpretations to different stakeholders and according to whether medicines management is delivered in primary (community pharmacy/general practice), secondary/tertiary (hospital) or at the interface between these. To further illustrate this scope, five broad groups of services have been outlined by the UK National Prescribing Centre (NPC) namely (1) Clinical medicines management (assessment, monitoring review of patient prescribed medicines, and involvement in specialist disease management clinics), (2) Systems and processes (to deliver safety and efficiency), (3) Public health to meet the needs of the local population (e.g., smoking cessation services), (4) Patient-centered medicine services (e.g., medication reviews), and (5) Interface medicines management (between primary and secondary/tertiary care) (NPC, 2002a,b). A more detailed discussion of pharmacy's involvement in medicines management is presented in Section 3.

Box 1

Summary of the Components of Medicines' Management (DH, 2004)

- Involving patients in the choice of treatment, respecting their views and priorities and enabling them to take a more active role in self-management.
- Deciding whether a medicine is needed.
- Selecting appropriate treatment.
- Providing patient-centered information.
- Monitoring for benefits and safety.
- Reviewing effectiveness of treatment.
- Deciding when to stop treatment.
- Identifying under-treatment as well as over-treatment.
- Reducing medicines wastage.
- Using nonpharmacological options where possible, including health promotion advice.
- Developing patient-friendly ordering and collection systems.
- Promoting better communication between prescribers, patients, carers, and other health professionals.
- Making the best use of resources—evidence-based formularies and guidelines; generic prescribing; synchronization of quantities; medicines no longer needed; optimization of doses.
- Identifying further areas of investment in treatments to produce improved health outcomes, for example prescribing aspirin or statins in patients at risk of coronary heart disease.
- Improving repeat prescribing systems.
- Using professionals appropriately.
- Managing demand.

Why Is Medicines Management Increasingly Becoming Important?

It is well recognized that poor management of medicines may lead to patients not deriving the full benefit of the medicine. Reasons for suboptimal use of medicines are multifactorial and may be related to the patient, the prescribed process, disease state, or inadequacies in the health system (Sabaté, 2003). The opportunities for medicines management to improve patient use of medicines are becoming more pronounced. Broadly, these include increased evidence-based treatment, improved patient safety, increased patient satisfaction, patients' improved knowledge of treatment, improved disease-related outcomes, improved quality of life, reduced practical difficulties in taking of medications, reduced adverse drug events and increased compliance (Blenkinsopp and Bond, 2008). Despite these more apparent benefits, there are other factors that are driving the medicine management agenda. In this section, we look at some of the sociopolitical drivers, in particular, the influence of a changing societal demographic, policy drivers and pharmacy's professional ambitions to extend its role.

Factors Driving the Medicines Management Agenda

A Changing Demographic

The world population is rising and rapidly ageing. The World Health Organization estimates that between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% and that the number of people aged 60 years and older will outnumber children younger than 5 years (WHO, 2015a). For European health systems, it is acknowledged that an aging population, coupled with low birth rates and a higher life expectancy, is one of the greatest social, economic, and public health challenges of the 21st century (Abbing, 2016). With little evidence to suggest that older people today are experiencing better health than their parents, aging brings with it an inevitable rise in chronic health conditions (WHO, 2015a). People with limiting long-term conditions have been found to be the most intensive users of the most expensive health services and as a result their use of health resource, including medicine, tends to increase (DH, 2012). Chronic medical conditions (e.g., heart disease, stroke, arthritis, osteoporosis, frailty, etc.) are the largest cause of disability and death in the world and the global response to the epidemiological and economic impact has been described as inadequate (Yach et al., 2004). Innovative solutions are therefore needed to ensure older people have equitable access to good quality healthcare and support to manage long-term illness.

Given the rising numbers of older people with chronic conditions, polypharmacy is a becoming more prevalent. The burden of taking multiple medications (polypharmacy) is associated with greater healthcare costs, increased risk of adverse drug events (ADEs) and drug-interactions, reduced functional capacity and medication nonadherence (Maher et al., 2014). Work undertaken to optimize safe medication use has highlighted the potential value of appropriate polypharmacy (e.g., prescribing for individuals with multiple conditions where medicines use has been optimized and where medicines are prescribed according to best evidence) but cautions about inappropriate polypharmacy (prescribing multiple medicines inappropriately or where the intended benefit of the medicines are not realized) (Duerden et al., 2013). Reconfiguring health services, roles, and responsibilities is therefore necessary to ensure that the increasing use of medicines is used effectively. In the case of pharmacy, there has been an evident shift in pharmacists' role in primarily the provision of patient education involving acute medications toward consultation-type services for chronic medications (Barnett et al., 2009).

Policy and Economic Drivers

Health policy development and implementation involves complicated processes engaging civil servants, managers, elected members of an authority, professional bodies, pressure groups, and other stakeholders (Ham, 2009). Policy and economic drivers are important factors that shape the drive for the more effective use of medicines. Health economics is increasingly becoming an important decision tool to ensure that medicine resources are used in the most cost-effective way (Babar, 2016).

Growing cost of care and medicines

The complexity and cost of medicines is increasing and ensuring the most effective use of medicines is growing. In most developed healthcare systems, the prescribing of medicines is the most common patient-level healthcare intervention, and is often the second highest level of spending after staff costs (NHS Digital, 2017). With an aging population and such a high spend, policymakers are conscious that medicine will be used most effectively. It has been estimated that about US $500 billion spend may be avoided through better responsible medicine use by health system stakeholders including policymakers/commissioners, clinicians, nurses, pharmacists, and of course patients (IMS Institute for Healthcare Informatics, 2012). The greatest inefficiencies in the health system have been identified as patient nonadherence, untimely medicine use, antibiotic misuse and overuse, medication errors, suboptimal generic use, and mismanaged polypharmacy (IMS Institute for Healthcare Informatics, 2012). As a consequence, medicine management interventions such as medication reviews to improve patient adherence to medicines are becoming a routine part of pharmacy practice. As a response, adherence interventions are increasingly becoming a priority for policymakers and commissioner of health services.

Improving medicine adherence

The term "adherence" is typically used when referring to medicine-taking and is defined as "The extent to which the patient's behaviour matches agreed recommendations from the prescriber" (Horne et al., 2006, p. 33). Unintentional nonadherence occurs when patients experience difficulty in following treatment recommendations due to individual constraints such as inadequate

treatment understanding, forgetfulness, or physical difficulties that prevent them from using their medication effectively. Problems of accessing prescriptions or the cost of medicines may be further causes of patient nonadherence. However, there is recognition that patients may intentionally decide not to take medications as instructed (Horne et al., 2005). This intentional nonadherence arises from beliefs, attitudes, and expectations that influence patients' motivation to begin and persist with the treatment regimen (Nunes et al., 2009).

There is recognition that nonadherence to medicines causes reduced quality of life, increased hospitalizations, and premature death (Ho et al., 2006; Vestbo et al., 2009). It has been estimated that in developed countries, adherence to long-term therapies in the general population is around 25%–50% and is much lower in developing countries (DiMatteo, 2004; Sabaté, 2003). The impact of poor adherence also grows as the burden of chronic diseases grows worldwide and as a consequence leads to poor health outcomes and increased healthcare costs (DiMatteo, 2004; Sabaté, 2003). Moreover, it has been estimated that nonadherence contributes 57% (US $285 billion) of the world's total avoidable cost due to suboptimal medicine use (IMS Institute for Healthcare Informatics, 2012). One report suggests that improving adherence from current levels to 80% across these five areas would save the NHS £500 million per annum (Trueman et al., 2010).

Intentions to develop interventions to improve medicine adherence have also been influenced by the considerable body of evidence that suggests patients have practical problems with taking medicines, may be reluctant to take them because of concerns about side effects, the consequences of dependency, or being unclear about the benefits (Pound et al., 2005). Some patients may not feel that physicians (General Practitioner GPs) have time to discuss and address such concerns (Dugdale et al., 1999; Moen et al., 2009). Furthermore the continuing conformity to the traditional patient role and deference to professional authority has been suggested to limit discussions about treatment (Barry et al., 2001). Shared decisions making has been shown to be appealing and desirable to most patients and to improve medicine adherence. Results from one meta-analysis indicated better patient-physician collaboration is associated with better patient adherence with the relationship being sustained for pediatric and adult populations, chronic and acute conditions, and primary physician and specialists (Arbuthnott and Sharpe, 2009). With pharmacy playing a crucial role in optimizing the use of medicines, they are uniquely placed to improve adherence to treatment. Pharmacist involvement in such activities are discussed in Section 3.

The cost of adverse drug events (ADEs)

Adverse drug events (ADEs) occur in all healthcare systems and can cause serious harm to patients. An adverse drug event (ADE) has been defined as "an injury resulting from medical intervention related to a drug" (Bates et al., 1995) and can include medication errors, adverse drug reactions (ADR's), allergic reactions, and overdoses. ADEs can result in serious patient injury, leading to hospital admission, disability, and even death. ADRs have been implicated in 6.5% of patient hospital admissions (Pirmohamed et al., 2004).

Recognizing the serious personal consequences and costs associated with ADEs, patient safety movements have increasingly grown and are now high on the healthcare quality agenda in many countries of the world (Donaldson, 2002). Building on early initiatives such as "*Pharmacy in the Future*" (DH, 2000), the implementation of medicines management schemes are now seen as a means to reduce the amount of illness caused by medicines not being used correctly, and cut waste. Interventions are being developed to reduce the impact of medication errors and "problematic polypharmacy" (Duerden et al., 2013). Although the majority of errors will be identified before a medicine reaches the patient (near miss), the rates of medication errors and preventable drug-related morbidity are unacceptably common. It has been estimated that a total of 0.7% of global total health expenditure, or US $42 billion worldwide, can be avoided if medication errors are prevented (IMS Institute for Healthcare Informatics, 2012).

Pharmacy's Professionalization Project

Alongside policy ambitions to improve the use of medicines and make better use of the skills that pharmacy can offer, there have been long standing calls within the pharmacy profession itself to develop new roles beyond the supply/dispensing function of pharmacists (Department of Health, 2000; Nuffield Committee of Inquiry into Pharmacy, 1986). Before the creation of the NHS in 1948, community pharmacists were often the first port of call for healthcare advice (Silcock et al., 2004). However, following the creation of the NHS, these pharmacies became independent contractors with payments chiefly coming from dispensing rather than sales of over-the-counter (OTC) medicines (Silcock et al., 2004). Since then, the rise in large scale manufacturing of medicines and predominance of original patient pack dispensing (with patient information sheets supplied), has seen pharmacists exclusive field of knowledge in compounding and formulating medicines, as well as their advisory role, diminish. With pharmacist's work increasingly becoming routine and deskilled, threats to professional claims led to suggestions that pharmacy had become an "incomplete" or "quasi-profession" (Denzin and Mettlin, 1968).

In response, pharmacy has embarked on a process of reprofessionalization (Birenbaum, 1982; Edmunds and Calnan, 2001). Macdonald (1995) uses the term "professional project" for occupational groups who are involved in a strategy of professionalization. A professionalizing project aims to convince the state and the public that the work of the occupational group is reliable and valuable. Professional initiatives have sought ways for pharmacists to move away from the mechanical aspect of dispensing and sale of retail products toward extending the pharmacists' role in more patient-centered and advisory services (Hepler and Strand, 1990). Whereas some have suggested that the criterion for pharmacy professionalism lies in its patient counseling and rationalizing medicine use (Gosselin and Robbins, 1998), others have expressed caution about developing the extended role agenda as a means of enhancing professional status. Harding and Taylor (1997) argue that reprofessionalizing strategies to extend the pharmacist's role in trying to redefine their role may serve to deprofessionalize the pharmacy profession further. Nevertheless, new models of care are

being developed, and medicines management practices are emerging, to ensure the current healthcare needs of the population are met (Murray, 2016; Smith et al., 2013).

Pharmacy's Involvement in Medicines Management

The term "responsible use of medicines" is used to imply the "activities, capabilities, and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them" (IMS Institute for Healthcare Informatics, 2012). Medicines management services help facilitate responsible medicine use by addressing unmet pharmaceutical needs, support patient medicine-taking and develop approaches which improve service efficiency and so reduce medicine waste. Pharmacists are involved in a broad range of medicines management services.

In this section, we initially discuss the influence of the patient-centered care agenda. An overview is then given of the various ways pharmacy is contributing to medicines management in primary care, secondary care, and at the primary-secondary care interface.

The Patient-Centered Care Agenda

A key component to modern medicine management is the patient-centered care agenda which gained prominence in 2001, when the Institute of Medicine (IOM) adopted the concept of as one of the six essential aims of improving healthcare in the United States (IOM, 2001). With patient-centeredness now considered an accepted part of a modern health system and morally valuable (Duggan et al., 2006), reforms of health policies have focused to redesigning care around the patient and provide greater choice (Porter et al., 2013). Berwick (2009) defines patient-centered care as "the experience (to the extent the individual patient desires it) of transparency, individualization, recognition, respect, dignity, and choice in all matters, without exception, related to one's person, circumstances, and relationships in health care." He argues that health professionals should recalibrate their work in order not to act as "hosts" for patients in the healthcare system, but "guests" in patients' lives. This patient empowerment challenges assumptions that health professionals "know best" and there are ongoing efforts to transition away from more "pateralistic" views of healthcare toward a patient-centered and self-management agenda (Barlow et al., 2002).

Patients are increasingly seen as central to the philosophy of medicines management. This has come from calls for patients and professionals to work together in order for patients to perceive a greater degree of control, choice, and therefore influence over their health and healthcare (Darzi, 2008). The rise of patient empowerment, as well as progressive deregulation and the rise of consumerism has also contributed to this movement (Nettleton, 2006). Increasing evidence suggests that patient-centered care is associated with satisfaction, self-management, and decreased health care utilization (Bertakis and Azari, 2011; Rathert et al., 2013). Medicines management services such as the activities described in this section, are constantly being influenced by the patient-centered agenda to ensure the patient remains central to their own healthcare.

Medication Review

It is acknowledged that medicines will fail to realize their potential to reduce the burden of chronic illness if there is poor adherence. As Haynes suggests increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (Haynes et al., 2002). One prominent strategy to improve medicine use is medication reviews. This has become an established role for pharmacists and their involvement is integrating them further into the wider multidisciplinary team. Reviews of medicines can occur in different healthcare service settings such as in community pharmacies, primary and secondary care, care homes, and so on. During such reviews practical problems with the use of medicines and adherence is discussed thereby improving the clinical effectiveness of medicines taken by patients. A medication review has been defined as a "structured critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste" (Shaw et al., 2002, p. 12). A framework has been proposed that classifies medication review into three types:

- Prescription review—Intended to identify prescription anomalies such as duplicate prescribing and does not require the patient or their clinical notes to be present at the review (includes Prescription Intervention MURs).
- Concordance/compliance review—Addresses patient medicines-taking behaviors and designed to discover patient views of their medicines and their willingness to take them (includes MURs).
- Clinical review—Includes consideration of both prescribed and purchased medicines and must be undertaken with the patient and with their clinical notes to enable a holistic view of the appropriateness of the medicines in relation to their conditions.

(Clyne et al., 2008)

Evidencing Medication Review Outcomes

Despite policy and professional drives to develop pharmacy medicine review services, trials to determine the efficacy of such interventions in improving patient health outcomes have been equivocal (Perraudin et al., 2016; Viswanathan et al., 2015). For example, several studies suggest that pharmacists are able to improve the appropriateness of prescribed medicines and reduce the use of high-risk medicines (Chrischilles et al., 2004), identify adverse effects (Bond et al., 2000), reduce inappropriate waste of

medicines (Jesson et al., 2005) and improve quality use of medications, and health outcomes (Jokanovic et al., 2016). Small scale studies conducted by committed pharmacists and GPs have tended to show the most benefit (e.g., Jesson et al., 2005; Zermansky et al., 2001). Larger scale studies or investigations of the impact in practice have also indicated that there is improved clinical outcomes, cost savings, and patient satisfaction following a pharmacist intervention (Elliott et al., 2017; Ramalho de Oliveira et al., 2010). Despite this positive evidence, evidence for medication reviews to improve patient outcomes have come under scrutiny. Some have found little difference in appropriate prescribing or ambivalent health outcomes following a review (MEDMAN Study, 2007; Holland et al., 2008; Krska and Avery, 2008; Latif et al., 2011), whereas others suggest that pharmacist home-based medication review could even increase hospital readmissions (Holland et al., 2005).

Community Pharmacy Medication Review Services: An International Perspective

Several countries have developed the community pharmacist's role toward reviewing patients' prescribed medication. Alongside the UK, Australia, the United States (US), New Zealand, and more recently Switzerland have the most established services. However, there is recognition that these medication review services vary in their comprehensiveness, minimum competency requirements for pharmacists, levels of interprofessional collaboration and remuneration (Chen and de Almeido Neto, 2007; Roberts et al., 2006).

Home medicines review (HMR)

Introduced in 2001, the Australian Home Medicines Review (HMR) service is one of the longest established community pharmacy medication review service. The HMR service was developed following negotiation by the pharmacy profession with the Australian Government to incorporate new, remunerated professional services into community pharmacies to better utilize the skills of pharmacists and for the community pharmacy network in Australia to remain viable (Roberts et al., 2006).

Medicines use reviews (MURs) and the new medicines service (NMS)

Commissioned by the NHS in 2005, the English MUR service is the first national NHS funded service that remunerates community pharmacists for undertaking a documented face-to-face consultation with a patient specifically to discuss their medication. The underlying purpose of MURs "aims, with the patient's agreement, to improve his or her knowledge and use of drugs" (DH, 2005). Outcomes resulting from MURs have been mixed (Latif et al., 2011; Latif et al., 2013a) but has spurred on policymakers to support other services such as the New Medicines Service (NMS) which was launched in 2011 to support people starting a new medicine for asthma/COPD, type 2 diabetes, hypertension, or antiplatelet/anticoagulant treatment (PSNC, 2011). Evidence suggests that the NMS is effective and cost effective compared with normal practice, more specifically, increased patient adherence to their new medicine translated into increased health gain at reduced overall cost (Elliott et al., 2017). However, adopting such services has been shown to be a multifaceted and complex process with workflow, infrastructure, and public and professional relationships all affecting NMS implementation (Latif et al., 2016a; Waring et al., 2016; Waring and Latif, 2017).

Medication therapy management (MRM)

In the United States, Medication Therapy Management (MTM) services provided by community pharmacists began to develop in the 1990s to assist GPs in managing clinical services and contain cost outcomes of drug therapy. MTM services have been described as a partnership between the pharmacist, the patient or their caregiver, and other health professionals and are designed to optimize therapeutic outcomes by improving adherence to medicines, enhance patient understanding of their medication and to reduce adverse drug events (Burns, 2005). Formal MTM services were introduced more widely across the United States in 2006 following reforms resulting from the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Barnett et al., 2009). This act required insurers to offer a MTM program to a target population of high-cost patients who are users of the social insurance programs "Medicare" and "Medicaid" and so have led to greater opportunities for community pharmacists to be reimbursed for medication management services (Barnett et al., 2009).

Medicines use review and adherence support services (MURs)

In New Zealand, Medicines Use Review and Adherence Support services (MURs) were introduced in 2007 and aimed to support adherence to medicines for selected patients (Lee et al., 2009). The New Zealand MUR has several similarities to the UK model. The MUR is a structured consultation involving review of a patient's medication, identifying any practical or medication-related problems, and providing relevant information about these. Similar to the UK model, an MUR accreditation training course provided by the New Zealand College of Pharmacists must be completed before the service can be offered. One difference is that MURs are not nationally funded as they are in the UK and local schemes must be agreed with the local health authorities (Lee et al., 2009).

Polymedication-checks

More recently Swiss community pharmacies have been given reimbursement opportunities to offer Polymedication-checks that have been fashioned on the UK MUR (Messerli et al., 2016) and other countries developing medication review services include Finland, Portugal, Canada, and Germany (Blenkinsopp and Celino, 2006). In less developed countries there are less well evolved programs and in these countries, insufficient training of professionals and lack of pharmacists have been cited as barriers for pharmacists' involvement in medication review services (Silveira de Castro and Correr, 2007).

Community Pharmacist Involvement in Other Medicines Management Activities

In this subsection we detail pharmacists' involvement in general practice settings and briefly explore pharmacist prescribing.

Pharmacists in General Practice

The extent to which healthcare professionals work together influences the quality of the healthcare that they provide to patients. Collaboration is defined by Zwarenstein and colleagues as "the process in which different professional groups work together to positively impact health care" (Zwarenstein et al., 2009, p. 2). Despite the well-known limitations of GP-pharmacist collaborations, including pharmacists working in silos, poor communication, and lack of time and remuneration for collaborative activities (Dobson et al., 2006), pharmacists are increasingly being integrated into general practice clinics. For example, evidence suggests the benefits of pharmacists colocated in general practice clinics (e.g., improve management of chronic conditions such as cardiovascular disease and diabetes) were more likely to be seen when there was interprofessional communication and collaboration (Tan et al., 2014). Positive outcomes have more frequently been observed when there was interprofessional telephone or face-to-face verbal communication when compared with pharmacists delivering medicine management interventions in isolation (Tan et al., 2014).

Pharmacists within general practice are increasingly becoming more common to deliver patient-centered interdisciplinary medication management services. Practice-based pharmacists may not only help reduce prescribing errors (Avery et al., 2012), but could help adherence to good practice guidance such as that from the National Institute for Health and Care Excellence (NICE), and the Medicines and Healthcare Products Regulatory Agency (MHRA). There are mounting calls for new models of care that introduce new roles or change existing roles in General Practice (Bienkowska-Gibbs et al., 2015). With their independent prescribing status, pharmacists are well placed to add value in improving safety, manage medicines, and acute illnesses and so directly alleviating GP workforce pressures (Stone and Williams, 2015).

Pharmacist Prescribing

As prescribing legislation in countries such as United States, Canada, Australia, New Zealand, and the United Kingdom continues to develop, there are more and more opportunities for pharmacists to extend their medicines management expertise into the field of prescribing (Tonna et al., 2008). For example, in Great Britain, legislation that came into effect in 2003 allowing pharmacists to undertake "supplementary" prescribing (a voluntary partnership between an independent prescriber (physician or a dentist), the supplementary prescriber and the patient, within the scope of an agreed named patient clinical management plan). In 2006, this further developed to allow for suitably trained pharmacists to become independent prescribers (Baqir et al., 2012).

Prescribing is defined as "to give directions, either orally or in writing, for the preparation and administration of a remedy to be used in the treatment of any disease" and is distinguished from diagnosing which is "the determination of the nature of a disease, injury, or congenital defect" (Pharmacist Prescribing Task Force, 2010). Prescribing has been described as a four-step process, the first which is to gather information (e.g., presenting complaint, medication history-taking), the second is clinical decision-making (e.g., diagnosis, medication appropriateness), the third is communicating prescribing information (to other health care professionals and the patient), and lastly to monitor and follow-up to ensure the treatment is working (e.g., review patient outcomes, adherence) (Coombes et al., 2011).

Today, pharmacists have been shown to undertake prescribing in various settings such as within primary care, community pharmacies, secondary care, and at the primary/secondary care interface; however the impact on pharmacist workload, patient outcomes, and how this role crosses professional boundaries has yet to be determined (Tonna et al., 2007). In secondary care pharmacist prescribing has been shown to improve medicine safety, enable efficient pharmacist medication reviews, and increase pharmacist integration into the multidisciplinary team (Bourne et al., 2016). However, the challenges of lack of support (financial and time resources), lack of acceptance by medical staff, and barriers to adoption by the pharmacy profession itself exist (Bourne et al., 2016).

For pharmacists to assume an increased role as prescribers, the pharmacy profession will need to ensure there is professional training that will help them develop not only the necessary skills for prescribing but also the scope of practice for individual practitioners. It has been envisaged that pharmacist involvement in prescribing will increasingly allow them to deliver more "comprehensive" medicines management. This may include the following steps: drug therapy selection; prescribing, initiating a monitoring plan, modifying therapy on the basis of ongoing assessments, and discontinuing therapy if deemed appropriate (Pharmacist Prescribing Task Force, 2010). With patients generally reporting a high level of satisfaction with pharmacist prescribing (Famiyeh and McCarthy, 2017) prescribing will continue to be an important area for future engagement in the medicine management process.

Medicines Management in Hospitals: The Role of Clinical Pharmacy

Since the 1980, pharmacists have sought "clinical pharmacy" roles that promote greater integration into the multidisciplinary care team (Harding and Taylor, 1997). Today these roles allow them to apply their pharmaceutical expertise to help to maximize medicine efficacy, minimize medicines toxicity and improve patient health outcomes (Kaboli et al., 2006). The hospital pharmacist oversees the complete medicine distribution cycle including assessment of the prescription according to the diagnosis, dispensing, preparation, through to administration to minimize waste and ensure quality care for patients. Pharmacists also have an important

role in assessing the suitability for patients' own medicines for use and reissue following discharge to avoid waste. For example, medication is designated unsuitable for reuse if:

- there is insufficient quantity,
- the dosage is changed,
- the medicine is stopped,
- use-by dates have expired,
- tablets in the container are mixed,
- there is evidence of physical deterioration,
- the medicine is inadequately labeled, or
- the container had no label or batch number (Spoon full of Sugar 2001)

The Role of the Drugs and Therapeutics Committee (DTC)

Drugs and Therapeutic Committees (DTCs) establish an agreed formulary and clinical advice in line with national guidelines which contribute to effective medicines management. DTCs also have a strategic role in monitoring prescribing practice, ensuring the most cost-effective medicines are prescribed and ensure adherence to nationally agreed treatment guidelines. They vary in numbers and it has been suggested that membership beyond 14–18 members may be more challenging to chair (Stephens, 2005). Typically committees include a prescribing lead or senior clinician, chief pharmacist, commissioners or financial experts, and lay representation.

Formularies and clinical guidelines should be based upon the principles of "evidence-based medicine." Sackett defines this as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996). DTCs have wide impact on prescribing habits beyond the hospital environment, for example, hospital DTCs has been shown to influence GP prescribing as a GP's choices of medicines is likely to be guided by local consultants' treatment protocols. The importance of pharmacist involvement for interprofessional work was recognized in the 1980s (Nuffield Committee of Inquiry into Pharmacy, 1986) and their recognition to contribute to formulary adherence (Baker et al., 1988). Although the core function of a DTC has been largely consistent over the past three decades, with expensive medicines being developed in a climate of austerity, pharmacists' unique medicine skills as well as greater involvement in general practice settings will mean the opportunity for further involvement on such committees will increasingly become important.

Medicines Management at the Primary-Secondary Interface

It is increasingly being acknowledged that transferring patients between care providers, such as on hospital admission or discharge represents a high-risk area period potentially leading to adverse drug events. It has been found that around half of the medication errors that occur in hospital are estimated to occur on admission or discharge (Vira et al., 2006). Medication reconciliation at transitions of care (admission, transfer, and discharge) aims to ensure the correct medications are supplied to the patient at all transition points, avoid medication errors such as omissions, duplications, dosing errors, or drug interactions, and therefore to promote seamless care. Internationally, medicines reconciled at admission is a high priority intervention and has been integrated into the World Health Organization's High 5 s Project due to its evidence of preventing medication-related harm (WHO, 2014a). The medicine reconciliation process has been defined as the "formal process in which health care professionals partner with patients to ensure accurate and complete medication information transfer at interfaces of care" (WHO, 2014a).

Pharmacists' unique training in medication management provides them with the skills to deliver and support medication reconciliation. Despite the heterogeneity between medication reconciliation interventions and how they are evaluated (Mueller et al., 2012), prevention of medication errors through pharmacist-driven medication reconciliation has been shown to avoid medication discrepancy-related errors (Bishop et al., 2015; Gillespie et al., 2009). It has been estimated that up to 67% of inpatients have at least one error in their prescription medication history at the time of admission (Tam et al., 2005), the most common of which is often the omission of a medicine (Cornish et al., 2005). Interventions aimed at reconciling patients' medications at admission have been found to be cost-effective (Campbell et al., 2007). One meta-analysis of pharmacist-led medication reconciliation programs indicated these to be beneficial at reducing ADE-related hospital revisits, all-cause readmissions, and Emergency Department (ED) visits, and supports the implementation of pharmacist-led medication programs (Mekonnen et al., 2016). Innovative and integrated pharmacy-led approaches to medicines management (from admission through to discharge) have been shown to reduce the length of hospital stay and instances of readmission (Scullin et al., 2007) and innovative ways to achieving effective seamless care should be promoted.

When a patient is discharged from hospital there is a transfer of responsibility from the inpatient provider to the patient and primary care physician. The medicine challenges during discharge may be more complex resulting in more discrepancies than on admission (Varkey et al., 2007) as medicines may be discontinued, switched to a new dosage schedule, or new treatments may be initiated. The medicines at discharge will be required to be reconciled with those medicines supplied in primary care and even with those still within the patients home and so medicine discrepancies may occur more frequently on hospital discharge than on admission. Patient discharge summaries are used to communicate between inpatient and outpatient providers. However, it has been highlighted that discharge summaries sometimes fail to provide important information, such as the primary diagnosis, discharge

medication, laboratory test results or may not reach the outpatient provider in a timely manner (Kripalani et al., 2007) and so may adversely affect patient care.

Medication Errors

Medical errors can occur at all stages of the medicines management process. A medication error has been defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of health professional, patient or consumer" and consistently reported to account for between 10% and 20% of all adverse events (Smith, 2004, p. 20). Key areas where medication errors can occur during the process of medicine delivery include inappropriate prescribing, preparing and dispensing, errors during administration (administering the incorrect dose, the incorrect medicine; administering the medicine via the incorrect route) and errors during medicine therapy monitoring.

Pharmacists in both primary and secondary care have a key quality control responsibility in checking patients' medication is appropriate and reducing incidents of medication errors. They initially have a responsibility to ensure their own systems and practices are robust and they adopt models to help identify and address system failures in error management (Garfield et al., 2009; Nesbitt et al., 2017). Other ways pharmacists can reduce medicine error rates may include enhancement of decision-support resources, better labeling/packaging of medications, more effective communication between professionals and patients, pharmacists' medicine review and counseling (Aspden et al., 2006). The incidence of medication administration errors has been reported to be high in long-term residential care (Szczepura et al., 2011). The prescribing in such settings has also been shown to be suboptimal for reasons including inappropriate polypharmacy, inadequate communication and poor handover protocols between staff, interruptions during drug rounds and the lack of clear responsibility for the review of patients' medicines (Parsons et al., 2011). Guidance and ways to optimize prescribing and medicines management in these settings are increasingly becoming important (Millar et al., 2017; NICE, 2014).

The role of technology is also becoming more prominent as a means to reduce medication errors. Pharmacist review of medication delivered on a clinical decision support software platform has been shown to reduce ADR incidence in acutely hospitalized older people (O'Sullivan et al., 2016). Automated Communication Tools and Computer-Based Medication Reconciliation have similarly been shown to reduce hospital discharge medication errors in medically complex patients (Smith et al., 2016). Electronic prescribing also significantly reduces medicine errors by providing timely, legible information. Electronic prescribing support programs offer the prescriber a list of possible medications and can also provide varying levels of decision support, including alerts for drug-drug interactions, drug-allergy contraindications, or checks of prescriptions concerning the patient's recent laboratory results. In the United States they are often referred to as Computerized Physician Order Entry (CPOE) systems and in hospital-related settings, implementing CPOE is associated with a greater than 50% decline in preventable ADEs (Nuckols et al., 2014). The expected outcome is for a more efficient and safer means for patients to obtain the medicines they need. Medication errors can occur in the pharmacy during the interpretation of a clinician's handwriting. E-prescribing is a system of electronically generating and filling patient prescriptions intended to reduce errors associated with handwritten scripts. There is evidence suggesting that e-prescribing can contribute to reduced ADEs of between 30% and 84% (Ammenwerth et al., 2008).

More extended interventions may include the deployment of pharmacists in general practice. In one trial, an information technology-based pharmacist intervention was shown to be more effective than simple feedback in reducing the number of patients at risk of measures related to hazardous prescribing (Avery et al., 2012). In this study, pharmacists received training to identify and intervene on clinically important errors namely: the prescribing of a nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) prescribed to those with a history of peptic ulcer without coprescription of a proton-pump inhibitor; a β blocker prescribed to those with a history of asthma and lastly, long-term prescription of angiotensin converting enzyme (ACE) inhibitor or loop diuretics to those 75 years or older without assessment of urea and electrolytes in the preceding 15 months (Sadler et al., 2014). Although more work and better quality data is needed, marginal health gains at a slightly reduced overall cost have been recorded (Elliott et al., 2014).

Medicines Management in Industry

An aging population with growing multimorbidity presents challenges for the pharmaceutical industry in light of increasing the complexity of independent drug therapy management and administration. Pharmacists' distinct body of knowledge in pharmacology, pharmacodynamics, pharmacokinetics, as well as awareness of patient use of medicines enables them to have a unique skill set for working in the pharmaceutical industry. A patients' age, levels of cognitive decline, and physical disease pattern (e.g., arthritis) can all impact on a patient's handling and administration of medicine and attention must be paid so the pharmaceutical drug product design adequately addresses the particular patient's needs (Stegemann et al., 2016). Older people are a heterogeneous patient population often with comorbidities and may require greater attention. Often polypharmacy is present and the changes in drug metabolism as well as other declines in functional attributes (e.g., visual, hearing, sensory, and motor functions) as well as swallowing difficulties, present unique challenges to ensure medicines are designed and packaged appropriately (Drumond et al., 2017).

Pharmaceutical design teams have the opportunity to improve medicine use by ensuring appropriate routes of administration, that there is ease in opening the packaging and containers and that user instructions are clear and easy to read. Drug packaging

technologies generally have remained the same over the years and further work is needed to ensure medicines are more user-friendly (Drumond et al., 2017). Patient-centric pharmaceutical drug product design is one strategy proposed to explore the interface between a drug product and an individual patients' use of a medicine. As well as being based upon sound scientific principles, there is acknowledgment of the layperson's response to the product design. It has been defined as "the process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target patient population over the intended duration of treatment" (Stegemann et al., 2016).

Facilitators and Barriers

Research into pharmacists' involvement in medicine management services has identified several facilitators and barriers to successful implementation. The more common facilitators and barriers are outlined later.

Common Barriers to Medicines Management

Pharmacists are widely regarded as the most accessible health professionals in the community but currently spend the majority of their time involved in activities associated with the dispensing of prescriptions rather than providing consultations or in medicine management services (Hassell et al., 2011; Lea et al., 2012). Undertaking extended medicines management role activities is challenging and there are many factors that have been shown to hinder the adoption of new extended roles including insufficient integration of community pharmacy input into patient pathways (Blenkinsopp and Bond, 2008). The variability in outcomes and influences that affect the successful adoption of medicine management services appear to be determined by a lack of perceived time to undertake such services, poor use of staffing within the pharmacy and lack of remuneration for undertaking such activities (Bradley et al., 2008a; Niquille et al., 2010). A lack of readiness to change by pharmacists and a perceived lack of workable strategies to adopt newer roles (Blenkinsopp and Bond, 2008; Bryant et al., 2009). Furthermore, their professional performance has been shown to be affected by a variety of factors. One literature search indicated that suggested that performance (particularly in relation to errors) is influenced by multiple factors, including personal characteristics such as age, gender, ethnicity, place of primary qualification, factors associated with the workplace (pharmacist workload and in particular prescription volume) as well as mental and physical health (Schafheutle et al., 2011).

Another barrier faced by pharmacists is the value and acceptance of pharmacy interventions to the public which is not always clear Latif et al., 2013a; Latif et al., 2018. Pharmacists may underestimate the willingness of the public to take part in such interventions (Rodgers et al., 2016). Service users typically have low awareness of such services and pharmacists' advice tends to be welcome when in line with expected core responsibilities (i.e., dispensing prescriptions/advice and treatment of minor ailments), but is less readily accepted if extended beyond their perceived professional boundaries (Eades et al., 2011). Despite the range of extended medicines management services, peoples' use of pharmacies remains predominantly for prescription supplies and management of minor ailments with perception of the pharmacist's role largely portrayed as one of "drugs experts" rather than experts on health and illness (Anderson et al., 2004). Another key factor is a lack of awareness among other healthcare professionals about the pharmacist's skills and attributes (Latif, 2013b). Further barriers include lack of mandate and legitimacy over extended work and GP-pharmacist relationships (Bradley et al., 2008b; McDonald et al., 2010), a lack of privacy or availability of a private space within the pharmacy (Latif and Boardman, 2008) and limitation of services guidelines that may hamper provision to the medially under-served (Latif et al., 2016b).

Common Facilitators to Medicines Management

Reasons reported by pharmacists for becoming involved in extended role activities include enhanced job satisfaction, a break from the routine task of dispensing and the potential to improve their public image to patients and GPs (Grindrod et al., 2010; Roberts et al., 2006). It is clear that addressing the barriers mentioned would facilitate implementation of extended medicine management services such as medicines review. Facilitators to practice change have been cited as: further training and support for pharmacists to enable them to build confidence, reduction in administrative work, improved used of pharmacy support staff (including using Accredited Checking Technicians (ACTs) to reduce the pharmacists' dispensing / checking workload, and better pharmacy layout and workflow (Roberts et al., 2006). Other important facilitators include improving the relationship between pharmacists and GPs (Chen and de Almeido Neto, 2007), increase in public awareness and demand for medicines management services (Rodgers et al., 2016), improved remuneration and clearer messages from the pharmacy profession itself about the future of professional practice (Roberts et al., 2006).

Emerging Medicines Management Opportunities

Healthcare organizations face new challenges and novel areas of medicines management are emerging. Pharmacy is well placed to capitalize on these new opportunities, to foster interprofessional collaboration and so further support patients to take medicines appropriately. In this section we touch on four of the many developing area of importance, namely, eHealth, antimicrobial resistance and stewardship, deprescribing and pharmacogenomics, and personalized medicines.

eHealth

Increasingly, technology is being seen as a convenient means for patients to access health advice. For example, an automated telephone communication systems (ATCS) can provide round-the-clock access to professional advice, deliver voice messages or collect health-related information from patients using either their telephone's touch-tone keypad or voice recognition software (Posadzki et al., 2016). It has been suggested that ATCS can change patients' health behaviors, improve clinical outcomes, and increase healthcare uptake with positive effects in several important areas including immunization, screening, appointment attendance, and adherence to medications or tests (Posadzki et al., 2016). Other ways telecommunication can be used is via text reminders to support adherence (Kannisto, 2016), medicine reordering via a smartphone app (Car et al., 2017) but also more directly through patient-pharmacist telephone consultations about newly prescribed medicines, as in the case of the English New Medicines Service (NMS) (PSNC, 2011).

It is clear eHealth will increasingly be used to improve medicines management and support patient health. EHealth has been recognized as offering opportunities to transform medicines management pathways and every step of the patient's medicines' journey (Car et al., 2017). EPrescribing and the increasing automation of pharmacy dispensing functions allows not only greater efficiency and safer dispensing of medication, but also the freeing up of pharmacists' availability with implications for further advanced training for new and emerging roles (Knoer et al., 2016). In the future, the continuing innovation in eHealth technologies as well as the rise in social media usage are likely to increase demand for more flexibility and novel ways in accessing healthcare; further research is needed to add to this growing evidence base.

Antimicrobial Resistance and Stewardship (AMS)

It has been well-documented that a causal relationship exists between antimicrobial use and misuse leading to the emergence of antimicrobial resistant pathogens (Bartlett, 2011). The pharmaceutical industry is unable to develop new antibiotics to keep up with the emergence of resistant bacteria (Nathan and Cars, 2014). The increasing prevalence of multidrug resistant bacteria led the World Health Organization to identify antimicrobialiotic resistance (AMR) as one of the major threats to human health (WHO, 2014b). Unless this is addressed, it has been suggested there could be up to 10 million deaths resulting from multidrug resistant bacteria with an economic impact of £66 trillion by the year 2050 (Public Health England, 2015). An EU initiative attempting to raise awareness of multidrug-resistant bacteria suggests that there are going to be no new classes of antibiotics in the foreseeable future (ECDC/EMEA Joint Technical Report, 2009).

Many local and global initiatives have been set up to combat antibiotic resistance using antimicrobial stewardship programs. The National Institute of Clinical Excellence (NICE) defines "antimicrobial stewardship" as "a healthcare-system-wide approach to promoting and monitoring rational use of antimicrobials to preserve their future effectiveness" (Cefai et al., 2015). Recently, the World Health Assembly adopted a global action plan on antimicrobial resistance, which outlines five objectives:

- To improve awareness and understanding of antimicrobial resistance through effective communication, education, and training,
- To strengthen the knowledge and evidence base through surveillance and research,
- To reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures,
- To optimize the use of antimicrobial medicines in human and animal health,
- To develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines, and other interventions.

(WHO, 2015b)

It is clear that significant investment in research into current practices and stewardship is needed globally and pharmacists will need to play key medicines management roles to ensure these are a success. As part of their professional role, pharmacists clinically screen all prescriptions to ensure legality, safety, and clinical appropriateness. Pharmacists can therefore play a significant role in the development and implementation of AMS initiatives in both primary and secondary care. Given their professional ambitions to extend their role, community pharmacists have the potential to significantly impact on all five of the above objectives. The effective utilization of AMS programs has the potential to reduce rates of AMR and consequently improve mortality and economic outcomes (Howard et al., 2014; Huttner et al., 2014). All pharmacists therefore have an important role in AMS, not just specialist antimicrobial or infectious diseases pharmacists. Community pharmacists are particularly well positioned to develop and implement new AMS initiatives. This is because they are often the last health professional seen before patient administration. It is therefore imperative to understand the perceived importance of AMS to community pharmacists, if extended roles into this area are to be contemplated.

Deprescribing

The process of deprescribing is receiving considerable attention in the literature (Tjia et al., 2013). Deprescribing has been defined "as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences" (Scott et al., 2015). Inappropriate polypharmacy, particularly in the older population has been shown to account for emergency hospitalizations (Budnitz et al., 2011), increased risks of falls, (Bennett et al., 2014) and

other adverse drug events (Opondo et al., 2012). A simple five-step protocol to deprescribing has been proposed with the following key steps:

1. Ascertain all medicines the patient is currently taking and the reasons for each one
2. Consider overall risk of drug-induced hazard in individual patients in determining the required intensity of deprescribing intervention
3. Assess each drug for its eligibility to be discontinued (e.g., no valid indication, actual or potential harm of a drug clearly outweighs potential benefit)
4. Prioritize drugs for discontinuation
5. Implement and monitor drug discontinuation regimen

(Scott et al., 2015)

It has been suggested that deprescribing should be considered in older patients presenting with a new symptom suggestive of adverse drug effects; medicine use in advanced or end-stage disease, terminal illness, dementia, extreme frailty; receiving high-risk drugs or combinations; and receiving preventive medicines where there is no evidence for continued use (e.g., use of statins in frail patients) (Scott et al., 2015). Pharmacists' greater involvement in deprescribing has the potential to relieve medicine burden, unnecessary suffering, and disability in older patients. Further research is needed to identify the circumstances under which pharmacists can undertake deprescribing and how good practice guidelines can be further developed to confer maximal benefit to patients.

Pharmacogenomics and Personalized Medicines

Drug design and development has conventionally been focused on identifying therapies based on targets of entire populations. At the time of prescribing a person's age, lifestyle, existing comorbidities, and other medications are taken into account. However, an individual's response to medicines may also vary in light of their unique and constant genetic predisposition. It is increasingly recognized that personalized healthcare that incorporates shared patient-professional decision-making can lead to better health outcomes, engagement, and increases the level of trust (Denford et al., 2014). Personalized medicine seeks to tailor treatment to the unique genetic make-up to promote more effective drug therapies, reduced incident of adverse effects and improved quality of life (Agyeman and Ofori-Asenso, 2015). It is likely that medicines management services will become increasingly important in facilitating personalized and integrated care for patients managing long-term conditions (Murray, 2016).

Pharmacogenomics is becoming a reality as it shifts from the research arena into routine clinical practice. The terms pharmacogenomics or pharmacogenetics are often used interchangeably to refer to how the use of the genetic information can be used to better target medicines to individual patients. More specifically, the term "pharmacogenetics" has been defined as "the study of interindividual variations in DNA sequence related to drug response" and "pharmacogenomics" as "the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level" (Committee for Proprietary Medicinal Products, 2002). The potential of pharmacogenetics is yet to be realized and many opportunities exist for novel medicines management roles (Clemerson and Payne, 2008). Although Elhassan et al. (2017) suggest that pharmacists' roles are currently ill-defined and limited, they outline three areas where opportunities exist for pharmacy:

1. *Establishing tests involving pharmacogenetics in clinical practices.*

The use of pharmacogenetics data to inform drug choice and dosage is currently used in specialized areas (e.g., in oncology). Although typically used at the point of prescribing to inform drug choice and dose, as pharmacists develop their role as independent prescribers, these will increasingly become important and relevant. Pharmacists may also develop their role in analyzing how an individual's genetic makeup affects prescribed medicines and so advise on the body's response to medications pharmacologically.

2. *Developing methodologies*

Pharmacists employed in academia, the pharmaceutical, and biotechnology industries have expertise in pharmacokinetics, pharmacodynamics, and the pharmacoeconomics and so are well positioned to contribute to pharmacogenetic research and development.

3. *Educating healthcare providers and helping in the development of infrastructure and create technologies for pharmacogenetics toward its actual implementation in healthcare system*

Establishing pharmacogenetics into pharmacy practice would need to be supported by clinical evidence, infrastructure, and financial incentives. There are indications that pharmacists may not yet have the skill set or confidence to become fully involved with clinical pharmacogenomics (Schwartz and Issa, 2017). In an era where precision medicine is becoming a reality, appropriate education and training for the profession is also needed to ensure pharmacists keep abreast of the developments of pharmacogenetics as they translate to improved patient care to ensure pharmacists are prepared for the opportunities into this area (Clemerson and Payne, 2008).

Concluding Remarks

Societal views of medicines and health continue to change, develop and shape policy, professional, and organizational responses to medicines management. The appropriate, effective, and safe use of medicines is now a global health policy priority. Despite medicines prescribing being the most common patient-level healthcare intervention, the management of medicines presents many challenges. The mounting challenges of antimicrobial resistance, suboptimal prescribing, inappropriate polypharmacy, low patient adherence to treatment, adverse drug reactions and interactions, medication administration errors, and inadequate communication across the primary/secondary care interface are just a few examples of the challenges that are faced.

Helped by their accessibility and locations (Todd et al., 2014), policymakers and commissioners are increasingly seeing the value the profession of pharmacy can bring to address these challenges, reduce pressures on more expensive secondary or family practice services (Imison et al., 2014), and support medicines management. The extended role of pharmacists extended medicines management services aligns well with pharmacy's "professionalization project" and movement away from retail and dispensing toward patient-centered services such as advice-giving and medicines optimization (Mossialos et al., 2015). Many new opportunities therefore await the pharmacists of the future and the climate is right for pharmacists to move forward and expand their professional roles. However a fully integrated medicine management program involving all organizations and stakeholders will need strong professional leadership. New skills and strategies are needed to ensure pharmacists are equipped for the medicine management challenges for the future. This could range from building on existing skills, for example, developing the technique of motivational interviewing to engage more meaningfully with patients (Rollnick et al., 2010), through to developing a new skills set, such as will be required for the practice of pharmacogenomics. The scope of pharmacist involvement in medicines management will mean this remains a cornerstone of pharmacy practice and it will be up to the profession and individuals to decide on its future.

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Historical Evolution of Pharmacy Practice

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History and Definition

Pharmacy is an old profession established as early as 4000BCE by the Sumerians; apothecaries were healers with the combined roles of doctor, pharmacist and priest (Bonanno et al., 2012). Similar roles existed in civilizations in India, China, and Egypt; however, the pharmacy profession has always been linked to the regulation of medicines supply and use (Bonanno et al., 2012). Pharmacy practice may be defined as the application of scientific knowledge and cognitive skills to improve patient outcomes and meet the health needs of the population.

The separation of the role of apothecaries into pharmacists and medical practitioners occurred at various times in different parts of the world. One of the landmark events in this process was in England, where following the Apothecaries Act of 1815 there was a clearer definition of the two streams of practice involving medicine and pharmacy, and the pharmacists' main role became the preparation of products for medicinal use (Pearson, 2007). The Flexner report in 1910 was also a significant driver in the separation of prescribing and dispensing activities in the United States with doctors concentrating on disease management and pharmacists restricting the scope of their diagnostic activities (presumably to common ailments) and concentrating on compounding medicines according to doctors' prescriptions (Bonanno et al., 2012).

Following World War II (WWII) laws were enacted that restricted many medicines to availability only on a doctor's prescription and limited the information able to be provided to the patient by pharmacists, leaving them with predominantly a medicines supply function and they consequently spent less time in contact with the public, other than prescribing treatments for minor ailments (Anderson, 2002; Higby, 2002; Holland and Nimmo, 1999; Pearson, 2007). Pharmacists relied on prescriptions and associated dispensing fees, sales of over the counter medicines, and a variety of health and beauty products to sustain their businesses and were not compensated for their professional services (Bonanno et al., 2012).

Up until the 1980s there were predominantly two areas of pharmacy practice—community pharmacy and hospital pharmacy with small numbers of pharmacists employed in other areas such as industry, academia and regulatory affairs. Prior to that time undergraduate pharmacy curricula comprised mostly science subjects such as chemistry, biology, pharmacognosy, pharmaceutics or formulation, and pharmacology. Other areas, such as law and ethics, were minor topics. Communication skills were less essential, as pharmacists were discouraged from questioning doctors and were not permitted to counsel patients about their medicines.

A pharmacist graduating in the early 1970s had therefore completed a curriculum that had a strong science base. There was little or no formal grounding in common ailments or even the dispensing process, but the basics of making tablets, suppositories, and

sterile products were taught. It was assumed that all the necessary practical aspects of community or hospital pharmacy would be learned during the 1 year of supervised practical training (internship) that followed graduation and which relied solely on the enthusiasm and expertise of the supervising pharmacist, assuming both were present. The newly registered pharmacist, especially in community practice, had little use for much of the knowledge and laboratory skills obtained while an undergraduate, but had hopefully learned sufficient during their internship not to be a danger to the public. The registration exam at the end of the internship was in place to ensure a minimum level of professional competency and to ensure public safety.

In most countries professional pharmacy bodies were formed to regulate the profession and advise or administer appropriate education and training. These bodies developed professional standards and codes of practice to enhance the standing of the pharmacy profession and protect the safety of the public (Bonanno et al., 2012).

In the intervening decades major changes occurred that vastly expanded the scope of practice of the profession. The WHO recognizes seven broad roles for the pharmacist—the "Seven star pharmacist"—Care-giver, Decision-maker, Communicator, Leader, Manager, Life-long learner, and teacher, although sometimes an eighth (researcher) is added (Bonanno et al., 2012; WHO Consultative group on the Role of the Pharmacist, 1997). While a strong science background remains an important underpinning for clinical expertise, since the 1980s the importance of "cognitive skills" (communication, law, ethics, clinical pharmacy, and disease state management) has increased and these constitute "pharmacy practice" in pharmacy curricula.

One could ask, "what brought about the change in the scope of pharmacy practice?" This question does not have a simple answer, certainly economic and political factors were involved, but a complex conjunction of events occurred following WWII that influenced both the need for change in pharmacy practice, and the direction of change.

A Change in Medicines Production

The pharmacist in the early 1900s spent much of his time compounding medications, either according to a detailed formula written by the doctor or according to his own or a standard formula, such as those available in a pharmacopeia (Holland and Nimmo, 1999). Customers would seek the pharmacist's advice regarding minor ailments rather than visit the doctor, and on most occasions, a product would be prepared specifically for that person. There was a fairly limited number of preparations, largely for self medication, that were made in the pharmacy to standard formulas or to the pharmacist's own formula and a few proprietary preparations (Sonnedecker, 2001). This situation continued until after WWII when commercially manufactured medicines became widely available in standard forms and dosages with high standards of quality control and labelling guidelines (Bonanno et al., 2012; Pearson, 2007). Over time successful pharmaceutical manufacturing companies took the role of making medicines away from the individual pharmacist. Doctors progressively abandoned the practice of writing extemporaneous prescriptions in favour of commercial products and by the 1960s the majority of prescriptions written were for manufactured dose forms (Higby, 2002; Sonnedecker, 2001). The extemporaneous dispensing of medicines by pharmacists decreased accordingly and changed the nature of pharmacy practice (Sonnedecker, 2001).

Pharmaceutical research increased markedly after WWII and over the following decades, leading to the availability of an increasing number of new medications (Bonanno et al., 2012). With increased numbers of medications available to treat disease there was a rise in polypharmacy, especially for older patients and those with chronic illnesses, and a subsequent increase in drug related problems. As unnecessary polypharmacy and associated problems increased the cost of health care for the individual and the community and led to increased morbidity and mortality, pharmacists were in an ideal position to use their knowledge and skills to improve patient outcomes and decrease costs (Bonanno et al., 2012).

A Change in Education of Pharmacists

Pharmacists who completed an apprenticeship were designated "pharmaceutical chemists," an appropriate description for someone whose primary responsibility was the preparation and dispensing of medicinal substances (Benrimoj and Frommer, 2004). Following WWII the education of pharmacists in most countries changed from an apprenticeship system to college or university based courses (Benrimoj and Frommer, 2004; Sonnedecker, 2001). The early curricula, focused on science and compounding, led to a profession that saw themselves as "chemists" (Benrimoj and Frommer, 2004).

After WWII, the knowledge and skills required by pharmacists differed greatly from the formulation knowledge required to produce elegant extemporaneous medicines. For example, the introduction of pharmacokinetics was a significant change that linked pharmacy to the cause and mechanisms of disease. This also helped reposition pharmacy practice in health care systems and began the evolution toward clinical contemporary pharmacy practice (Benrimoj and Frommer, 2004).

Over the ensuing decades university courses increased in length from 2 years, to up to 6 years. Longer courses enabled the introduction of a range of pharmacy practice subjects aimed at improving pharmacists' competency in areas of communication, clinical pharmacy, public health, and therapeutics. This has led to graduates with enhanced knowledge and skills in patient-centered care and helped catalyze the change in the practice of pharmacy.

A Change in Information Availability

The use of computers to assist with dispensing became more common from the 1980s, and computerized dispensing and record keeping is now ubiquitous (Higby, 2002). The use of computers made it simpler and easier to maintain records of patients'

medicines, which enabled pharmacists to be aware of their patients' medicine taking history and to intervene more quickly if wrong doses or interacting medication were prescribed, contributing to better outcomes. The additional time available enabled pharmacists to counsel patients on the appropriate use of their medication.

The widespread use of the Internet has also meant that the public has easy access to a wide range of information about medicines and disease—not all accurate or evidence-based. This had led to a public that may be better informed, but that also demands information and expects accurate, informed answers to their questions. Pharmacists now have the ability to retrieve, synthesize and apply published literature to support evidence-based practice and provide appropriate medicines information to their patients and other health professionals.

A Time for Change

The profession of pharmacy was faced with a loss of function as a compounder. The majority of medicines were now available only on the prescription of a medical practitioner. At the same time, as a result of increased numbers of available medicines, treatment regimens became more complex. An expectation developed that information should be available to the patient and that supply of medicines alone was insufficient to ensure their safe and effective use. Laws that had previously restricted patient information provided by pharmacists were changed to encourage them to assist the public to use medicines as intended. In addition, changing community values, increased public sector health services, and increased health spending added to the impetus for improved patient outcomes from medical care.

A tension arose in the profession that was expressed in the need to expand the scope of pharmacy practice, to utilize the knowledge and skills of the pharmacist to assist patients to manage their medication regimens and improve outcomes and to move away from a product—focused service.

Universities recognized that in addition to a strong science base to pharmacists' knowledge they also needed "cognitive" skills to enable them to best fulfil their changing role and Pharmacy Practice departments were established to facilitate the teaching of these skills. Pharmacy graduates now have increased knowledge of the side effects and potential interactions of medicines, skills in communication, and medicines management, the time to utilize these skills in their practice and the legal obligation to do so. The practice of pharmacy was evolving.

Pharmaceutical Care

The concept of pharmaceutical care was introduced as early as the 1970s; however in 1990, the landmark paper published by Hepler and Strand (1990) formalized the concept and provided a definition (Weidenmayer et al., 2006). This encouraged the development of new practice standards, the recognition of the need for collaborative practice relationships, and changed the face of pharmacy practice. The amended definition that describes pharmaceutical care as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life" has been accepted worldwide and is acknowledged as a means for pharmacists to use their knowledge, skills, and availability to improve patient outcomes (Farris et al., 2005; Weidenmayer et al., 2006).

Pharmaceutical care requires that pharmacists accept responsibility for the outcomes of pharmacotherapy in their patients—requiring the documentation, monitoring, and review of therapy. It is a collaborative process that aims to prevent, or identify and solve, medicinal product and health related problems, leading to team-based care where the patient is involved and responsible along with their other health care providers. It is designed to promote health, prevent disease and to ensure that drug therapy regimens are safe and effective (Bonanno et al., 2012; Holland and Nimmo, 1999).

Pharmaceutical care activities have been shown to improve the quality and cost-effectiveness of health care (Weidenmayer et al., 2006). Pharmacists assess therapeutic need, prevent or manage adverse drug reactions, develop patient-specific management plans, manage chronic disease and monitor outcomes. Pharmaceutical care has been broadened by use of the term "cognitive pharmaceutical services" to encompass outcomes related to general patient health and not simply related to outcomes of drug therapy (Moullin et al., 2013).

The implementation of pharmaceutical care services worldwide was strengthened following the International Pharmaceutical Federation Congress held in Tokyo in 1993 and the release of a WHO document on the role of pharmacists in healthcare. The full implementation of pharmaceutical care may, however, be somewhat limited by the difficulties associated with different cultures, languages, and health systems (Farris et al., 2005; van Mil et al., 1999).

Modern Pharmacy Practice

While dispensing by pharmacists remains an important activity, particularly in community pharmacy, the scope of pharmacy practice has broadened substantially since the 1950s, moving from a profession that was product-centered, with a focus on the preparation and supply of medicines, to one that is patient-centered. The current scope of pharmacy practice is focused on services that require specialist knowledge and skill, such as medication history taking, providing medicines information, initiating and

monitoring drug therapy, and counseling patients on their medication regimens and health promotion to improve health outcomes. The technical aspects of pharmacy practice, such as dispensing and medicines supply management can be delegated to trained technicians or to robotic dispensing systems (Holloway et al., 1986). While pharmacists are still needed to oversee these functions, their time is now free to provide cognitive services. The expertise of pharmacists and the services they are able to provide in a wide variety of roles still need wider recognition by the general public, other health professionals and governments (Speedie and Anderson, 2017). A remuneration system, not dependent on medicines supply, must also be in put in place to enable pharmacists to provide an expanded range of patient care services.

While it would be nice to believe that all pharmacists, in all settings, were providing optimal pharmaceutical care, sadly that is not currently the case. The ability to provide a comprehensive range of pharmacy services may vary and be restricted by local laws and a shortage of qualified pharmacy personnel (Bonanno et al., 2012). Where these restrictions do not apply there is still, however, marked inconsistency in the quality of pharmacy services provided, and in the willingness of pharmacists in practice to embrace change, maintain the professional development required and demonstrate the skills that the pharmacy profession has fought to have recognized. Pharmacists may be their own worst enemy in resisting efforts to introduce practice change and develop new roles that utilize their knowledge and skills (Rosenthal et al., 2010).

Whilst it should be recognized that pharmacy practice varies in different countries and also according to practice environment—community, hospital or other, the responsibility for ensuring safe, effective and rational use of medicines now lies with pharmacists. Many countries have now granted pharmacists prescribing rights, recognizing their ability to select appropriate therapy, monitor continuing therapy and manage complex patients. Pharmacists as supplementary prescribers and according to a specific area of expertise, have the ability to initiate, modify or discontinue therapy according to established protocols. Some countries have extended independent prescribing authority to pharmacists practicing in an area of specialty (Bonanno et al., 2012; Sosabowski and Gard, 2008).

Evolution of Community Pharmacy Practice

Between the end of WWII and the 1970s community pharmacy was principally focussed on supply of mass produced medicines and over the counter medicines, coupled with retailing of health and beauty products. With increasing numbers of prescriptions to dispense pharmacists spent more time in their dispensaries focusing of medicines supply and less time interacting with patients, other than for primary care purposes (Bonanno et al., 2012). While this is still the case for many pharmacists, practice is changing as a range of patient-centered services—provision of medicines information, medicines management services (e.g., "MedsCheck" and Home Medicines Review) provision of services to aged care facilities, public health programs (including immunization, blood pressure management, cholesterol testing, smoking cessation assistance), and chronic disease management (diabetes, asthma, hypertension) are implemented. Pharmacists are now increasingly being recognized and remunerated by governments and insurers for a range of these patient-centered services (Davies et al., 2014). Much of the pharmacists' role in medication management is, however, directed toward prescribers rather than patients (Duffall et al., 2017).

A modern pharmacy may use technicians to undertake aspects of dispensing or robots to manage the technical aspects, freeing the pharmacist to provide an expanded range of patient focused services (Holloway et al., 1986). The range of activities undertaken by technicians varies widely across the world from supervised practice to independent practice (Koehler and Brown, 2017). Where there is a shortage of pharmacists, technicians' and other pharmacy support cadres' provision of pharmacy services is fundamental to public access to medicines (Koehler and Brown, 2017). While regulation and recognition of the activities of technicians is generally lacking and education and training standards vary widely, it is recognized that they are integral to pharmacists' ability to expand their scope of practice (Koehler and Brown, 2017). Regardless of new services offered through community pharmacy and the use of technicians in some countries, dispensing still occupies the majority of time spent by pharmacists and many pharmacists are still reluctant to explore new roles and deliver patient-centred services (Davies et al., 2014; Farris et al., 2005; Holland and Nimmo, 1999; Rosenthal et al., 2010).

The public is also largely unaware of the extent of the changes to the pharmacists' scope of practice, perhaps due to an out-dated view of community pharmacy or lack of awareness of currently available services, and they are yet to take full advantage of pharmacists' potential as medical advisors and advocates (Adamcik et al., 1986; Speedie and Anderson, 2017). The ultimate goal, however, is for community pharmacies to be recognized as providers of professional pharmacy services, not simply as retailers of health-related products (Moullin et al., 2013).

New Community Pharmacy Services

As the community pharmacist is the most accessible health practitioner, pharmacists are, and are likely to continue to be, the primary source of advice and assistance regarding common or "minor" ailments. An increasing range of potent medications, from H2 antagonists to asthma medications, is available for supply over the counter requiring supervision and advice by the pharmacist, enhancing the pharmacists' role as providers of primary care.

Patients now have access to a diverse range of information, both reliable, and unreliable. As medical and medicines information is easily accessible the public will increasingly require assistance in its interpretation and pharmacists may find a role assisting others to understand the available evidence and as advocates for patients in health care settings. Through its direct access to the population

community pharmacy also has the potential to influence public health by promoting programs such as those aimed at improving oral health, smoking cessation, chronic disease management (Ibrahim et al., 2012).

Home Medicines Review for persons living at home and Residential Medication Management Review for persons living in aged care facilities are pharmacy services in Australia that are remunerated by the government. A Home Medicines Review is a comprehensive clinical review of a patient's medicines in their home by an accredited pharmacist on referral from the patient's general practitioner (Australian Government Department of Health). While these services are provided through a community pharmacy, the comprehensive reviews are time-consuming to produce and are generally conducted by specifically credentialed consultant pharmacists (Benrimoj and Frommer, 2004).

Although extemporaneous prescriptions have largely disappeared from most community pharmacies, there is still an occasional need for individualized medicine to be compounded to meet specific patient requirements and specialist compounding pharmacies have arisen to meet this need (Minghetti et al., 2014). These specialized pharmacies prepare compounded medicines for particular patients on behalf of noncompounding community pharmacies that do not have the facilities or the raw materials to compound medicines.

The advent of dose administration aids has facilitated development of medicines supply services by community pharmacies to aged care facilities and the general public (Silcock et al., 2004). These were initially offered free of charge in place of prepackaged/commercial preparations. Their use has contributed to increased patient safety through decreased administration errors and ease of monitoring of medicines. The wider use of this service, and the increased cost of providing it, has prompted the need for a charge and its continued viability will depend on a satisfactory remuneration model (Farris et al., 2005; Silcock et al., 2004).

Evolution of Hospital Pharmacy

Pharmacists in hospitals have demonstrated positive impact on improved outcomes of care, decreased adverse events and shorter lengths of stay thereby reducing health costs (Cruthirds et al., 2013; Dooley et al., 2003; Lucca et al., 2012).

Up until the 1970s the majority of hospital pharmacy departments were confined to larger hospitals, were likely to be located in hospital basements and primarily had a supply and manufacturing function. Other than for outpatient dispensing, hospital pharmacists rarely saw a patient or spoke to a doctor. Hospital pharmacists then recognized that there was a decreased need for compounded medicines, other than sterile or oncology patient-specific preparations, and increasing scope for improving the safety and effectiveness of drug therapy (WHO Consultative group on the Role of the Pharmacist, 1997). Pharmacy services in hospitals therefore changed to become increasingly patient-focused with pharmacists progressively included as members of the health care team. In some countries, hospital pharmacy services have not developed at the same rate, principally due to restrictive legal and professional frameworks (van Mil and Schultz, 2006). The transition of patients between hospital and home has also become a major focus for hospital pharmacists recognizing the potential for drug related problems to occur at these interfaces (van Mil et al., 1999; Vuong and Marriott, 2006).

The development of "clinical ward pharmacy" where the pharmacist, in possession of accurate patient information, constructively contributes to decision-making and patient care and intervenes to improve patient outcomes, was the result of decades of change and relationship building. Clinical pharmacy services required pharmacists to have unrestricted access to inpatient medical notes, results of tests, previous medical history, to interact with the healthcare team in addition to the ability to visit patients in the wards to obtain an accurate medicine history and counsel on prescribed medication (Weidenmayer et al., 2006).

The first move toward clinical pharmacy was the introduction of "satellite" pharmacies that positioned pharmacists closer to the wards and more available to answer questions from nursing and medical staff and to obtain necessary information about patients (WHO Consultative group on the Role of the Pharmacist, 1997). Counseling the patients on discharge was also more efficient if undertaken on the ward. Slowly pharmacists won the right to undertake ward rounds, mostly independently, to speak to patients to gather medication histories and view medication orders. This knowledge facilitated the identification of drug related problems such as missing medication, duplicated therapy, drug interactions, and dose discrepancies. Pharmacists were able to be present at ward nursing handover meetings, although it was some time before they were permitted to make notes in the patient's permanent medical record (Weidenmayer et al., 2006). As hospitals employed a number of pharmacists they were able to share experiences and educate each other about interpreting test results, drug related problems and disease management.

Clinical pharmacy requires an expert knowledge of therapeutics, disease state management and the ability to assess laboratory tests, together with excellent communication and interpersonal skills, promoted a strong pharmacist-patient relationship and a closer interaction with other health professions (Adamcik et al., 1986; Anderson, 2002). As the knowledge and skills of the pharmacist were recognized they assumed roles in a range of outpatient clinics where they manage complex patient medication therapies using evidence based decision-making and may have supplementary or independent prescribing rights. In practice a number of models may exist in different countries depending on their workforce capacity.

As qualified technicians may have responsibility for the majority of medicine supply functions in hospitals, pharmacists now also provide additional services such as medicines information including drug protocol design and drug policy development, formulary development, or clinical trials.

The evolution of hospital pharmacy has not proceeded at the same rate in many countries as it has in the United States, United Kingdom, Canada, and Australia. In an effort to increase the standard of hospital practice globally, in 2008 the International Pharmaceutical Federation (FIP) organized a meeting that led to the publication of a number of consensus statements that defined a

baseline standard of practice for hospital pharmacy (International Pharmaceutical Federation, 2014). While it is recognized that not all hospitals will be able to meet all/most of these standards, they provide a guide for pharmacists wishing to improve practices in the hospitals where they work (Bonanno et al., 2012).

Evolution of Academic Pharmacy

Over the period since WWII, there have been a number of significant changes to pharmacy education. For centuries, the exclusive mechanism for entry into the profession was through an apprenticeship (Bonanno et al., 2012). Under this system the aspiring pharmacist would work side-by-side with the established pharmacist, learning by observing and doing medication-related activities under the tutelage of the master pharmacist, leading to widely varying levels of expertise. The apprenticeship was supplemented, especially in later years, by coursework and examinations to ensure a basic level of competency prior to registration (Sonnedecker, 2001).

From the 1800s, many universities opened pharmacy schools; however, degrees in pharmacy as the means of entry into the profession appeared much later (Bonanno et al., 2012; Sonnedecker, 2001). Gradually pharmacy degree courses that were predominantly science-based were mandated as an alternative to apprenticeships and then as the sole means of obtaining registration as a pharmacist. Many countries have retained the requirement for a year in practice (internship) following the formal university degree before being eligible for registration. This year in practice is, in some countries, now being incorporated into the university curriculum. It is important that pharmacist education and pharmacy curricula are "needs-based." Pharmacy curricula need to be able to adapt to local needs and to changes in practice, however, no core curricula are able to be described that would suit the needs of all countries in producing pharmacists suited to their individual local needs (WHO Consultative group on the Role of the Pharmacist, 1997). The pharmaceutical services that are to be provided by graduates need to be considered when designing the curricula to ensure that graduates meet those needs and are "fit for practice" (Anderson et al., 2010).

The product-centered role of the pharmacist translated into an education that was geared to providing knowledge on the source of medicines, their action in the body and the formulation of medicines into appropriate dosage forms. Pharmacy degrees were therefore very strongly oriented toward sciences such as chemistry, pharmacology, and pharmaceutics, and the technical and legal aspects were associated with dispensing. The introduction of the concept of pharmaceutical care that heralded a change in direction of pharmacy practice also led to a change in the direction of pharmacy education. From the 1990s the majority of courses have increased in length and incorporated substantial experiential learning to embed knowledge and skills and attributes such as empathy, cultural competence, and clinical reasoning (Anderson, 2002; Bonanno et al., 2012).

In the United States, also in 1997, a decision was made that the entry-level pharmacy degree would be a PharmD, requiring a minimum of 2 years of pre-pharmacy courses and a four-year pharmacy degree with integrated practical experiences. Many other countries throughout the world are moving toward a PharmD to increase the supply of clinically trained pharmacists and change the scope of the pharmacy profession locally (Kahn, 2011). The difficulties faced in introducing a clinically oriented degree in many countries relate to the lack of appropriate clinical training sites, maintaining a contemporary curriculum and the dearth of academic staff with appropriate qualifications and experience (Kahn, 2011). In many of the countries where the PharmD has been introduced graduates face resistance from other health care providers such as doctors and nurses to establishing a new scope of practice for pharmacy (Kahn, 2011).

Whether the degree is a Bachelor, Masters, or Doctorate, curricula now have a strong emphasis on patient care, public health and health promotion activities and the necessary associated skills and the level of competency required for registration has become more rigorous (Bonanno et al., 2012). The changes to pharmacy curricula have also required a major commitment by universities to faculty development and the employment of clinical teachers and teacher-practitioners. Teaching methodology is moving away from formal, large lectures to more active learning strategies that are student-centric rather than teacher-centric to encourage students to be responsible for their own learning and to develop life-long learning skills (Weidenmayer et al., 2006; WHO Consultative group on the Role of the Pharmacist, 1997). The integration of science and practice is becoming more commonplace and helps students understand the relevance of the science they are learning to the clinical pharmacy and patient centred care they expect to practice. Experiential learning opportunities are recognized as important as pharmacists practice in a more collaborative, multidisciplinary environment.

Continuing professional development (CPD) is mandatory in many countries to ensure that pharmacists maintain their knowledge and skills in their area of practice, especially in view of the rapid pace of change and an increasingly well-informed general public. It is critical to the continued evolution of the profession that appropriate CPD opportunities exist (Council on Credentialing in Pharmacy, 2014; International Pharmaceutical Federation, 2016).

Many countries have numerous pharmacy schools and adequate academic capacity to produce more pharmacists than are necessary to meet that local need (Kheir et al., 2009). Pharmacists therefore find employment in countries with low pharmacist numbers attractive. Expatriate pharmacists are able to partly fill the need for pharmacists in countries that are unable to locally educate adequate numbers to meet demand (Hasan et al., 2011). Pharmacists educated in low-income countries may conversely find that employment in other countries is more lucrative than in their home country and choose to practice outside of their home country. Pharmacist mobility can have benefits for the individual in providing an opportunity to practice and learn skills in a new environment, but it can be detrimental to countries where there are insufficient local pharmacists.

Evolution of Other Areas of Pharmacy Practice

A diverse range of pharmacy practice opportunities exist as areas where pharmacists use their skill and knowledge to provide better patient outcomes, whether this is in providing interpretation of laboratory tests, developing or providing health and medicines information or responding to local or global emergencies. In addition to Community, Hospital, and Academic pharmacy, and recognition of pharmaceutical scientists, FIP includes in its Board of Pharmacy Practice, five additional broad areas of practice—Clinical biology, Health and medicines information, Industrial pharmacy, Military and emergency pharmacy, and Social and Administrative pharmacy.

Pharmacists in general practice clinics are variously termed Primary Care pharmacists, Consultant pharmacists or Ambulatory Care pharmacists, although these terms may not be interchangeable, but simply overlapping in their areas of responsibility. The services they provide include comprehensive medicines management and associated independent or supplementary prescribing (Carmichael and Hall, 2015).

Pharmacists in industry have a broad range of roles including research, formulation development, quality control, clinical trials and medicines information (Bonanno et al., 2012). Since the 1990s, roles for pharmacists in industry have been decreasing in many countries as specially trained personnel—analytical chemists, pharmaceutical scientists (who are not pharmacists) and administrators with business degrees are now fulfilling many of the roles traditionally undertaken by pharmacists.

Evolution of Pharmacy Practice Around the Globe

The role of pharmacists, and the practice of pharmacy, differs not only according to the laws and economic capacity of the country but also on workforce availability and capability.

USA and Canada

The pharmacy profession in the United States stemmed from the practice of medical practitioners to employ assistants to compound the medicines they prescribed (Anderson, 2002). Although formal education of pharmacists began in 1821 when the Philadelphia College of Pharmacy and Sciences was founded, the majority of those practicing as pharmacists had no formal qualification until after 1905 when states began to require graduation from a course in pharmacy to qualify for registration (Sonnedecker, 2001).

Much of the stimulus for change in the profession and the evolution of pharmacy practice globally occurred following events in the United States. In 1951 pharmacists' freedom to supply medicines without a medical prescription was restricted by law forcing pharmacists to spend more time dispensing and possibly changing the public perception of the scope of pharmacy activities (Bonanno et al., 2012). The USA Medicare and Medicaid legislation in 1965 was the stimulus for the creation of an organized health workforce and for the growth of hospital pharmacy practice (Higby, 2002). Funding was made available to universities to expand their enrolments in health science courses, including pharmacy (Higby, 2002).

Pharmacy education in the United States was initially 2 years, but had increased to 3, then 4 and 5 years before, in 1997, American Council on Pharmaceutical Education decreed that they would no longer accredit Bachelor of Science programs, effective from 2000 and all colleges of pharmacy must convert to the PharmD as the sole professional entry-level degree, including mandatory periods of experiential learning. Pharmacy graduates, particularly those planning to work in clinical care roles, commonly undertake an additional 1 or 2 year hospital residency program. Pharmacy graduates undertaking these residency programs are able to consolidate and advance their skills in delivery of patient care services.

The ethical code of the American Pharmaceutical Association in 1952 precluded pharmacists from discussing the composition or therapeutic effects of a doctor's prescription with the patient (Carmichael and Hall, 2015; Higby, 2002; Holland and Nimmo, 1999). The 1975 Millis report called for a shift in focus of the profession from product to patient and suggested that pharmacists should be trained to provide direct patient care to improve public health—the beginnings of clinical pharmacy. In 1976, The American Pharmaceutical Association established the Board of Pharmaceutical Specialties to recognize specialty areas of pharmacy practice (Keeley, 2002). Board certification is a voluntary process that is open to all registered, practising pharmacists following satisfactory completion of a qualifying examination.

Although the term "pharmaceutical care" was first introduced in 1985, it was not until 1990 that the provisions of the Omnibus Budget Reconciliation Act enabled, in fact required, US pharmacists to review drug use, counsel patients and document interventions in a patient profile. The law required pharmacists to screen for a full range of drug related problems and to incorporate this information into a patient-specific profile. This direction was very quickly extended to provision of these services to all patients (Hradecky, 2001).

A similar change in the scope of practice occurred in Canada due to recognition of increasing rates of morbidity and mortality and the value of the pharmacist in dealing with the increased complexity of medication and in improving patient outcomes (Bonanno et al., 2012; Schindel et al., 2017). Innovative models of practice have developed throughout Canada that provide medicines review services and integrate pharmacists into health care teams and specialty care clinics (Canadian Pharmacists Association, 2015). The province of Alberta was the first to legislate an advanced scope of practice and authorize pharmacists to prescribe, but most provinces have now recognized and remunerated this new model of pharmacy practice service delivery

(Canadian Pharmacists Association, 2015; Schindel et al., 2017). A compensation framework for pharmacy services was also introduced in 2012 (Schindel et al., 2017).

UK

Modern pharmacy developed after the Apothecaries Act of 1815, the formation of the Pharmaceutical Society in 1841 and the establishment in 1842 of the first school of pharmacy in Britain at the Society's headquarters in Bloomsbury square (Bonanno et al., 2012; Copeman, 1967).

The education of pharmacists was largely through an apprenticeship system until 1924. The University of London's BPharm course was the first degree specifically to be approved as part of a formal entry route to the profession. From 1954 to 1967 two routes to becoming a pharmacist were available—the three-year Pharmaceutical Chemist Diploma involving a minimum of 2 years apprenticeship in a pharmacy and passing the Royal Pharmaceutical Society's membership examination, or a three-year BPharm degree followed by a year's apprenticeship in a pharmacy and success at the Society's examination in forensic pharmacy. The three-year BPharm was discontinued in 1997 and replaced by the four-year undergraduate Master of Pharmacy with a yearlong internship (Anderson, 2002). This change occurred in response to the Bologna Agreement within the European Economic Area and the Nuffield committee recommendations to extend the scope of the pharmacy degree (Silcock et al., 2004; Sosabowski and Gard, 2008).

The introduction of the government funded National Health Service in 1948 undermined the existing primary care function of pharmacy by shifting consultations about illness to the general practice setting where they were free of charge (Bonanno et al., 2012; Davies et al., 2014). Pharmacist activity was consequently limited to dispensing of doctors' prescriptions.

Between the 1970s and 1990s hospital pharmacy in the United Kingdom underwent a period of change following the identification of an unacceptable level of drug administration errors in British hospitals (WHO Consultative group on the Role of the Pharmacist, 1997). Pharmacists in hospitals became aware of the opportunity for improving the effectiveness and quality of drug therapy, supported by the Gillie report that recommended the introduction of "ward pharmacy" (WHO Consultative group on the Role of the Pharmacist, 1997). Pharmacists working in the wards communicated with their nursing and medical colleagues and became more involved in the management of drug therapy and this developed into "clinical pharmacy." As pharmacists' time became more involved with clinical pharmacy activities a number of routine tasks were delegated to technicians. Pharmacists were encouraged to interact with patients and provide them with information and assistance regarding their medicines (Anderson, 2002).

The scope of pharmacists' activities and practice has now widened considerably. The Royal Pharmaceutical Society has introduced a comprehensive program to encourage pharmacists to continue their development over their career and recognizes several levels of a practitioner from novice to expert. Pharmacists in the United Kingdom may be employed in clinics alongside doctors, appropriately qualified pharmacists have been granted prescribing rights and the community pharmacists may provide medicines review services for their patients and for those in aged care (Silcock et al., 2004). The role of pharmacists who work in Primary Care Trusts or directly with GPs is now termed "primary care pharmacy" (Silcock et al., 2004; WHO Consultative group on the Role of the Pharmacist, 1997) While these roles were initially created to help make prescribing more cost-effective within National Health Trusts, their function has now expanded. Management of drug budgets is still an important role that also includes clinical governance, medication review, and prescribing or prescribing advice (Silcock et al., 2004).

Europe

The European Union is yet to introduce harmonization in the delivery of health care in member countries, and there are therefore many differences in healthcare policies and practices throughout the region leading to much diversity in pharmacy practice in community and in hospitals, and in the provision of pharmaceutical care (van Mil and Schultz, 2006). Pharmacies in Scandinavia are relatively large and focus primarily on medicines, whereas pharmacies elsewhere in Europe are smaller and also stock a range of health and beauty aids and other nonmedical items (van Mil and Schultz, 2006).

University education of pharmacists occurred much earlier in Europe than elsewhere with a university degree mandatory from 1875 in Germany (Bonanno et al., 2012). The predominantly science focus that continues in most European pharmacy curricula was important for the development of a robust pharmaceutical industry. The lack of a significant clinical component, however, limits the extent of adoption of patient-centered care, although this is changing as clinical pharmacy is being introduced into European curricula (van Mil et al., 1999; van Mil and Schultz, 2006).

The first approach to the introduction of pharmaceutical care was undertaken in 1992 by the Danish College of Pharmacy Practice (van Mil and Schultz, 2006). Other countries became aware of the concept through discussion at congresses and the FIP Statement of Professional Standards issued in 1998. In 1994, The Pharmaceutical Care Network of Europe was formed with the aim of stimulating research and assisting countries to embed pharmaceutical care in the health care systems; however, by 2000, it was evident that there was still little pharmaceutical care activity in many European countries (van Mil and Schultz, 2006). Pharmaceutical care standards were established in the Netherlands in 1996 and in Germany an agreement was signed in 2004 combining the family pharmacist with the family physician and providing remuneration by insurers for pharmaceutical care services (van Mil and Schultz, 2006). In 2005, the provision of pharmaceutical care also became a legal obligation for Belgian pharmacists, while in Italy it is generally the domain of hospital pharmacists. Programs currently exist in Portugal for pharmacist involvement in the management of disease states such as diabetes, asthma, and hypertension. In Scandinavian countries, pharmaceutical care in community pharmacies generally focuses on identification and resolution of drug-related problems (van Mil and Schultz, 2006).

Japan

The Japanese Pharmaceutical Association was formed as early as 1893 partly to support the separation of prescribing and dispensing (Bonanno et al., 2012; Nakagawa and Noriaki, 2017). Their efforts were not completely successful, however, although the proportion of prescriptions now being dispensed by doctors is decreasing, particularly in larger cities. The number of prescriptions dispensed by doctors in rural areas remains high (Yamamura et al., 2006).

The pharmacy curriculum is of 6 years duration, including 6 months experiential placement in hospital and community practice (Nakagawa and Noriaki, 2017; Yamamura et al., 2006). There is also an increasing emphasis on ensuring graduates have the competency to provide an increasing number of clinical services. Individual institutions have recently introduced two-year residency programs, similar to those in the United States and Canada (Nakagawa and Noriaki, 2017). A variety of board certification programs have also been developed to increase pharmacists' capabilities in a range of specialty areas, such as infectious diseases and oncology (Nakagawa and Noriaki, 2017).

As technicians are not recognized in Japan, pharmacists remain responsible for all dispensing in both hospital and community settings (Yamamura et al., 2006). In hospitals, pharmacists have responsibility for specific compounding services for hospital use, manufacturing of sterile preparations, drug information services, and management of clinical trials. Hospital pharmacists are also becoming involved in multidisciplinary teams and providing clinical pharmacy to individual patients on the wards - taking medication histories, monitoring drug use and educating patients on their medication (Nakagawa and Noriaki, 2017). In community settings, pharmacists dispense prescription medication, provide over-the-counter medicines, and advice and a limited range of clinical services, predominantly history taking and patient counseling. Primary Care pharmacists are able to manage all aspects of a patients medication needs and are available 24 h/day and may provide these services in patients' homes (Nakagawa and Noriaki, 2017).

Although pharmacists in Japan are not currently providing a full range of cognitive pharmaceutical services, their practice is changing toward a more patient-centered approach.

Middle East

Pharmacy education and practice vary markedly across the Middle Eastern region. This is largely due to ongoing conflict, the result of oppressive regimes, and economic factors. The pace of change in pharmacy practice, even in well-resourced middle-eastern countries has been slow. Those countries that are economically stable have, however, made significant advances in pharmacy practice.

To meet local needs within the region, there has been a change in education and an increase in the number of pharmacy schools (Al-Jumaili et al., 2013). Pharmacy schools are seeking external accreditation of their programs, and many are revising their curricula to place a greater focus on patient care skills (Kheir et al., 2009). The PharmD has been introduced in many countries to increase the clinical focus of pharmacy education and thereby influence practice (Hasan et al., 2011).

Many countries in the region are not graduating sufficient pharmacists to meet their local needs and rely on expatriate pharmacists from countries with an oversupply, such as Egypt, India or Jordan where education is generally very science-focused with little emphasis on clinical, patient-oriented skills (Hasan et al., 2011; Kheir et al., 2009). This limits the development of patient-centered services in the region.

The role of pharmacists in community pharmacies in the Middle East differs according to economic, regulatory, and organizational frameworks within each country (Hasan et al., 2011). While local graduates are employed in the hospital sector, in academia or in regulatory affairs, community pharmacies have a relatively poor public image and are manned mostly by expatriates (Kheir et al., 2009). Opportunities to practice clinical pharmacy and patient-centered care are generally limited, although this varies between countries (Al-Jumaili et al., 2013; Hasan et al., 2011).

Asia

Schools of pharmacy in Asia have predominantly focused on graduating pharmacists to be capable of working in the rapidly expanding pharmaceutical industry in the region. This is especially true in India where the majority of graduates find employment in industry (Azhar et al., 2009; Basak and Sathyanarayana, 2010). This is changing, however, as most countries evolve to education with a focus on clinical competencies (Basak and Sathyanarayana, 2010).

Pharmacy education in India has been rapidly expanding, due to rapid industrialization in the pharmaceutical sector, privatization, and economic growth (Basak and Sathyanarayana, 2010). The high number of graduates exceeds the local requirements and many seek employment elsewhere, often supplementing locally trained pharmacists in developing countries (Basak and Sathyanarayana, 2010). The Pharmacy Council of India introduced a PharmD program in 2008 that emphasizes the clinical and patient-oriented aspects of the pharmacy profession, however acceptance of the clinical expertise of pharmacists is low and clinical positions are limited (Basak and Sathyanarayana, 2010).

In many Asian countries, there is no separation of prescribing and dispensing, and the community pharmacists' role is significantly limited, demonstrating under-utilization of their expertise by the general public, other health practitioners and governments (Azhar et al., 2009; Chua et al., 2013). The main role for pharmacists in this setting is providing advice regarding minor ailments or direct purchase of a medication or supplement, including traditional therapies (Chua et al., 2013). Hospital

pharmacists have a somewhat expanded role as they have access to the patient's medical record and counsel patients on the use of their prescribed medication (Inoue et al., 2016).

In countries where prescribing and dispensing are separated, there is an expanded role for the pharmacist, both in the community and in hospital (Inoue et al., 2016).

Under-Resourced Countries

There are significant disparities in the number of pharmacists per 10,000 population in well-resourced countries compared to those that are under-resourced (Anderson, 2002; Azhar et al., 2009). Well-resourced countries such as USA, Canada, Australia, and the UK have more than nine pharmacists per 10,000 population, whereas under-resourced countries, such as Malawi, Zambia, Uganda, and Tanzania, have less than one pharmacist per 10,000. The low number of pharmacists per capita has implications for inequalities in access to medicines and medicine expertise, with many pharmacists employed in administrative positions. In addition, as most pharmacists work in large population centers, the number of pharmacists and the availability of pharmacy services in rural areas are much lower (Anderson, 2002; Azhar et al., 2009). Without pharmacists, the health care system is unable to cope effectively with most medicine-related issues (Azhar et al., 2009). The evolution of pharmacy practice in under-resourced countries is therefore hampered not only by economic realities but also due to the severe shortage of pharmacy workforce and lack of recognition by governments and other health professionals of the knowledge and skills of pharmacists (Anderson et al., 2009; Azhar et al., 2009). In many countries, doctors are able to dispense thus decreasing the opportunities for pharmacists to provide pharmaceutical care (Azhar et al., 2009; Kahn, 2011).

Health needs are generally serviced by a mix of privately owned pharmacies, NGO operated facilities, and public hospitals and clinics (Anderson, 2002). The main tasks of pharmacists working in hospitals and clinics must therefore focus on ensuring the supply and dispensing of appropriate, quality medications (Anderson, 2002). Pharmacy technicians, who may have some level of training and often work without supervision, supplement pharmacy services in many of these countries, but they may not be capable of providing an appropriate level of service (Azhar et al., 2009).

Counterfeit medicines are problematic and many governments are conducting campaigns to control this problem and assure the quality of both locally manufactured and imported medicines (Bonanno et al., 2012). Pharmaceutical care and clinical pharmacy cannot be introduced, while the number of registered pharmacists is below what is required to simply sustain the system and ensure a reliable supply of needed medicines. Ongoing efforts are needed to ensure capacity building of skilled medicine expertise to meet the pharmaceutical needs of populations (Anderson et al., 2010). The teaching of pharmacy practice skills helps to ensure that the workforce will be ready for change as workforce levels increase.

Increased pharmacy student enrolments and increased numbers of pharmacy schools are only possible when there is an adequate academic workforce (Anderson et al., 2009). Alignment of curricula with current pharmacy practice standards is important to graduate a pharmacy workforce able to provide the best health care for the population and the leadership skills necessary to change practice (Anderson et al., 2009).

A Look into the Future

In the future, the expertise of pharmacy practitioners will increase and be recognized by governments, other health professions and the public, and its potential to improve global health will be fully realized. Consumer health expectations will continue to rise and the need for a reliable and accessible source of health information will provide an important role for pharmacists. The education of pharmacists will continue to provide comprehensive clinical training to enable delivery of an expanded range of services; however, it is important that the scientific basis of this knowledge is not lost. With biotechnology, genomics, proteomics, and nanotechnology, the prospect of personalized medicine will become a reality—at least in high-income countries.

In many settings, even in well-resourced health systems, and particularly in community pharmacy, pharmacists are still mostly occupied fulfilling supply functions and spend little time on the provision of cognitive pharmacy services (Bonanno et al., 2012). This may, in part, be due to uncertainty concerning reimbursement for many of the new and innovative professional services and these may only expand when pharmacists are paid for their clinical expertise (Canadian Pharmacists Association, 2015). The most appropriate model for payment has yet to be established. Uncertainty may also be due to a lack of confidence or a perceived lack of skills, although a plethora of educational opportunities are available to meet gaps in knowledge and skills (Rosenthal et al., 2010).

Increased use of technology and technicians to assist with routine activities has provided pharmacists with more time for patient care activities, but many are not taking advantage of the opportunities available (Rosenthal et al., 2010). It may be that some current members of the profession are not fully committed to change (Holland and Nimmo, 1999; Rosenthal et al., 2010). There is some evidence that these attitudes are changing, and it is hoped that future generations of pharmacists, clinically trained and expecting to perform patient care activities will be less risk averse and willing to embrace change in pharmacy practice (Harrison et al., 2012; Luetsch, 2017). As the new generation of health professionals recognizes the expertise of pharmacists in medication management, and as the older, more traditional cohort retires, the existing opposition to changed pharmacists roles will likely disappear, a trend that is currently occurring in many areas of practice.

What will pharmacy practice look like in 10, 20, or 50 years? Over the past 50 years pharmacy practice has evolved from a medication-focused role to a patient-focused, role and it is likely that this trend will increase with pharmacists' knowledge and

expertise concerning the safe, effective, and rational drug use making them an integral part of the patient care team. Can we envision a future where community pharmacies are providing a wide range of patient care services that are recognized by governments and the public as an important health resource that is easily accessible and able to provide high standards of medicines information, primary care and medication management activities, improving health of the public and reducing health inequality?

Changes in the legislative framework to facilitate pharmacists' changing scope of practice and an acceptance of the pharmacists' skills by other healthcare professions, while apparent in some jurisdictions, are not yet widespread. Challenges to be overcome therefore include legislative requirements, lack of competent human resources, lack of support from other health professions and health system constraints, including lack of access to patient data.

Specialisation is already occurring in some practice areas where distinctly different knowledge and skills are required and in some countries, specialisation and advanced practice are formally recognized, credentialed and compensated (Carmichael and Hall, 2015; Council on Credentialing in Pharmacy, 2014; Waddell et al., 2016). The areas of pharmacy practice recognized by FIP could be considered areas of specialization—Academic pharmacy, Clinical biology, Community pharmacy, Health and medicines information, Hospital pharmacy, Industrial pharmacy, Military and emergency pharmacy and Social and administrative pharmacy. Other specialty areas that may require additional education or certification, such as oncology, geriatrics, diabetes, fertility, HIV, psychiatry, nuclear medicine, nutrition support, the compounding of specialty medications, and pharmacotherapy are also being recognized. Generally, specialization requires additional training and some level of postgraduate qualification in an area related to the area of advanced practice (Council on Credentialing in Pharmacy, 2014). It is likely that this trend will continue as the extent of knowledge in pharmacy increases and our profession follows the model of our medical and nursing colleagues. Pharmacy education, both undergraduate and postgraduate, will need to be reassessed frequently to ensure that graduates have the knowledge and skills necessary to allow them to provide advanced services as either generalists or specialists.

It would be wonderful to envision a future where all of the world's population have access to safe and effective healthcare and access to a range of quality pharmacy services delivered by competent pharmacists.

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Codes of Conduct/Ethics in Pharmacy Practice

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Introduction

This chapter introduces the concept of codes of conduct/ethics in pharmacy practice, and explores what codes are, why and how they might be developed in a manner that positively impacts on the practice of pharmacy. It offers exploration of answers to four questions, namely: (1) What is a code? (2) Why might a code be developed? (3) How might a code be developed? (4) Why might a code fail to achieve its aims? Conclusions and recommendations incorporate key learning from the evidence base and exemplars in various jurisdictions, in a manner that aims to provide tangible guidance to those embarking on the development or revision of a code for pharmacists and other pharmacy professionals.

What Is a "Code"?

A "code" may be described as a public statement of what behaviors represent acceptable engagement between an organization (or profession) and other parties, including: the public, members (or employees), among members in the organization and/or, as with the health care practitioner-patient relationship, between individuals "inside" and "outside" the organization. Supported by the expectation that individuals and business entities will respect the policies and laws governing the society in which they exist, codes seek to guide decision-making through situations that cannot be resolved by the "letter of the law" or a literal interpretation of existing policy. Codes also provide all stakeholders with a benchmark against which questionable behavior might be evaluated.

Organizational codes commonly include reference to governance or control, and are generally underpinned by concepts, such as equity and justice, and a public commitment to corporate social responsibility or ethical management of the organization. Such public statements are increasingly prominent in public bodies, charitable organizations, business, banking, and the professions.

Professional Codes, Policies, Standards, and Guidelines

Professional codes align with policies, standards, and guidelines affiliate to that profession. Associated "standards" illustrate minimum requirements associated with demonstration of professional competence, and such standards may include reference to competency frameworks, that is, detailed lists of behaviors that collectively describe what a member of that profession should be able to demonstrate and does in practice. "Guidelines" provide, for example, sample approaches to the delivery of specific services, and generally detail the steps to be taken to assure appropriate conduct or behavior. As it is not possible to predict and construct standards and guidelines to cater for all circumstances a practitioner might face, a code infers what should be considered ethical and/or professional behavior when available standards and guidelines don't apply directly to the situation. Codes applicable to health care professionals generally include reference to the "four principles" of health care ethics, namely, respect for autonomy, beneficence (do good), nonmaleficence (do no harm), and justice (resource allocation) (Beauchamp and Childress, 2009). Most importantly, codes for health care practitioners should accommodate the application of professional judgment by individual practitioners and guide ethically defensible decision-making through professional dilemma scenarios (Exhibit 1).

Codes are generally referred to as codes of Ethics (e.g., Alberta, Australia, British Columbia, New Zealand, Ontario, and United States) or codes of conduct (e.g., Ireland and the Royal Pharmaceutical Society, United Kingdom). However, there are exceptions, such as the decision by the "General Pharmaceutical Council" (GPhC), the pharmacy regulator in the United Kingdom, to refer to "Standards for Pharmacy Professionals" rather than a Code (GPhC, 2017).

Some authors differentiate between "conduct" and "ethics" by referring to a code of conduct as being rules-based or a minimum standard that can be demanded of every member of the profession in a manner that can be regulated, and a code of ethics as an "ethical maximum" that derives from a belief that "being good is not enough" and/or identifies the pursuit of excellence as an attitude inherent to individual professional practice (Hernandez et al., 2017). While this is an important background debate and may be relevant when interpreting the range of perspectives that might contribute to the development of a code, comprehensive review of the literature underpinning this debate is beyond the scope of this chapter. Contemporary codes generally seek to accommodate a range of stakeholders, including members of the public and regulatory bodies. An ongoing challenge is to balance the desire to be precise and explicit, in a manner that members of the public can trust and regulators can enforce, while also providing guidance to members of the profession for situations where standards and guidelines do not apply and they need to employ professional values to decision-making through the resulting ambiguity.

For convenience, the generic term "code" is used throughout this chapter.

While the Ontario College of Pharmacists (OCP), College of Pharmacists of British Columbia (CPBC), and Alberta College of Pharmacists (ACP) refer to codes for technicians; and GPhC refers to registration of technicians, regulation of technicians is not constant among jurisdictions. Direct reference to pharmacist(s) is assumed unless otherwise indicated.

Most codes and/or policies refer to competency frameworks, against which to compare a pharmacist's behavior(s) in order to determine whether the behavior(s) represents a breach of the code. In context, each behavior represents a combination of relevant knowledge, skills, and/or professional attitudes that must be developed to an acceptable standard, and then demonstrated throughout the professional's lifespan. For example, the professional "understands and applies the requirements of pharmacy and medicines law" or "makes and justifies decisions in a manner that reflects the (code) for pharmacy and pharmacy and medicines law." A range of related behaviors underpin any given competency, for example, that a pharmacist "practices legally" or "practices ethically." Competencies are generally grouped into domains of responsibility. The collective of all competencies deemed essential for a practicing pharmacist forms a competency framework. The International Pharmaceutical Federation's (FIP) describes the role of the pharmacist through a seven-star concept in which the pharmacist is described as a caregiver, communicator, decision-maker, teacher, lifelong learner, leader, and manager (WHO, 2006), and provides one example of a collaboratively prepared "Global Competency Framework," which incorporates four domains as follows: (1) Pharmaceutical Public Health Competencies, (2) Pharmaceutical Care Competencies, (3) Organization and Management Competencies, and (4) Professional/Personal Competencies (FIP, 2012). Variations of this framework and other examples are available on the websites of national regulatory bodies and professional organizations.

Codes, standards, and guidelines are terms that might be used interchangeably or with nuanced interpretations in some settings or jurisdictions. Provided the reader is clear as to whether the focus is on minimum standards or on approaches to the delivery of services in a professional manner and/or represents a declaration of a profession's core principles and values, it is possible to align most discussions regarding concepts in ethical governance with Exhibit 1.

Exhibit 1 Codes, policies, standards and guidelines—concepts in ethical governance

Concepts	*Descriptions*
Professional code	Sets out expectations of members' behavior and articulates core values of the profession (in context).
Policies	Broad statements of how to adhere to the code, how breaches will be dealt with and, for example, whether the code is enshrined in legislation.
Standards	Specification of minimum acceptable requirements for behaviors, decision-making, and overall professional competence.
Guidelines	Description of recommended/sample approaches for behavior(s), decision-making, and demonstration of professional competence.

As society's "norms" change over time, most contemporary codes require revision at least every 5–7 years, and are reviewed at earlier intervals when societal issues demand more immediate consideration. Examples of changing societal "norms" likely to impact on the practice of pharmacy in the future include emerging technologies, such as genetic profiling or changing expectations regarding Medical Assistance in Dying (MAID). Evolving societal "norms" also engage professional values and ethical principles evident in codes for pharmacists as discussed later.

Professional Values and Ethical Principles Evident in Codes for Pharmacists

As highlighted in the "International Pharmaceutical Federation (FIP) statement of professional standards, Codes of Ethics for Pharmacists" (FIP, 2014), pharmacists' ethical obligations tend to be common across settings. The range of concepts likely to be found in most existing codes include: honesty and integrity, commitment to patient safety and best interests, accountability for actions and management of potential conflicts of interest, collaboration with relevant stakeholders, ethical allocation of scarce resources, respect for the confidentiality of patient information, respect for cultural differences, appropriate exercise of conscientious objection especially with respect to continuity of care, and a commitment to maintain competence through continuing professional development (CPD). FIP's stated objective is to enable national associations and regulators of pharmaceutical practitioners, through their individual Codes, to guide pharmacists in their relationships with patients and carers, and with other health professionals and society generally (FIP, 2014). FIP highlights that codes should also guide individual pharmacists in their daily practice of the profession. While its proposed Code remains focused on what the individual should do, the FIP also aspires to the development of transdisciplinary codes.

Professional Values as a Basis for Developing Transdisciplinary Codes

A comparative study of professional and interprofessional values (Tsou et al., 2015) compared values identified in professional codes, from 13 North American health care professional associations, with ethical principles identified as essential for interprofessional collaboration (IPC). The professions represented include medicine, dentistry, nursing, pharmacy, occupational therapy, physical therapy, and speech-and-language therapy. The six IPC principles, namely, altruism and caring, excellence, ethics, respect, communications, and accountability, were generally consistent across the professions' codes. Two further ethical principles, integrity and justice, were common across the majority of the 13 professions' codes reviewed. Apart from referring to "caring" rather than "altruism and caring," the American Pharmacist's Association's (APhA) Code referred to all eight of these principles, or "elements of professionalism." Comparison of codes in use in Australia, Canada (Alberta, British Columbia, and Ontario), Ireland, New Zealand, United Kingdom, United States, and FIP, indicates that key values underpinning pharmacy practice, as represented by these eight ethical principles, are also consistent across jurisdictions.

Why Develop a Code?

Codes may be developed to provide information, to guide, to govern, to provide grounds for sanction, to pledge commitment or any mixture of these functions. Appropriately developed codes may (1) provide clarity to members of the public, policy makers, managers, and other health care professionals regarding standards of conduct or behaviors that society can expect of members of a profession; (2) guide members regarding standards of conduct or behavior that is expected of members; (3) guide educators regarding standards of conduct or behavior that aspiring members should have demonstrated prior to registration with the regulatory body, or during educational remediation initiatives undertaken by registrants; (4) protect public interest by enabling the regulator to remove from the register any practitioner who breaches the code in a manner that poses a potential risk to public health or welfare; and/or (5) facilitate the profession's "social contract" with the public. Aspects of each of these objectives merit further consideration.

A Code as a Declaration of What Society May Expect of Members of the Profession

A code should provide clarity to patients and other members of the public, policy makers, managers, and other health care professionals as to what behavior(s) they may expect from the profession and its members. Every code will inevitably highlight the member's individual responsibility to maintain professional competence, including assuring a pharmacist's familiarity with professional standards and guidelines, and the appropriate application of knowledge and skills underpinning the practice of pharmacy. However, pharmacists are also required to behave with integrity, to demonstrate professionalism and ethical decision-making, and to be accountable in this regard for their actions and omissions. Qualities related to integrity, accountability, professionalism, and ethical decision-making can be underwritten by a code to which all pharmacists must subscribe. Any person or organization dealing with a pharmacist would then be entitled to (1) expect that a pharmacist will behave in accordance with the principles laid down in the code, and (2) judge the pharmacist's behavior according to the code.

A Code as a Guide to Practitioners

Codes for pharmacists are inevitably founded on the premise of a duty of care to the patient, thus obliging the pharmacist to always make professional judgments in the patient's best interests. The inference is, of course, that acting in the patient's best interests is not

always easy and, as a pharmacist has access to a body of knowledge or expertise generally not available to a patient, this results in information asymmetry between the pharmacist and patient. The pharmacist could use that expertise for his/her own benefit rather than in the interests of the patient. The patient would not necessarily know if the pharmacist was behaving appropriately . . . a concept commonly referred to as moral hazard. Moral hazard is what makes conflict of interest (CoI) possible, that is, "when an individual's personal interests would lead an impartial observer to question whether the individual's professional actions or decisions are unduly influenced by considerations of significant personal interest" (Beauchamp and Childers, 2009, p. 314). The perceived risk is that CoI will result in a set of conditions in which the exercise of professional judgment concerning a patient is unduly influenced by a secondary interest, such as financial gain, self-preservation against legal liability, or personal beliefs (Ruble, 2015).

As the pharmacist holds a position of trust, he/she must recognize the existence of information asymmetry, acknowledge that this asymmetry puts the patient at a disadvantage in the relationship, and realize that nondeclaration of any potential CoI would represent a breach of trust.

There are many such potential sources of conflict, both internal and external to pharmacists, which raise the possibility of impairing decision-making process to the extent that a pharmacist's, or his/her employer's, self-interest may inadvertently override the patient's best interests. The avoidance of situations, or dilemmas, where self-interest is at risk of prevailing is generally not possible for pharmacists—especially those working in patient-facing roles (Roche and Kelliher, 2009, 2014). As a code highlights core principles and values relevant to pharmacy practice, it can provide guidance for the exercise of professional judgment when negotiating professional dilemma scenarios and/or decision-making through potential CoI's in everyday practice and, when necessary, help outline grounds for identifying and/or justifying deviations from standards and guidelines.

A code may also provide pharmacists with a shared language to facilitate more robust discussion of conflicting ethical concepts in dilemma scenarios, so that differing individual ethical positions can be identified and debated, thereby fostering moral development in the individual practitioner (Rest et al., 1999; Roche et al., 2017).

A Code as a Guide to Educators

A code provides guidance against which the outcomes of educational programs may be evaluated. It guides educators by articulating standards expected at the point of registration with the regulatory body governing pharmacy, and by providing a tool that educators can use to underpin the professionalization process throughout an educational/CPD program. Legislation, standards, and guidelines may identify to the student what behaviors are expected of pharmacists; and policy documents and standard operating procedures may clarify how a practitioner should behave, but the code incorporates professional values underpinning pharmacists' responsibilities in a manner that cannot generally be accomplished when restricted by the demands of writing legislation. We might say that the code seeks to capture principles, such as not putting one's own interests ahead of a patient's interests, or not putting the interests of the profession ahead of society's interests and enables educators to expand beyond *what* a student should do, in order to focus on *why* student pharmacists should behave in a particular manner.

Student codes are common in higher education institutions internationally, for example, Australia, Canada, Ireland, New Zealand, United Kingdom, and United States. Notwithstanding that the profession's code may need to be adapted appropriately for the context of the university setting, for example, specifics related to interaction with patients may need amendment, student codes generally reflect the profession's underlying ethical principles. This approach has the added advantage that all institutions in a given jurisdiction can utilize the same version of the code as a baseline for student learning. Where "code of conduct" commitment ceremonies are utilized, they provide an additional opportunity to motivate student engagement with the professionalization process early in the pharmacy degree program.

In Trinity College, Dublin, (the author's home university) the commitment ceremony takes place early in the second semester in the program. During the first semester students undertake "professionalism and ethics" workshops, write a "professional identity essay," and engage in individual and group activities that focus their attention on what it means to be a professional and on how the code interacts with the professionalization process. Satisfactory completion of all activities and assignments is essential for eligibility to attend the commitment ceremony. Commitment to the code is an essential requirement prior to student's first experiential learning event, or practice placement, which takes place during the second semester. The student code therefore becomes a focus of attention for all students early in the degree program. While students are concurrently introduced to how fitness to practice (FtP) and remediation processes in the School of Pharmacy align with the code, it is the positive commitment to the code that is emphasized throughout, that is, a code can provide a tangible link to the profession's core values early in the students' university experience.

A Code to Serve the Public Interests and Support the Regulatory Process

Regardless of whether a code is a legislative provision or available as a voluntary guide, a code serves the public interests when it enables and motivates ethical relationships between pharmacists and patients or other individuals with whom pharmacists interact, and when it supports professional and ethical management of situations for which there are no clear standards or guidelines available. A code should assure that any member of the public employing the services of a pharmacist could expect to encounter the highest professional standards in the delivery of pharmacy care, treatment, or service. It should also reduce the risk of misunderstanding when differentiating between defensible behavior(s) on the part of the pharmacist, and when poor professional

performance (PPP) or professional misconduct (PMC) occurs. ("Poor professional performance," in relation to a registered pharmacist, means any failure of the registered pharmacist to meet the standards of competence that may be reasonably expected of a registered pharmacist (Pharmacy Act, 2007) and "Professional misconduct," in relation to a registered pharmacist, means any act, omission, or pattern of conduct that—(1) is a breach of the code of conduct for registered pharmacists, (2) is infamous or disgraceful in a professional respect (notwithstanding that, if the same or like act, omission, or pattern of conduct were committed by a member of another profession, it would not be professional misconduct in respect of that profession), (3) involves moral turpitude, fraud, or dishonesty of a nature or degree, which bears on the carrying on of the profession of a pharmacist, or (4) if the registered pharmacist has been granted a license, certificate, or registration by a body outside the state relating to the practice of pharmacy is a breach of a standard of conduct, performance, or ethics that—(a) applies to a person holding that license, certificate, or registration, and corresponds to a standard contained in the code referred to in *paragraph* (*a*) or a standard breach of which amounts to conduct of the kind mentioned in *paragraph* (*b*) or (*c*), *but does not include an act, omission, or pattern of conduct that consists of a wrongly but honestly formed professional judgment* (Pharmacy Act, 2007). The definitions for "poor professional performance" and "professional misconduct" provided are inferred throughout but readers should note that the terminology used, and associated definitions, may vary between jurisdictions. A code should therefore assure that patient interests are not subordinated, intentionally or otherwise, to the incompetence or interests of the pharmacist or the organization by whom s/he is employed.

However, a profession's code may also be used by wider society as a means of controlling professional behavior and of directly supporting the regulatory process. Reference to the code in legislation and/or alignment of reference to the code with the operation of Committees of Inquiry engaged with FtP hearings may integrate the code with the regulatory process, and related sanctions. As breach of the code may be one basis from which review of acts, omissions, or patterns of conduct might be deemed to constitute professional misconduct or poor professional performance (Pharmacy Act, 2007), a breach may therefore be the allegation in a complaint of "professional misconduct." Even in the absence of any harm to a patient being demonstrated, a FtP inquiry may result in sanction(s) being applied. Ireland is one example of a jurisdiction in which a breach of the code is grounds for an allegation of PMC during a disciplinary hearing or FtP Inquiry (Pharmacy Act, 2007).

As most legal systems operate on the basis of adjudicating on whether harm caused was the fault of an individual or organization, a process that admits "omissions," and patterns of conduct or behavior as evidence at an inquiry is atypical. Given the information asymmetry that exists between a pharmacist and a patient or member of the public, it is undoubtedly the case that some aspects of a pharmacist's behavior requires interpretation by peers in order to defend a related imposition of sanctions or penalties. Therein lies a core justification for "self-regulation" of the professions.

A Code to Facilitate the Profession's Social Contract with the Public

Society also envisages each profession as a collective and if an individual pharmacist is to be considered a professional, s/he must both personally meet the standards expected of a member of the profession, and have a profession to which s/he can belong. As it is a society that grants the status of profession, and the norms of a society change over time, a society may have changing expectations of a group to which it grants professional status. Welie (2004, 2012) describes this relationship as a dynamic social contract between the public and the profession. A code should articulate how the profession seeks to honor its social contract to society.

The distinguishing attributes of a profession traditionally include, for example, (1) *A systematic body of knowledge or theory*, (2) *authority recognized by clients*, (3) *broad community sanction of this authority*, (4) *a regulative code of ethics, and* (5) *a professional culture sustained by professional associations*' (Andersen, 2004). Continuing professional development, in addition to other supports, can provide structured access to the "body of knowledge" and the theoretical basis of the "regulative code of ethics," but knowledge alone is not a basis on which to assure understanding of the expectations inherent in a code.

Society's recognition of the potential benefit of medicines underpins its preparedness to take the risk that harm may be caused in pursuit of the desired benefits, but its acceptance that medicines can also cause harm underpins its justification for the restriction of access to available medicines by the general public (Roche and Kelliher, 2014). This restriction could otherwise be considered as an infringement of civil liberties—a risk managed by the granting of a custodian role, wherein legislation restricting access to certain "controlled" substances (medicines) identifies circumstances in which the pharmacist may hold and be a legitimate supplier of such substances, in the form of this social contract with the profession. Therefore, the public, believing that it has been promised an altruistic approach to this "custodian role," enters into a mutual agreement with the profession, and grants the profession privileges and social status. The code might be utilized by the wider society as a means of controlling professional behavior according to this perception of the mutual agreement. The public, in the form of its representatives, has an opportunity to impact on the development and amendment of national policy governing the practice of the profession as and when changing societal norms demand, and both public representatives and members of the public can engage directly with the development of a profession's code.

How Might a Code be Developed?

The process for developing a code should incorporate: (1) clarification of the profession's core values and/or principles that underpin professional practice; (2) identification of and engagement with relevant stakeholders; and (3) articulation of aligned policies, standards, and guidelines. A code may be enshrined in legislation to a greater or lesser extent, or it may be a voluntary code introduced, for example, by a professional body or representative organization. The nature and enforceability of associated policies,

standards, and guidelines will vary accordingly. National or jurisdictional legislation may dictate that the regulatory body will have authority and/or responsibility for the development of a code. Legislative underpinning of the code has implications for initiation and support for the process, the range of stakeholders likely to engage, and resourcing. Provisions for enforcement of a code will derive from the extent to which it is referred to and provided for in legislation, for example, whether the requirement is simply that a code exists or that, for example, breach of a code is specifically identified as a basis on which an allegation of PMC might be made (Pharmacy Act, 2007). While a "voluntary" code is likely to be supported by a large proportion of the membership of the profession, and peer pressure to behave according to the code may be in abundance, the members who choose not to engage cannot generally be forced to do so.

Strategies for Drafting "Pharmacy" Codes: Insights from the Literature

While codes proposed by FIP and in jurisdictions previously referred to [e.g. Australia, Canada (Alberta, British Columbia, and Ontario), Ireland, New Zealand, the United Kingdom and the United States], and their supporting policies, standards, and guidelines, are a publicly available source of information for any individual or group developing a code, review of the literature is inevitably recommended as a part of the process. The studies referred to in this section are neither exhaustive nor exclusive. However, they provide a range of perspectives and approaches that might further stimulate the reader to consider the benefits and limitations of choosing one format over another.

"Theoretical Considerations" for a Meaningful Code

A conceptual framework for drafting a code might distinguish "obligations" according to whether the identified responsibility is to patients/clients, fellow professionals, or society (Jamal and Bowie, 1995). Jamal and Bowie propose that provisions in a code should specifically address the need to (1) avoid "moral hazard" by assuring that decisions are objective and independent, bearing in mind that the *necessary conditions for objectivity are competence and diligence* (Jamal and Bowie, 1995, p. 709); (2) maintain professional courtesy, while also accommodating jurisdiction-specific controversy as to whether advertising should be restricted; and (3) serve the public. However, these authors caution that, while provisions related to the avoidance of moral hazard are generally uncontroversial, the public can be suspicious of provisions protecting professional courtesy and/or restricting advertising and competition, and public interest provisions can be controversial when the public and the profession disagree as to precisely what is in the public interest. For example, as codes might be seen to be self-serving and designed to protect the economic interests of the profession by restricting competition, rather than as a means of protecting the public from unethical behavior, reference to advertising emphasizes that professional recommendations should be objective and independent, and restrictions on advertising should be imposed only to prohibit deception.

Provision for a pharmacist's principled objection to take part in delivery of services that may be legally available in the jurisdiction can be a source of public-profession disagreement regarding what is in the public interest—contemporary examples being the use of medicines in Emergency Hormonal Contraception (EHC) or Medical Assistance in Dying (MAID). Jamal and Bowie (1995) find the obligation of confidentiality to be particularly problematic, especially when the best interests of society are pitted against the best interests of an individual. Disagreement among members of the public would probably arise if a code prioritized protection of the public interest by (1) decreasing the requirement for confidentiality (as breach, in a structured manner, has potential to positively impact on the public good) and (2) reducing the emphasis on duty of care to the individual patient (as this has potential to impact negatively on, e.g., resource allocation). Nonetheless, the conceptual framework proposed might be appropriate for some jurisdictions and discussion identifies key principles that might be included in the code.

"Reasons" for Having a Code of "Pharmaceutical Ethics"

Hernandez and coworkers emphasize that the Spanish Code's purpose is to provide a stimulus for pharmacists in their day-to-day work, with the aim of doing good and avoiding evil, and that it must apply at both an individual and group level. The process used in development of this code involved a review of "sources of information on the extant professional codes of conduct" (Hernandez et al., 2017: p. 403) that was undertaken by a multidisciplinary working group comprised of national experts in hospital and community pharmacy; a professor from each of the disciplines of Pharmacy Ethics, Communications Ethics, Bioethics and Philosophy of Law; and a Supreme Court Judge. They propose a code that sets out principles related to and underpinning pharmacist responsibilities to (1) patients, (2) other health care professionals, and (3) society. They differ from Jamal and Bowie (1995) by referring also to other health care professionals (rather than limiting reference to coworkers in one's own profession) and thereby introducing specific reference to interprofessional collaboration. Notable inclusions that refer to pharmacists' obligations to patients', including that "patients are entitled to the intervention of the pharmacists . . .in any of the processes in which medicine is involved" and "a pharmacist promotes the patient's right to avail of safe, effective treatment," incline toward a rights-based approach to pharmacy services. Obligations to other health care professionals include cooperation with others and avoidance of unfair competition, and specifies a responsibility to contribute to science by researching in his/her discipline. Professional responsibilities to society appear to be particularly demanding including that "a pharmacist ensures fair distribution of the health care resources based on objective, transparent criteria, particularly when those resources are limited," and if a pharmacist wishes to exercise a right to conscientious objection, s/he must inform the competent authority/regulator "so that the patient will not be deprived of the pharmaceutical care." The lists of obligations, to patients, other health care professionals and society, may provide baseline material for any pharmacists or groups developing or revising a code for their own jurisdiction.

Exhibit 2 Sample-guiding principles for the development of a code

1	Faculty, staff, and students should have significant input throughout the process.
2	It should apply to students as well as to all those who interact with them.
3	It should contain a preamble to set the tone for the code.
4	It should outline expectations that would apply across all settings.
5	It should be concise and written using the first person language.
6	It should contain a glossary of terms.
7	It should contain a section requiring a signature to indicate commitment to the code.

Gerber et al., 2015

Development of a Code of Conduct for a "University Faculty"

Development of an operational definition of "professional conduct" in the form of a code that would outline expectations around conduct was a key objective for the "Professionalism Committee," a diverse group of 11 staff and faculty members, at the Faculty of Pharmaceutical Sciences at the University of British Columbia (UBC) (Gerber et al., 2015). This Committee determined the need to model, foster, and articulate the values, standards, and expectations of students and faculty members in upholding professional attitudes and behaviors, in order to provide a framework for education and use as a tool to mentor students who fall short of expectations, that is, they envisaged a nonpunitive document aimed at raising awareness of expected conduct, and the code does not specify procedures for dealing with lapses in conduct.

The process by which the code was developed and adopted and the challenges encountered during the process are clearly outlined. The approach incorporated input from staff, consultation with students and University Senate approval of the final document. The literature review, undertaken by all Committee members, included an environmental scan of existing codes in schools of pharmacy in the United States and Canada, and consideration of professional documentation at the faculties of Medicine and Dentistry in UBC. The process of reviewing other codes was structured by providing template questions for consideration, for example, (1) "what elements of the format/structure do you like?" and (2) "would something similar . . .be relevant, worthwhile and doable for our faculty's code?" (Gerber et al., 2015, p. 147). Individual interviews, by the Chair, ascertained members' views on professional conduct—similarly structured by the provision of questions in advance. Views and opinions thus collected were analyzed into themes and presented to all faculty members as raw, unedited, and anonymized data. Subsequent development of themes, by committee members, was informed by this data. Faculty members and students were actively consulted throughout the process. As staff members raised concerns regarding the need to sign to indicate commitment, this requirement was removed from the final version of the code as approved by the University Senate.

The Committee ultimately developed key guiding principles for the development of a code in a university environment, summarized in **Exhibit 2**.

It is apparent that there are significant resource implications for this approach to the development of a code. Its findings also highlight the importance of peer-engagement in the development of a voluntary code, and that, when resistance develops, compromise may be required. The sharing of these and other key learning have the potential to provide support and insight to any group intending to develop or revise a code.

Codes for a "National Pharmaceutical System"

A multidisciplinary working group, including experts in medical ethics, history of medicine and pharmaceutical sciences, proposes a code for pharmacists, and separates sets of ethical guidelines for pharmaceutical manufacturers, pharmaceutical importers, pharmaceutical distributors, and policy makers (Salari et al., 2013).

The code incorporates discussion on key themes identified from literature review as follows: respect for patient's dignity and autonomy; beneficence; nonmaleficence; justice; empathy and resilience; honesty; and cooperation—a familiar list of values or principles in the context of contemporary codes.

The decision to produce separate sets of ethical guidelines derives from their expectation that ethics, which will be appropriate for manufacturers, importers, distributors, and policy makers will not be adequate for the patient–pharmacist relationship. This indicates that pharmacists in different sectors might be subjected to varying levels of control.

The conclusion reached, including that development of codes and guidelines is just the first step, and implementation relies on educational interventions that target the development of moral reasoning and include opportunity to discuss ethical dilemmas relevant to the principles in the code as they relate to the practice of pharmacy, should be accommodated when developing a code.

Enabling the Development of Codes

Literature review identifies challenges with respect to clarification of appropriate aims and underpinning legislation for enforcement of codes; the range of settings in which a code applies; differentiation between expectations articulated in codes and related standards or guidelines; consistency in alignment of codes with policy, standards, and guidelines; effective education for and understanding of the code's aims and application; and valid strategies for implementation and enforcement of codes.

Exhibit 3 Advantages of regulatory body oversight of the process of code development

1	The regulatory body has access to the legal, clinical, regulatory, and educational expertise to practically differentiate legislative requirements of conduct for pharmacists and develop a code that is congruent with the current legal and professional expectations of the profession in the jurisdiction involved.
2	The regulatory body has access to all registered pharmacists, thereby enabling relevant representative views of all pharmacists to be properly reflected in the code, and in order for associated standards to be meaningful and relevant to the diverse contexts in which the code would apply.
3	The regulatory body oversight enables collaboration and sharing of information with other regulatory bodies.
4	The regulatory body has the professional and statutory authority to conduct consultations and collate information in the development of a code.
5	The regulatory body can be publicly perceived as a more independent, objective voice than a professional body, thereby increasing the likelihood that members of the public and other stakeholders will engage with the process.
6	The regulatory body can provide resources and a structure for pharmacists, the public, and other stakeholders to engage and become involved in the code's development, implementation, and use.
7	The regulatory body can develop and disseminate aligned supporting documents (policies, standards, and guidelines).
8	The regulatory body can develop and provide continuous professional development (CPD) modules to help pharmacists understand the implications of the code, and to apply the principles outlined in the code to their individual practice setting.

GPhC, 2017 (adapted)

Despite these challenges, there are a number of factors that have the potential to support the development of effective codes, not least of which is the involvement of regulatory bodies—a range of potential advantages to their involvement is outlined in Exhibit 3.

The growth in the evidence base provides more comprehensive baseline from which to develop, or revise, a code. The evidence base relates to the potential structure and content of the code itself, and to appropriate processes applicable to development of an effective code. Literature related to interprofessional learning supports an increase in mutual understanding of the different roles provided by each profession and the different goals outlined in existing codes—potentially opening up opportunities to develop multidisciplinary codes. Questionnaires, responses to surveys, draft codes, responses to draft codes, and assessment of launches from other jurisdictions are available online which streamlines the process of development and allows partnership in addressing issues faced by pharmacists on a global scale (FIP, 2014).

Education for and Understanding of the Code's Aims and Applications

Many educational initiatives, incorporating ethical decision-making frameworks, dilemmas scenarios, and case studies, are openly available on regulatory body's websites throughout the world. Given a regulator's responsibility to provide accurate information in a public-friendly manner, these initiatives are expected to be methodologically robust and provide access to the literature and/or theory underpinning the material—at least to the extent that they may provide a baseline for those developing new educational interventions to support the introduction of a code. The advent of technology enhanced learning (TEL) initiatives, such as online modules and discussion fora, in addition to more traditional paper-based approaches to CPD, has expanded access to available educational initiatives for practitioners working in isolation and/or in geographically remote areas thereby enabling them to engage with evolving societal "norms" relating to their professional code.

Pharmacists' call for education or CPD regarding the implications of a code for practice has been reiterated in recent research in Serbia and Canada (Crnjamski et al., 2017; Gregory et al., 2016), among others. The more familiar that Serbian pharmacists were with their code, the more useful they found it as a guide in making ethical decisions in practice (Crnjanski et al., 2017), that is, findings confirm that pharmacists need to develop and maintain competence related to the practical application(s) of a code in order to effectively use it as a support and guide when exercising professional judgment to make ethically defensible decisions. Canadian pharmacists found that clinical reasoning strategies related to new responsibilities, such as immunizations and prescribing, inherently challenge the code's relevance to modern practice (Gregory et al., 2016). These findings highlight that as the scope of practice evolves, pharmacists need ongoing opportunities to discuss and debate how a code applies in new contexts and how to reason through dilemmas posed by conflicting ethical principles. Findings included that, where a code is enshrined in law, pharmacists reported placing priority on legislative requirements when facing ethical problems/dilemmas, indicating a preference for a "rules-based" approach to decision-making.

Notwithstanding distinction(s) that may be perceived to exist between regulated and voluntary codes and taking account of the literature as it describes various approaches to the development of codes for pharmacists and other relevant professionals, it is clear that an ideal process used to develop (or revise) a code should incorporate: (1) clarification of the profession's core values; (2) identification of and engagement with relevant stakeholders and, subsequently or in tandem; (3) publication of appropriate policies, standards, and guidelines as included in the sample process provided in Exhibit 4.

Why Might a Code "Fail" to Achieve its Aims?

A code, if the format likely to evolve from concepts outlined in this chapter, might fail to achieve its aims as a result of generally recognized challenges and barriers to the development and use of codes—summarized in Exhibit 5.

Exhibit 4 Literature informed guidelines to code development

1 If a code does not already exist:
   1. determine what jurisdictional organization is or will be responsible for the introduction of a code; development of associated policies, standards, and guidelines; review at appropriate intervals; education of pharmacists regarding application of the code and/or enforcement of the code;
   2. confirm the basis on which the organization intending to develop the code has responsibility and/or authority to do so; and
   3. agree to a strategy for development of a code, including allocation of resources and personnel, access to expertise, and the process for final approval and implementation.

2 Review existing literature and available resources (e.g., websites of regulatory bodies, and public services) to identify and investigate (1) existing codes in pharmacy and in other health care professions in the jurisdiction in question, and in relevant other jurisdictions and (2) supporting documentation, including policy documents, standards of practice, relevant guidelines, and/or additional guidance from regulatory or professional bodies.

3 Review relevant legislation and policy to assure that the code is congruent with the current legal and professional expectations of the profession in the jurisdiction involved, and to articulate, insofar as possible, what is acceptable conduct, and what is misconduct.

4 Clarify, in a manner that aligns with the agreed strategy for development of the code: to whom the code will apply, in what setting(s) the code will apply, whether the code will apply only in the workplace or also when the pharmacist is outside of the workplace, and whether all principles in the codes have equal standing or that one be considered primary, for example, the pharmacist's "duty of care" to the patient.

5 Complete a stakeholder analysis, that is, identify and list the individuals and organizations that will be contacted and involved, to include members the public, individual pharmacists, and representatives from pharmacy's professional organizations, pharmacist educators, representatives from relevant other health care professions, policy makers, and relevant experts. While the extent to which a code is legislatively underpinned (or not) will influence the process of stakeholder engagement, the ideal is to engage, as a minimum, the above stakeholders.

6 Design and prepare surveys, or other relevant data collection tools, for use with stakeholders. These may include a list of ethical concepts for consideration, tools derived from the literature. and/or an outline of one or more draft codes for consideration and comment.

7 Engage stakeholders.

8 Collate and review stakeholder feedback and action, as appropriate.

9 Prepare a draft code.

10 Engage stakeholders to obtain feedback on the draft code.

11 Collate and review stakeholder feedback and action as appropriate. Consensus among stakeholders, while preferred, is not necessarily required.

12 Agree, with the organization's own management team, a final draft of the code.

13 Attend to any legislative requirements, for example, approval by the Council of the regulatory body for pharmacists, approval by other regulatory bodies, for example, the Competition Authority, and/or approval by government official or minister.

14 Publish the code.

15 Disseminate the code, and relevant explanatory material, to all stakeholders that engaged in the process.

16 Implementation of the code should include, but not necessarily be limited to, the following: (1) assure understanding among the members of the profession, through ongoing CPD and appropriate quality assurance mechanisms, (2) enable mediation processes by which misunderstandings related to the code can be addressed, and (3) enable enforcement of the code if and as facilitated by legislation or other powers.

Exhibit 5 General challenges and barriers to the development and use of codes

1 A code cannot provide definitive answers for ethical dilemmas encountered in the course of professional practice, that is, where there is no obvious right or wrong way to proceed, and it cannot give firm justification for making one professional judgment rather than another.

2 Evaluation of professional conduct is a complex multidimensional construct that requires a combination of approaches at individual, interpersonal and institutional, or society-wide level.

3 A range of contributory factors, that is, person-specific, task-related, and organizational, serve to impact on an individual practitioner's conduct, so that both individual deficits and organizational or systems failures would need be considered when making a determination regarding the defensibility of observed behavior(s), for example, pharmacists may be responsible under the code for the acts or omissions of persons operating in the pharmacy under their supervision, where organizational deficits interfere with the availably of appropriate resources and/or expertise.

4 Health care has become multidisciplinary in nature and members of the health care team may be bound by different codes (or by none at all), potentially introducing conflicting responsibilities and obligations.

5 Health care has become multiagency in delivery and when resources are limited funding organizations and managers may influence the nature of the care which can be provided in circumstances where obligations imposed by them may not align with the practitioner's code, for example, resource constraints can bring the principle of societal benefit or the "greatest good" into conflict with the health care practitioner's primary duty of care to the individual patient.

6 The pace of scientific advance(s) combined with a complex array of "information" sources available to the public make "appropriately informed" status, as currently envisaged by the courts, increasingly improbable—thereby compromising the consent.

Adapted from Goldie et al., 2013; Phipps et al., 2011; Roche & Kelliher, 2009.

A code might also "fail" if it was found that, for example, expectations inferred by the code were unreasonable, that information provided was inaccurate, and/or that conflicts existed between a code and other relevant "rules," would risk making the Code unenforceable, and would be likely to prompt review and amendment as appropriate.

However, appropriate attention to the implementation process has the potential to identify unanticipated challenges and weaknesses in a proposed code as they arise, especially where implementation processes support pharmacists' understanding of how the

code should be applied in practice, enable mediation when misunderstandings arise, and where legislation enables sanction following a finding of "breach" of the code, implementation processes address matters related to enforcement.

The Need to Assure Understanding (of the Code) Among Members of the Profession

Pharmacists' familiarity with codes improves their use as a guide to ethical decision-making in practice, and pharmacists themselves recognize the need for ongoing discussion and debate regarding how a code applies in new contexts and how to reason through dilemmas posed by conflicting ethical principles, (Crnjanski et al., 2017; Gregory et al., 2016).

Obligations aligned with codes are not always obvious to the uninformed reader and/or pharmacists may be confronted with different interpretations from academics, peers, and tutors/managers within the education system and professional milieu (Bebeau, 2009).

If understanding is to be assured, then those developing the code should make available CPD initiatives in which obligations are made explicit, and which highlight conduct that might be a source of potential disagreement regarding the defensibility of behaviors. Initiatives already in use, with many examples freely available on regulatory body's websites, include paper-based and vodcasts/podcasts of animated scenarios and vignettes that raise, debate, and/or propose reasoned responses to professional dilemmas scenarios; "tests" of multiple choice questions addressing ethical concepts; and, in some jurisdictions, interactive e-learning modules that provide comprehensive review of the range of ethical concepts and conflicts that might arise.

Dilemma scenarios used in CPD initiatives should include recommendations from the literature and learning from inspections and legal cases in the jurisdiction in question. The material should be adapted to the "local" nuances of pharmacy practice, and to the code being introduced, in a manner that accommodates various learner styles and practice contexts.

Processes suited to decision-making through ethical dilemmas are increasingly included in guidance documents, and samples from the RPS and OCP provide examples that might support pharmacists' development. The RPS advocates a six-step approach to professional judgment formation when faced with a professional dilemma scenario (**Exhibit 6**), whereas the OCP takes a more extended approach to its advice regarding dilemma resolution and encompasses ethical decision-making and subsequent reflection in its prosed framework (**Exhibit 7**).

However, the moral reasoning competencies that underpin ethical reasoning, that is, the cognitive or thinking processes individuals go through to arrive at a decision when faced with a dilemma, must also be learned and practiced (Rest et al., 1999). Activation of "reasoning" depends on an individual having acquired the competencies to identify: (1) the ethical concepts that are in tension to create a dilemma, (2) what actions might be justifiable, and (3) how others might be affected by the behavior implied by each action option. Consideration of a professional dilemma scenario therefore involves deliberation(s) related to different courses of action an individual might take when faced with the dilemma proposed and the making of a judgment regarding which of the available actions would be most morally and/or professionally justifiable. To align with the evidence base, CPD initiatives should seek to incorporate the cognitive skills of logic (by providing frameworks for decision-making), role-taking (by utilizing scenarios that include multiple perspectives in conflict) and peer interaction and debate (Rest et al., 1999; Roche and Thoma, 2017; Roche et al., 2017).

The Need to Enable Mediation to Address Misunderstandings Among Stakeholders

Education of all stakeholders regarding the obligations of pharmacists and implications of the published code is a key component of their engagement in the development process. However, when true dilemmas arise, differentiation between defensible behavior(s)

Exhibit 6 Six-step approach to the exercise of professional judgment

1	Identify the ethical dilemma or professional issues
2	Gather relevant information
3	Identify the possible options—need a code to do this through ambiguity?
4	Weigh up benefits and risks of each option
5	Choose an option
6	Record

Royal Pharmaceutical Society, 2017.

Exhibit 7 A framework for ethical decision-making

1	Identify the issue and examine the facts
2	Apply guidelines and standards
3	Evaluate possible resolutions
4	Implement and document your decision-making
5	Review and reflect

Ontario College of Pharmacists, 2017

on the part of the pharmacist and perception(s) by others that the code has been breached can be problematic—and dissemination of generic information may not address concerns.

The availability of a publicly available, clearly defined, transparent, and easily negotiated process, by which any stakeholder can raise a concern or make a complaint regarding the behavior of a pharmacist, is an essential part of the process. Timely communication with complainants and comprehensive attention to concerns raised are essential components. However, complaints do not always merit disciplinary action or investigation at a "fitness to practice" inquiry. There may be occasions when, for example, disagreement arises as to whether a pharmacist had a "conflict of interest," or an unavailable service was anticipated. A mediation process should be available, where an impartial third party helps resolve the matter in a private, confidential, collaborative, and "nonbinding" manner, as this may provide an appropriate course of action in some cases.

The Need to Enable Enforcement of the Code: If Applicable to the Context

When sanctioning power is enshrined in legislation, a code can be one of a number of regulatory devices employed to protect the public by enabling, when proven to be necessary in a formal inquiry, conditions, or restrictions on practice by individual practitioners.

The standard of proof by which the regulatory body must prove allegations, such as an allegation of professional misconduct based on a violation of a code, will generally be either "beyond reasonable doubt" or "beyond the balance of probabilities"—although individual jurisdictions may vary in this regard. Expert witnesses may be used as a means of supporting such allegations—or, indeed, by registrants arguing that the expectations inferred by the regulatory body are not reasonable and/or impossible in the context of the exercise of professional judgment by pharmacists in the jurisdiction. These varying perspectives must be considered when developing a code and comprehensive differentiation between what "should" be done and what it is reasonable to insist "must" be done should be prioritized. Where principles in a code conflict, or where principles in a code are determined to conflict with legislation, policies, standards, or guidelines, such conflicts may undermine the likelihood of proving an allegation of professional misconduct (or poor professional performance) "beyond reasonable doubt."

Options related to sanction generally include the attachment of conditions to a pharmacist's registration, and/or removing the pharmacist's right to practice for a defined period or, where remediation is not envisaged, removal of the pharmacist's right to practice indefinitely. Options related to conditions generally include those of an educational nature. Guidelines regarding sanctions and conditions generally require them to demonstrate proportionality and leniency, and take account of aggravating and mitigating factors, that is, justified on the basis that they are the least restrictive means by which to protect public health, and underpinned by an expectation that the outcome of the proposal will remediate the professional deficits that are perceived to pose a risk to public safety. Mitigating factors might include health issues, such as addictions to alcohol, drugs or gambling, or the potential that the breach of the code resulted from a failure of understanding by the pharmacist. In cases where expert opinion identifies that relevant health issues may be remediated by treatment and/or public protection assured by a monitoring process, related conditions might be attached to the pharmacist's registration; where an inquiry determines that a failure of understanding underpinned the breach of the code that deficit may be addressed by appropriate mentoring and/or educational interventions.

The objective of such educational interventions will include, for example, (1) assessment of the extent of professional deficits underpinning poor practice identified during the disciplinary inquiry and (2) to prompt engagement with a remediation program involving learning and development activities including training and/or mentoring to remedy deficits identified. Knowledge and skill deficits may be addressed by existing programs and assessed by exam or observation. However, where deficits identified relate to professional identity formation and/or moral reasoning competencies, assurance that deficits with the potential to impact on public health are much more difficult to assure. To align with the evidence base, consideration should be given to individualized programs, incorporating specialist educational methodologies, described in the literature (**Exhibit 8**).

Exhibit 8 Evidence-based approaches to educational remediation further to disciplinary inquiries

1. Educational remediation should take account of a range of contributory factors, for example, person-specific, task-related, and organizational, which serve to increase or decrease the risk of breach of codes by individual practitioners.
2. Remediation begins with an identified problem or deficiency, and the process may need to consider the individual's "knowledge, skills, and attitudes" in the context of the system and organizational culture in which the behavior is observed.
3. Remediation should enable pharmacists to explore the extend to which their professional identity has formed, and differentiate where they are individual, team, or society-level oriented.
4. Remediation should enable pharmacists to become aware of, and develop the ability to manage potential conflicts of interest arising from, the personal, professional, and commercial influences on decision-making that exist in the practice environment.
5. Remediation should enable pharmacists to assure they have sufficiently developed competencies underpinning development, the four components of namely moral sensitivity (i.e., awareness of how actions chosen affect other people), reasoning (the ability to apply moral principles or ideals when developing a solution to a dilemma scenario), motivation (i.e., the prioritization of moral values over competing values and influences) and implementation (i.e., perseverance and courage to implement actions), operate as interactive elements in the development of a professional.

Austin et al., 2004; Bebeau, 2009; Bebeau & Faber-Langendoen, 2014; Caldicott & D'Oronzio, 2015; Maize et al., 2010; Parran et al., 2013; Phipps et al., 2011; Rest et al., 1999; Rest, J.R., Narvaez, D., 1994; Roche et al., 2017; Roche & Kelliher, 2014; Roche & Kelliher, 2009; Winslade et al., 2007.

Websites

(Australia) The Pharmaceutical Society of Australia: www.psa.org.au
(Canada) The Alberta College of Pharmacists: pharmacists.ab.ca
(Canada) The College of Pharmacists in British Columbia: www.bcpharmacists.org
(Canada) The Ontario College of Pharmacists: www.ocpinfo.com
(Canada) The National Association of Pharmacy Regulatory Authorities: www.napra.ca
(Croatia) The Croatian Pharmaceutical Society: acta.pharmaceutica.farmaceut.org/hfd.html
(FIP) International Pharmaceutical Federation: www.fip.org
(Ireland) The Pharmaceutical Society of Ireland www.psi.ie
(New Zealand) The Pharmaceutical Council of New Zealand: www.pharmacycouncil.org.nz
(United Kingdom) (RPS) Royal Pharmaceutical Society https://www.rpharms.com/
(United Kingdom) The General Pharmaceutical Council: www.pharmacyregulation.org
(USA) The Accreditation Council for Pharmacy Education (ACPE): www.acpe-accredit.org
(WHO) The World Health Organization: www.who.int

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Community and Ambulatory Pharmacy Practice

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Introduction

Community pharmacy practice has evolved dramatically over the years. The role of the pharmacist in the early 1900s primarily involved the preparation and dispensing of pharmaceutical compounds for medicinal use (Pearson, 2007). The 1950s brought the expansion of large-scale manufacturing of medications as well as restrictions on most therapeutic products to require a physician's prescription (Pearson, 2007). These changes greatly impacted pharmacy, reducing the autonomy of the community pharmacist and limiting their role further. Between 1965 and 1990, pharmacy practice began to shift from one of primarily dispensing, to a more clinical, patient focused model (Penna and Knowlton, 2003, p. 38). Several critical factors influenced this evolution, including the increased number and complexity of available medications, more advanced pharmacist training, changes in health-care infrastructure and reimbursement, and a demand by patients for accurate, accessible health information (Rutter, 2013). In Hepler and Strand (1990) coined and described the term pharmaceutical care. This has become widely accepted as the current model of pharmacy practice in those countries with the most advanced health-care systems. The pharmacists' unique skill set is used to optimize pharmacotherapy in order to improve health outcomes and reduce drug costs.

This objective of this chapter is to discuss changes to the traditional dispensing business model and to explore the evolving role of the community pharmacist. New and innovative areas of pharmacy practice will be discussed including medication review, point-of-care testing, and pharmacogenomics.

Changing Community Pharmacy Landscape

Over the last few decades, the profession of pharmacy has dramatically changed. The scope of practice has expanded to help meet the health-care needs of the public and to reduce the pressures placed on the broader system. This section will further explore the different pharmacy business models and those factors that have contributed to the current evolution.

Ownership Models

Historically, community pharmacies were run as independent businesses by local pharmacists (Pearson, 2007). These pharmacies where generally not affiliated with each other or any other larger corporate body (Grootendorst et al., 2008). The pharmacist was the owner/operator of the business. Beginning as early as the 1900s, pharmacy chains, banners, and franchises started to appear and with time have acquired a large portion of the retail pharmacy market. A banner is an independent pharmacy affiliated with a larger group in order to capitalize on bulk purchasing and branding and uses a recognized name (Grootendorst et al., 2008). Chain pharmacies are owned by large corporations and employ pharmacy managers to run their pharmacies (Grootendorst et al., 2008). Franchises are licensed by larger corporations to individual pharmacist owners. These pharmacist owners are expected to adhere to a set of operational standards and generally pay fees and make purchases from the parent company (the franchisor) (Grootendorst et al., 2008). Currently, the retail pharmacy industry is comprised of over 61,000 pharmacies across the United States and includes a combination of independent pharmacies (36%), chains and franchises (33%), mass merchants (13%), and supermarkets (14%) (National Community Pharmacists Association, 2016). These numbers are similar across Canada, but with a larger portion of pharmacies being independently owned (49%) (Ontario College of Pharmacists, 2015). Some have argued that the movement away from independent ownership has reduced pharmacist autonomy and negatively impacted the profession. Others have suggested that this shift away from a retail focus is instrumental if the pharmacist is to take on a more clinical, primary health-care role. Additionally, newer models such as mail-order pharmacies, centralized fill operations, and specialty distribution networks will continue to challenge the historical business model.

Dispensing and Workflow

In recent years, pharmacists have seen their roll expand to include a portfolio of clinical service offerings such as medication reviews, prescription renewals, clinical adaptations, and vaccinations. **Table 1** summarizes the fees and claims data for government sponsored pharmacist services in Canada, by province. In addition, drug reform and generic deflation have placed increase pressure on the traditional dispensing model (Canadian Foundation for Pharmacy, 2018). As a result, pharmacists have found themselves challenged with time, workflow and staffing issues, and the ability to offer consistent, sustainable services to their patients. These challenges are the direct result of attempting to balance conventional pharmacy dispensing services with the consistent provision of clinical programs. In order to transition into a workflow model that allows for the provision of sustainable clinical services, it is necessary to understand a number of key concepts.

Drug Reform and Generic Deflation

As public and private payers struggle to meet increased health-care costs, they have looked to pharmacy as a source of cost reduction. Generic deflation, reduced fees, capped mark-ups, and banned professional allowances have all impacted the profitability and potential future sustainability of community pharmacies.

Ontario is an interesting case example that highlights the dramatic impact of such legislative change. The drug reform of 2006 prohibited pharmacies from accepting rebates from drug manufacturers and reduced the maximum price for generic medications listed on the Ontario drug benefit (ODB) formulary to 50% of the brand name (previously 63%) (Schill, 2010). Traditionally, rebates, or kickbacks, were provided by generic drug manufacturers directly to pharmacies for stocking their product and resulted in a significant proportion of pharmacy revenue. These were replaced with "professional allowances," which were to be used for patient care and had value restrictions (20% through publicly funded plans, but no restrictions for private plans). As a result of these changes, independent pharmacy revenue was reduced by 34%.

The drug reform of 2010 was comprised of three major changes: (1) reduction of the maximum prices for generic products listed on the ODB formulary to 25% of the brand name and which was to be phased in for private plans, (2) elimination of professional allowances immediately for ODB recipients and to be phased out for private plans, and (3) prohibit private label generic prescription drugs (Wood, 2010). At the time, up to 70% of professional allowance funds were used for operating costs of the pharmacy, so its elimination drastically reduced profitability. There was, however, $100 million CAD set aside to cover pharmacy professional services on a fee-for-service basis to offset a portion of the losses (Wood, 2010).

Table 1 Fees and claims data for government-sponsored pharmacist services, by province (Updated September 2017)

	British Columbia	*Alberta*	*Saskatchewan*	*Manitoba*	*Ontario*	*Quebec**	*Nova Scotia*	*New Brunswick*	*Prince Edward Island*	*Newfoundland/ Labrador*
Patient care plans		$100 per Comprehensive Annual Care Plan (CACP, 130,378 claims); $125 for pharmacists with additional prescribing authority (APA, 123,506 claims); $60 per Standard Medication Management Assessment (SMMA, 38,770 claims); $75 if pharmacist has APA (36,364 claims); $20 for follow-ups without APA (373,447 claims for CACPs, 47,140 for SMMAs); $25 for follow-ups with APA (463,930 claims for CACPs, 56,136 for SMMAs)								
Medication reviews/ management	$60 per Medication Review–Standard, max. 2 annually, 6 months apart (177,114 claims); $70 per Medication Review—Pharmacist Consultation, max. 2 annually, 6 months apart (17,794 claims); $15 per Medication Review Follow-Up, max. 4 annually (19,235 claims)	Medication reviews a component of CACPs and SMMAs (see Patient care plans above)	*$60 per Medication Assessment (seniors) (11,795 claims); $20 per follow-up, max. 2 annually (3465 claims)* *$60 per Medication Assessment and Compliance Packaging (1845 claims)*		$60 per MedsCheck (543,902 claims); $75 for MedsCheck for Diabetes (163,168 claims); $90 for MedsCheck for Long-Term Care Annual (69,833 claims); $150 for MedsCheck at Home (24,799 claims); $25 per follow-up (163,242 claims for MedsCheck; 44,308 claims for MedsCheck for Diabetes Education); $50 per quarterly follow-up for MedsCheck for Long-Term Care Quarterly (198,510 claims)		*$52.50 per Basic Medication Review (3728 claims); $150 per Medication Review Service (seniors) (669 claims); $20 for follow-ups, max. 2 annually (118 claims)*	*$52.50 per PharmaCheck (low-income) (12,318 claims)*	*$52.50 per Medication Review (2130 claims); $65 per Diabetic Medication Review (948 claims); $20 per follow-up for Medication Reviews, max. 4 annually (1047 claims); $25 per follow-up for Diabetic Medication Reviews (369 claims), max. 4 annually*	*$52.50 per Medication Review (seniors); $52.50 per Medication Review for Diabetes (all ages); max. 72 claims annually; (1629 claims)*

(*Continued*)

Table 1 Fees and claims data for government-sponsored pharmacist services, by province (Updated September 2017) (*cont.*)

	British Columbia	*Alberta*	*Saskatchewan*	*Manitoba*	*Ontario*	*Quebec**	*Nova Scotia*	*New Brunswick*	*Prince Edward Island*	*Newfoundland/ Labrador*
Immunization	$10 (557,533 claims for flu; 13,156 claims for pneumonia; 655 claims for pertussis; 620 claims for HPV; 11,218 claims for other)	$20 (533,053 claims for flu); authority for other immunizations, inc. travel vaccines (no public funding)	$13 (90,374 claims for flu)	$7 (79,050 claims for flu; data not available for pneumonia, HPV, Tdap [tetanus, diphtheria, pertussis])	$7.50 (1,010,548 claims for flu); authority for other immunizations, inc. travel vaccines (no public funding)		$12 (104,170 claims for flu)	$12 (63,315 claims for flu for seniors and high-risk groups)	$12.36 (9280 claims for flu); authority to immunize again other infectious diseases, no public funding	$13 (3757 claims for flu)
Administration of drugs by injection		$20 per assessment and administration of drugs by injection (169,419 claims)	Authority to administer drugs by injection; no public funding	Authority to administer drugs by injection; no public funding	Authority to administer drugs by injection and inhalation for education and demonstration; no public funding	Authority to administer drugs to demonstrate appropriate use; no public funding	Authority to administer drugs by injection; no public funding	Authority to administer drugs by injection; no public funding	Authority to administer drugs by injection; no public funding	Authority to administer drugs by injection; no public funding
Adaptation/ altering of prescriptions, including continuity of care and renewals	$10 to renew and adapt (226,296 claims)	$20 per assessment for renewal/adaptation/ discontinuation (533,393 claims for renewals; 151,679 claims for adaptations)	$6 to renew, alter dosage form or alter missing information (249,608 claims)	Authority for continuity of care prescribing and prescription adaptations; no public funding	Authority to adapt or renew; no public funding	$12.50 per renewal (30 + days), max. 1 per person annually (158,358 claims)	*$14 per Prescription Adaptation (293 claims)*	Authority to adapt or renew; no public funding	*$14.83 per adaptation (123 claims)*	*$11.96-$12 per Medication Management adaptation (33,918 claims)*
Refusals to fill	$20	$20 per assessment (8523 claims)	*1.5X dispensing fee, max. $17.10 (16 claims)*		*$15 as part of Pharmaceutical Opinions program*	*$8.96 for first 48,500 prescriptions; then $8.37 (67,444 claims)*	*$14 (49 claims)*		*$14.83 (14 claims)*	*$23.92-$24 (32 claims)*
Therapeutic substitutions	$17.20 (8753 claims)	$20 per assessment (claims included under adaptation)				Authority to substitute for out-of-stocks; no public funding	*$26.25 (366 claims, for proton pump inhibitors only)*	Authority to substitute; no public funding	*$14.83 (6 claims for eligible drug classes)*	*$11.96-$12*
Emergency prescription refills	Authority for emergency refills; no public funding	As part of prescription renewals	$10, max. 1 claim per patient per 28 days (claims data n/a)	Authority for emergency refills; no public funding	Authority for emergency refills; no public funding		Authority for emergency refills; no public funding	Authority for emergency refills; no public funding		$11.96-$12

Minor ailments	As part of CACPs, SMMAs by those with additional prescribing authority	$18 per Minor Ailment Assessment for 16 conditions (14,512 claims)	Authority to assess and prescribe for 12 self-limiting conditions ("minor ailments"); no public funding		$16 per assessment for 7 conditions where no diagnosis is required and for 12 where diagnosis and treatment are known (107,666 claims)	Authority to assess and prescribe for 31 conditions; no public funding	Authority to assess and prescribe for minor ailments; no public funding	Authority to assess and prescribe for 30 conditions; no public funding	Authority to assess and prescribe for minor ailments; no public funding
Initial-access prescribing or to manage ongoing therapy (exc. minor ailments)	$25 per assessment for initiating medication therapy with APA (206,395 claims) $20 per assessment for emergency prescriptions (26,777 claims)	Collaborative Practice Agreements with physicians enable pharmacists to select, initiate, monitor and modify drug therapies; no public funding	Authority for prescribing by Extended Practice pharmacists within the scope of their specialty; no public funding. Authority to prescribe in "state of emergency;" no public funding	Authority to initiate Schedule 1 smoking cessation therapy; see below for funding details for smoking cessation services	To reach therapeutic target: $15.50–$19.50 for initial evaluation (based on condition); $40 annually for min. 2 follow-ups for certain conditions; $50 annually for min. 3 follow-ups for insulin-dependent diabetes; $16 per follow-up for anticoagulation, max. 1/month. (128,557 claims for all)	Authority to assess and prescribe in emergencies; no public funding	Authority to initiate smoking cessation therapy; no public funding. Authority to assess and prescribe in emergencies; no public funding	Authority to assess and prescribe in emergencies; no public funding	Authority to initiate smoking cessation therapy; no public funding
Pharmaceutical opinions				*$15 per opinion (212,910 claims for "Change to prescription," 96,697 claims for "No change to prescription," 17,501 claims for "Not filled as prescribed")*	*$19.79 (198,552 claims)*				

(*Continued*)

Table 1 Fees and claims data for government-sponsored pharmacist services, by province (Updated September 2017) (*cont.*)

	British Columbia	*Alberta*	*Saskatchewan*	*Manitoba*	*Ontario*	*Quebec**	*Nova Scotia*	*New Brunswick*	*Prince Edward Island*	*Newfoundland/ Labrador*
Smoking cessation	$10 per dispensing of nicotine replacement therapy, max. 3 annually (claims data n/a)	As part of SMMAs and follow-up SMMAs; max. 4 follow-ups	*Up to $300 annually ($2 per minute) for Partnership to Assist with the Cessation of Tobacco (PACT) (4940 claims)*	Authority to prescribe for smoking cessation; no public funding	*Up to $125 annually: $40 for initial consult; $15 for up to 3 primary follow-ups; $10 for up to 4 secondary follow-ups (6288 claims)*	$16 to prescribe for smoking cessation as part of minor ailments (30,423 claims out of total for minor ailments)	Authority to prescribe for smoking cessation as part of minor ailments; no public funding		Authority to prescribe for smoking cessation as part of minor ailments; no public funding	Authority to assess and prescribe for smoking cessation; no public funding
Other services	$10 for trial prescriptions (claims data n/a)	$20 for assessment of appropriateness of new prescription medications (trial prescriptions, 19,323 claims)	2X dispensing fee, max. $22.80 for emergency contraception prescribing (7721 claims); $25 for medication reconciliations (seamless care) with prescribing or *1.5X dispensing fee, max. $17.10 for medication reconciliations; $7.50 for trial prescriptions; $3.50/day for Direct Observed Therapy for Hepatitis C drugs; $3.50/day for methadone managed care*		Authority to perform a procedure below the dermis for education and demonstration; no public funding $70 for naloxone program, initial kit; $45 for replacement kit (17,543 claims)	$18.02 for emergency contraception prescribing (107,378 claims)				*$23.92-$24 for Antibiotic Medication Adherence; $11.96-$12 for follow-ups, max. 1 per antibiotic (96,286 claims); $23.92-$24 for COPD Medication Adherence; $11.96-$12 for follow-ups, max. 2 (163 claims). Authority for trial prescriptions; no public funding*

NOTE: All content in italics indicates that public funding is available only to eligible beneficiaries of the provincial drug plan.

Information current as of September 2017 and collected from provincial ministries of health and provincial pharmacy associations. Claims data are for fiscal year ending March 31, 2017, with the exception of Quebec where the data is for year ending December 2016.

*In Quebec, legislation requires private insurance plans to pay the same fees as the public plan for pharmacists' services, except for refusals to fill and Pharmaceutical Opinions. This chart gives claims data for the public plan only.

Reforms are not limited provincially. National programs such as the pan-Canadian Pharmaceutical Alliance (pCPA) aggressively negotiate drug pricing reductions across Canada. pCPA's goal is to achieve lower consistent drug prices, increase access to new drugs, and improve consistency of coverage nationally. The Alliance capitalizes on the combined buying power of the provinces and reduced duplication of negotiations (Husereau et al., 2014). On April 1, 2018, 70 of the most commonly prescribed drugs in Canada were reduced by 25%–40%, resulting in overall discounts of up to 90% of the price of their brand-name equivalents. Most are drugs to treat chronic diseases such as high blood pressure, high cholesterol, and depression. The changes are estimated to save an additional $3 billion dollars over the next 5 years.

In the end, drug reform and generic deflation have threatened the sustainability of community pharmacy. Dispensing profitability has greatly declined over the past decade, and this trend will likely continue as the fraction of generic medications increases (PMPRB, 2014). Pharmacists are beginning to explore expanded scope services as alternative revenue streams, with the hope that these services will drive profitability in the future. In order for pharmacies to successfully transition into a workflow model that allows for the sustainable provision of these clinical services, it is necessary to understand a number of key concepts:

1. Understand the evolving roles of all the key pharmacy players
2. Pharmacy labor investments are instrumental to sustainability
3. Traditional measures of pharmacy productivity are no longer applicable
4. Pharmacy contribution for professional services is higher than dispensing activities
5. Embrace technology to enhance productivity

Understand the Evolving Roles of All the Key Pharmacy Players

The ability to offer sustainable patient-centered services extends beyond the pharmacist. Dispensary assistants and regulated pharmacy technicians are instrumental in the successful implementation of these programs. Their primary goal is to:

Champion the dispensing function such that pharmacist time dedicated to technical tasks can be limited and devoted instead to patient-centered services.

As the roll of the pharmacist has evolved so as that of the technician. Many pharmacies have yet to capitalize on this expanded role. Integrating a registered pharmacy technician into practice offers a viable solution to the workflow issues faced by many pharmacists, particularly when maximizing the technician's scope. In order to do this, however, we must clearly understand what a pharmacy technician can do under their own authority as a regulated health-care professional.

In general terms, the division of responsibilities can be defined as:

- *TECHNICIANS* are accountable and responsible for the technical aspects of both new and refill prescriptions (i.e., the correct patient, drug dosage form/route, dose, doctor) and;
- *PHARMACISTS* remain accountable and responsible for the therapeutic/clinical appropriateness of all new and refill prescriptions and all therapeutic consultation.

More specifically, a regulated pharmacy technician can:

1. Ensure that a prescription vial contains the right drug and quantity
2. Accept verbal prescriptions (excluding narcotics/controlled/and targeted substances)
3. Receive and provide prescription transfers (excluding narcotics/controlled/ and targeted substances
4. Perform a procedure on tissue below dermis (e.g., using a lancing device)

While the objective of integration is to optimize the roles of the technician and pharmacist, workflow will be dependent on a number of individual variables including:

1. prescription volume
2. OTC traffic
3. physical layout
4. staff experience
5. patient demographics

There is no "cookie-cutter" approach to maximize workflow and productivity. It may be necessary for pharmacies to experiment in order to balance all these variables.

Moreover, in addition to diverting technical tasks, technicians can play an indirect role in the professional programs themselves. In order to do this, they must be able to:

1. Define the Service
    a. What are you offering the patient?
    b. Understand basic process to deliver the service
        - Nature of the consultation, duration of appointments, items covered

c. Inherent benefits of the service

- Personalized approach
- Maximum results from drug therapies
- Support through regular follow-up
- Answers to questions

2. Screen for patients
3. Notify the pharmacists about eligible patients
4. Call patients to remind them about appointments
5. Provide other follow-up support

By optimizing the integration of regulated pharmacy technicians, the efficiency of the dispensing function can be improved, and the focus of the pharmacist can shift to offering professional services.

Pharmacy Labor Investments are Instrumental to Sustainability

One of the fundamental errors made by pharmacy managers and owners when initially integrating clinical programs into their practice is that they fail to make the necessary investments in labor. The expectation is that the programs will be offered using the traditional labor model. This may work during periods of low prescription volume. However, during busy periods, the staff will almost always revert back to their traditional dispensing model and abandon any attempt to offer clinical programs. This sends a mixed message to customers and will fail to differentiate the pharmacy as a facility that excels in expanded scope.

Traditional Measures of Pharmacy Productivity are No Longer Applicable

The traditional pharmacy business model was entirely transaction based. Dispensary productivity was assessed using measures such as scripts per labor hour or wage cost per script. This was appropriate for a model centered on dispensing. A typical pharmacy would be deemed productive if it were able to achieve a productivity of anywhere between 5 and 8 scripts per labor hour or a cost to fill of about $4–5 per script.

Unfortunately, these productivity measures do not apply to a service-based model. Most clinical services are reimbursed according to a fee-for-service model. Fees are dependent on the time required to offer the service and the complexity of the program. Pharmacy management will find it difficult to evaluate the return on investment of these clinical programs if they rely on antiquated productivity measures. As such, productivity of these clinical programs must be assessed separately from the traditional dispensing services. A measure such as wages as a percentage of sales would address both the investment in labor required to offer the service and the resulting revenue generated from the fees. A return of 20%–25% works well for most currently funded programs. Consequently, the financial success of the programs could be more accurately assessed, and changes to labor investments could be made based on these thresholds.

Pharmacy Contribution for Professional Services is Higher than Dispensing Activities

Pharmacy contribution is defined as the net profit delivered to the overall business by the pharmacy department. This typically includes profit from dispensing and professional service fees. Services have improved pharmacy contribution and store profitability on an absolute dollar basis and on a net Contribution per Rx basis. Services do not carry some of the typical costs incurred by dispensing activity, namely, no costs of goods sold (COGS), no total loss, no other Rx expenses. Services have a higher cost per script for Rx Wages. The value-added function of this interaction solely rests with the pharmacist and their patient intervention. Figs. 1–3 help to explore these concepts.

Embrace Technology to Enhance Productivity

Finally, with today's steady prescription, growth pharmacy operators are looking for new and creative ways to handle prescription volume. They are experimenting with innovative solutions to help them reduce labor productivity costs, free up pharmacists' time, and maintain the important patient relationship. Technology can play a vital role in optimizing dispensary workflow, and technological advancements have dramatically changed the way that pharmacies fill their prescriptions and the way that pharmacists interact with their patients. The most significant of these changes include:

1. Paperless Workflow
2. Automated Dispensing
3. Centralized Fill
4. E-refills/Paging
5. E-prescribing
6. Medication Synchronization

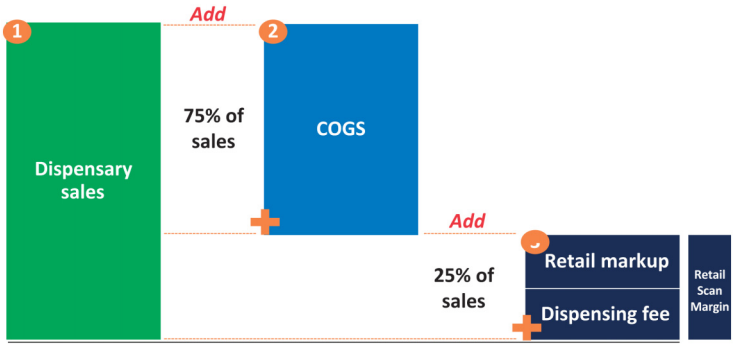

Figure 1 Dispensary sales include three key components: cost of goods sold (COGS), retail markup, and dispensing fee.

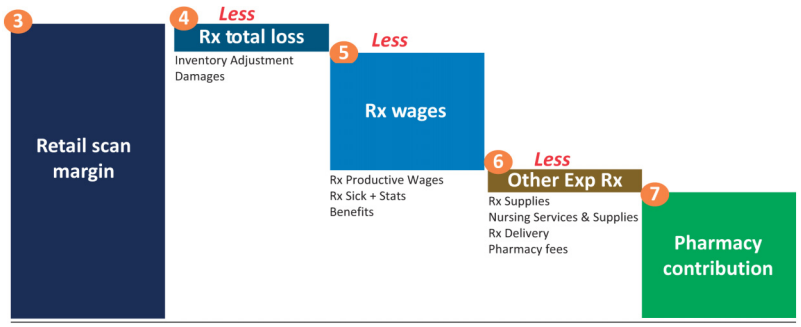

Figure 2 There are additional direct expenses incurred to deliver dispensary sales, which reduce the retail scan margin and equate to the pharmacy contribution.

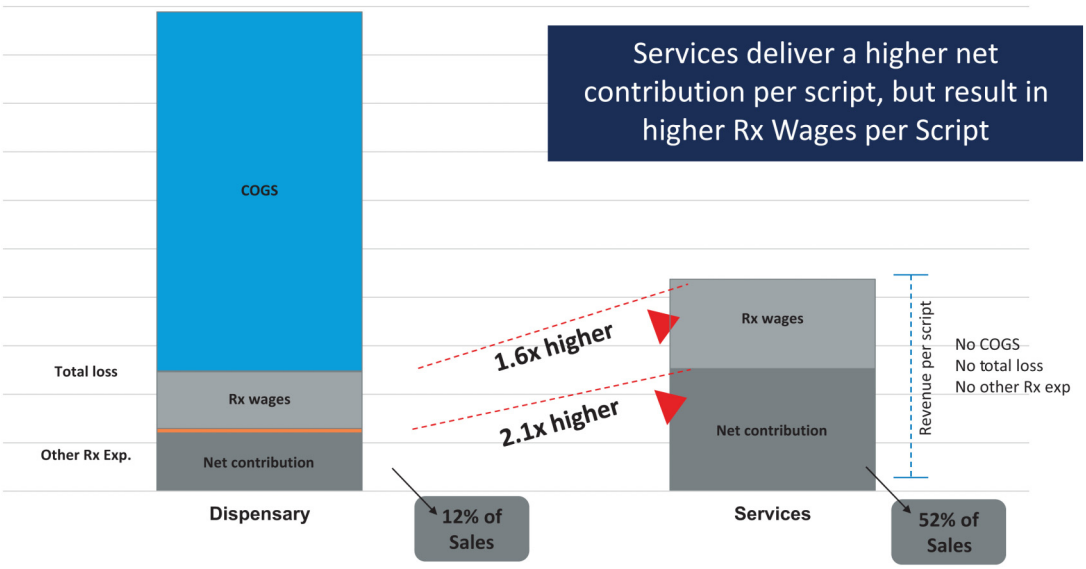

Figure 3 Pharmacy contribution for professional services is higher than dispensing activities.

Traditional dispensaries rely very heavily on paper. Everything from hardcopies, to logs, to transfers are documented on paper and manually filed. This is an extremely tedious, time-consuming process. Scanning technology has allowed us to transition to a paperless environment. Low-value tasks such as basket staging and prescription filing have been eliminated completely. All documentations are stored electronically and can be readily retrieved. The benefits to productivity and labor are enormous.

In the atmosphere of a busy dispensary, every minute counts. Automated dispensing machines or dispensing robots have the ability to fill and label prescriptions very quickly and accurately. They have been shown to improve both dispensary efficiency and patient safety. As pharmacists look for additional ways to free up time for direct patient care activities, and as the cost of these devices continues to decline, we are certain to see them more frequently in community pharmacies.

A natural extension of the automation process is central fill. Using central fill, pharmacies can aggregate prescriptions from multiple locations and funnel them to a centrally located prescription fulfilment center. Once there, prescriptions are assembled, verified, packaged, and are delivered back to the originating pharmacy. Although, this model is not yet common in Canada, it is widely used by national chains in the United States. The cost to fill a prescription can be reduced to as low as $1 per script, as compared to $4–5 in a traditional pharmacy. These productivity gains have the potential to dramatically change dispensary workflow.

Technological solutions also impact the way that patients interact with their pharmacies. E-refills allow patients to have access to e-mailed refill reminders and then to automatically request that their prescriptions be prepared. In addition to the obvious adherence benefits, these solutions relieve congestion at the pharmacy and allow for workload to be systematically completed in advance. For those patients that do chose to visit the pharmacy directly, paging systems allow them to wander the store and be contacted when their prescription is ready. Again, this allows for a more streamlined workflow and reduces the stress and anxiety experienced by pharmacy staff as a result of unplanned spikes in prescription volume.

E-prescribing, as defined by the Centre for Improving Medication Management (CIMM), is the computer-based electronic generation, transmission and filling of a prescription, taking the place of paper and faxed prescriptions (2008). A literature review by Porterfield et al. identified the benefits of e-prescribing, including reduced prescribing and medication errors, increased efficiencies for physicians and pharmacists, cost savings for the health-care system, and increased medication adherence (Porterfield et al., 2014). A nonrandomized prospective study by Kaushal et al. found an almost sevenfold decrease in error rates 1 year after implementation of e-prescribing (Kaushal et al., 2010). Efficiencies within the pharmacy were seen through reduced paperwork, less call-backs to physicians for clarifications, and less time spent faxing prescriptions and reauthorizations to pharmacies (CIMM, 2008). Cost savings can be expected through a reduction in adverse drug events, resulting in reduced visits to physician offices and emergency rooms (Surescripts, 2012). The implementation of e-prescribing has also led to improved medication adherence, with a study by Surescripts showing a 10% increase in number of prescriptions being picked up when compared to written prescriptions (2012).

Medication synchronization or medsync is defined as the synchronized filling and refilling of chronic disease state medications, all on the same day, using pharmacy software technology to coordinate and calculate fill quantities and streamline dispensing. Traditionally, community pharmacy dispensing has been reactive; waiting on a patient to request a refill. By syncing a patient's entire medication list to be due at the same time, it proactively addresses refill compliance, which can lead to improved medication adherence. A study by the National Community Pharmacists Association (2013) showed improvements of adherence by 50%, and first-refill abandonment was reduced by over 90%. There was also an increase in the number of prescriptions filled by patients by 0.75–1 per year. Software upgrades that coordinate the refilling of medications in a timely and effective manner promote these benefits to various stakeholders. This technology allows community pharmacy to increase efficiency, improve adherence, as well as reduce third-party payer health-care costs due to patient noncompliance.

Patient Care Services

Community pharmacy has expanded beyond the simple distribution of drugs to include a myriad of patient care services. This section will explore some of these opportunities and highlight the successes and challenges that pharmacists have faced with their implementation.

Medication Reviews

A medication review, in general, may be defined as a service in which a pharmacist uses their unique expertise in pharmacology and pharmacotherapy to review a patient's medication regimen with the goal of identifying actual or potential drug therapy problems. Medication reviews can vary widely depending on the jurisdiction's scope of practice, program requirements, and reimbursement. Examples of different types of reviews include comprehensive prescription and nonprescription reviews, adherence reviews, targeted clinical intervention reviews, as well as reviews focusing on deprescribing and therapeutic substitutions (Noseworthy, 2013). At minimum, these sessions are typically appointment-based and include reviewing the patient's prescription medications and collaborating with the patient and their circle of care, in order to optimize drug therapy. The pharmaceutical division within British Columbia's Ministry of Health defines a review as follows:

> "A medication review is a patient-care service that seeks to enhance a patient's understanding of, and improve the health outcomes of, their medication regimen" (Ministry of Health, 2016 p.12).

Medication reviews also offer a unique opportunity to engage the patient to play a larger role in their own medication management and to promote interprofessional collaboration with the ultimate goal of improving health-care outcomes.

Experience To-Date

Over the past decade, medication reviews, from the simplest to the most complex, have come under scrutiny from both government and third-party insurers. These payors have begun to demand evidence to substantiate the continued reimbursement of the programs. Theoretically, medication reviews provide an opportunity to optimize health outcomes and render cost savings through

the mitigation or amelioration of drug-related therapeutic issues (Malet-Larrea et al., 2017). Initially, several meta-analyses had found that medication reviews resulted in positive patient outcomes such as improved medication adherence, reduced hospitalizations, and achievement of biomarker targets (Hatah et al., 2014). The average compensation for a medication review in 2014 was $68.86CAN (Houle et al., 2014). In the United Kingdom, medication reviews with follow-ups (MRF) reimbursed at 22€ per patient-month yielded cost savings for the National Health Services (NHS) within 6 months, at 97€ per patient. For every 1€ invested to MRF, there was a return of 3.3–6.2€ (Malet-Larrea et al., 2017). This evidence has been met with some controversy as conflicting studies have concluded that medication reviews provide no cost savings relative to traditional care (Loh et al., 2016). These differences may be explained by the wide variation in program and documentation requirements, reimbursement, scope, and outcomes measured. Table 2 provides some examples of different medication review programs.

More recently, the Ontario Pharmacy Evidence Network (OPEN) evaluated billing data for medication reviews performed in Ontario as part of the government funded MedsCheck program. Pharmacies were less likely to conduct an annual medication review

Table 2 Examples of various medication review programs

Program	*Location*	*Payer*	*Service*	*Eligible patients*	*Fee*
Medication Review (15)	Newfoundland and Labrador (NL)	NL Prescription Drug Program	Medication Review	NLr Prescription Drug Program beneficiary (1) • All ages if diagnosed with diabetes on one or more diabetic agent • Over 65 with chronic conditions managed by 3 or more medications	$52.50 CAN
Pharmacare Insured Professional Services (18)	Nova Scotia (NS)	Government of NS	Advanced Medication Review Service	NS Beneficiary of Seniors' Pharmacare Program • ≥1 chronic disease and, • ≥4 chronic Rx medications or 1 high-risk drug and, • Not residing in nursing home or care facility or receiving compliance packaging	$150 CAN
			Basic Medication Review Service	NS resident on ≥3 chronic Rx medications	$52.50 CAN
MedsCheck (15)	Ontario (ON)	ON Ministry of Health and Long-Term Care	MedsCheck	Ontario Drug Benefit (ODB) or Youth Pharmacare (OHIP+) (2) beneficiary • ≥3 Rx medications for a chronic condition (2)	$60 CAN
			Diabetes MedsCheck	Ontario Drug Benefit (ODB) or Youth Pharmacare (OHIP +) (2) beneficiary • ≥1 Rx diabetic medication (2)	$75 CAN
			Home MedsCheck	Eligibility for MedsCheck or Diabetes MedsCheck and not able to visit pharmacy due to physical or mental issues (2)	$150 CAN
Rx Review Program	Colorado	Colorado Department of Health Care Policy and Financing (Medicaid)	Medication Review	Colorado Medicaid beneficiaries on ≥5 Rx medications for over 3 consecutive months (4)	• $150USD face-to-face • $90 USD • Phone appointment (5)
PharmAssist (6)	Montana	State of Montana Department of Public Health and Human Services	Medication therapy management	All Montana residents	• Initial: 50 USD (15 min) • Additional time or follow ups: 25 USD (15 min)

(1) http://www.health.gov.nl.ca/health/prescription/provider_guide/program_claiming_policies.pdf.
(2) http://www.health.gov.on.ca/en/pro/programs/drugs/ohipplus/docs/ohip_pharmacist.pdf.
(3) http://www.health.gov.on.ca/en/pro/programs/drugs/medscheck/medscheck_original.aspx.
(4) https://www.colorado.gov/pacific/sites/default/files/Rx_Review_Pharmacist_Q&A.pdf.
(5) https://www.colorado.gov/pacific/sites/default/files/RxReview_Invoice%20Form_11.2016.pdf.
(6) Montana Department of Public Health and Human Services. PharmAssist Program—information for pharmacists. Available from: www.dphhs.mt.gov/prescriptiondrug/pharmacists.shtml.
(7) https://dphhs.mt.gov/Portals/85/hrd/documents/expeditedcontractorreferral.pdf.

as their prescription volume increased (Pechlivanoglou et al., 2016). Also, pharmacists tended to more frequently conduct medication review on those patients with less complex medication regimens. Time and workflow were identified as barriers to sustained implementation. Documentation was also identified as an issue. Less than half of the reviews recorded the reason for medication use and only 75% indicated any assessment of medication-taking behavior.

In the end, pharmacy medication review programs, despite their widespread use across North America, have been scrutinized for quality and cost effectiveness. Although anecdotal reports indicate a high degree of patient satisfaction with the service, evidence to support cost savings and positive health outcomes is mixed, at best. Pharmacies that have been able to overcome the time, and workflow challenges have generally made an investment in pharmacist labor in order to ensure the sustainability of the program and, typically, utilize nontraditional appointment-based models in order to offer high-quality service.

Disease State-Specific Consultation Programs

Disease state-specific programs are variations of medications reviews that target patients with specific chronic conditions. Most commonly, these programs focus on cardiovascular disease, diabetes, and smoking cessation. The goals of these programs are to improve the overall health of these patients with the hopes of lowering their drug and disability costs. Several insurance providers have piloted disease state-specific consultation programs with varying reimbursement models for pharmacy.

Green Shield Canada (GSC), since 2015, has offered a pan-Canadian cardiovascular program for all Green Shield beneficiaries under the age of 65. The Pharmacist Health Coaching Cardiovascular Program was developed based on the positive evidence of the Rx Reach study which found that intensive hypertension control managed by pharmacists greatly exceeded those outcomes in patients receiving standard of care. Outcomes included statistically significant reductions in systolic blood pressure and in the percentage of patients that achieved blood pressure targets within the 6-month study duration (Ontario College of Pharmacists and Green Shield Canada, 2018). The goals of the cardiovascular program include:

1. Provide guidance and support to patients to achieve target blood pressure and cholesterol measurements.
2. Implement strategies that help improve patient adherence to cardiovascular drug therapy.
3. Offer effective coaching and follow-up to help patients adopt healthy lifestyle behaviors that will positively impact their cardiovascular and overall health.

This program offers compensation to pharmacists at $60 CAN for the initial visit and $20 CAN for scheduled follow-ups (Green Shield Canada n.d., p. 4).

Smoking Cessation

Tobacco-related health-care costs remain a huge public heath burden in both Canada and the United States. In Canada alone, these costs exceed $6.5 billion annually (The Conference Board of Canada, 2012). As such, governments and third-party payers have looked to the expertise of community pharmacists to help patients engage in quitting smoking. Several Canadian provinces and a number of insurers have offered reimbursement to pharmacists for participating in structured counseling services. As of 2018, Alberta, Saskatchewan, Ontario, and Quebec have publically funded pharmacy smoking cessation programs already in place (Canadian Pharmacists Association, 2015). Additionally, in provinces where pharmacists have prescribing authority, they can utilize this authority to prescribe smoking cessation therapies (Ontario College of Pharmacists, 2012). **Table 3** outlines the details of the Ontario model (Ministry of Health and Long-term Care, 2018).

Unfortunately, initial uptake of the Ontario smoking cessation program has been poor. Pharmacists have cited insufficient reimbursement and time and workflow challenges as the most common barriers to successful implementation. Only a small fraction of Ontario smokers participated in the program during the 2011–12 fiscal year (Wong et al., 2015), which has raised concerns about the future of the program.

Minor Ailment Prescribing and Assessment

Minor ailment is an umbrella term used to describe diseases or conditions that are self-limiting in nature. Despite the terminology, minor ailments result in a large number of annual physician visits. By expanding pharmacist scope of practice to include minor ailment prescribing regulators hoped to free up physician time, improve access to care for patients, and reduce overall health-care costs. In the United Kingdom, the National Health Service (NHS) has adopted a pharmacist/physician collaborative minor ailment model since 2000 (Paudyal et al., 2011). A systematic review of the program concluded that the introduction of pharmacy-based minor ailment services in the United Kingdom resulted in a high rate of symptom resolution, low rate of reconsultation, and a decrease in the number of consultations at general practices (Paudyal et al., 2013). These findings suggest pharmacy-based minor ailment programs do not jeopardize care and may alleviate work burden from general practitioners. In North America, several Canadian provinces have expanded the scope of pharmacist practice to allow for the assessment and prescribing of minor ailments. Public funding for the programs exists in Alberta, Saskatchewan, and Nova Scotia (Canadian Pharmacists Association, 2015). As an example, in Saskatchewan, pharmacists are publically reimbursed $18 CAN when the minor ailments assessment results in a prescription (Lynas, 2013). **Table 4** lists the schedule of drugs appropriate for prescription by pharmacists for specified minor ailment or self-care conditions in Saskatchewan. Despite the positive experiences reported by both patients and pharmacists that

Table 3 Criteria and points of contact for the publicly funded Ontario pharmacist smoking cessation program

Step	*Activity*	*Details*	*Interaction options*	*Recommended time*	*Reimbursement*
1	(Session #1) 1. Readiness assessment 2. Patient enrolment/consent	Patient completes questionnaire to identify desire to quit smoking Patient provides consent to program and sets an expected quit date with the Pharmacist	Any Pharmacist In person	5–10 min	$0.00 Unlimited provision
2	(Session #2) 1. First consultation 2. My quit plan	In-depth Pharmacist consultation to discuss the patient's smoking and medication history, health risks, triggers, quit date, and smoking cessation plan	Certified Pharmacist In person preferred Telephone (if agreeable to patient)	20 min	$40.00 Max: Once per 365 days
3	(Session #3) Primary follow-up	Pharmacist provides ongoing support to the patient by addressing concerns and issues, management of withdrawal symptoms, etc.	Certified Pharmacist In person Telephone E-mail	10 min	$15.00 Max: Three per 365 days
4	(Session #4) Primary follow-up				
5	(Session #5) Primary follow-up				
6	(Session #6) Secondary follow-up	Pharmacist provides ongoing support to the patient by addressing concerns and issues, management of withdrawal symptoms, etc.	Certified Pharmacist In person Telephone E-mail	3–5 min	$10.00 Max: Four per 365 days
7	(Session #7) Secondary follow-up				
8	(Session #8) Secondary follow-up				
9	(Session #9) Secondary follow-up				
10	Program evaluation	Pharmacist documents final patient outcomes	Any Pharmacist	2 min	$0.00 Required: Once per 365 days

Table 4 Schedule I drugs appropriate for prescription by pharmacists for specified minor ailment or self-care conditions

Condition	*Medications*
Migraines and headaches	Ibuprofen all strengths Naproxen all strengths Diclofenac Almotriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan Eletriptan (frovatriptan
Cold sore	Acyclovir cr/oint/oral Famciclovir Valacyclovir
Mouth ulceration (mild)	Triamcinolone dental paste
Oral thrush	Nystatin drops
Acne (mild–mod.)	Benzoyl peroxide (BP) up to 10% Clindamycin phosphate Clindamycin/BP Clindamycin/ tretinoin Erythromycin/BP Erythromycin/ethyl alcohol/avobenzone/octinoxate Erythromycin/tretinoin Adapalene cr 0.1%, 0.3%; gel 0.1% Adapalene 0.1%/BP 2.5% Tazarotene 0.05%, 0.1% cr or gel Tretinoin cr or gel all strengths Tretinoin/avobenzone/octinoxate cr all strengths

(*Continued*)

Table 4 Schedule I drugs appropriate for prescription by pharmacists for specified minor ailment or self-care conditions (*cont.*)

Condition	*Medications*
Atopic dermatitis (mild–moderate)	Hydrocortisone cream 1%, 2.5%
	Desonide 0.05%
	Betamethasone valerate
	Clobetasal butyrate
	Diflucortolone valerate
	Hydrocortisone valerate
	Mometasone furoate
	Triamcinolone acetate
Diaper rash	Clotrimazole hydrocortisone 1% cr/oint
Insect bites	Hydrocortisone 1% cr/oint
Skin infections	Fucidic acid cr/oint
(bacterial)	Mupirocin cr/oint
Tinea infections (athlete's foot, jock itch, ringworm)	Terbinafine 1% cr
	Ketaconazole 2% cr
Dyspepsia/GERD	Cimetidine 300, 400, 600 mg
	Famotidine 40 mg
	Nizatadine 150, 300 mg
	Ranitidine 150, 300 mg
	Esomeprazole 20, 40 mg
	Lansoprazole 15, 30 mg
	Omeprazole 10, 20 mg
	Pantoprazole 40 mg
	Rabeprazole 10, 20 mg
Hemorrhoids	HC/zinc sulfate
	HC/zinc sulfate, pramoxine
Dysmenorrhea	Celecoxib
	Diclofenac
	Ketoprofen
	Mefenamic acid
	Naproxen sodium
Pain	Diclofenac
	Diclofenac/misoprostol
	Naproxen
	Celecoxib
	Meloxicam
Allergic rhinitis	Levocabastine
	Beclomethasone
	Mometasone furoate
	Fluticasone proprionate

Source: Jensen, K., Feb 2018. Guidelines for Prescribing for Minor Ailments and Patient Self-Care. https://medsask.usask.ca/professional/guidelines/.

have participated in minor ailment programs, some stakeholders have raised concerns with respect to pharmacist training, diagnosing as a scope of practice, and inherent conflicts of interest (Lee and McCarthy, 2015).

Immunization

The role of pharmacists in immunization and vaccination varies across the world; in some countries, pharmacists are primarily involved in ensuring the safe supply and dispensing of vaccines, as well as advocating for immunization, while in other countries, they are empowered to play a more active role, as they are legally authorized provide vaccination. It is estimated that ten million lives per year could be saved by increasing access to medicines and vaccinations. Community pharmacists are therefore in a strong position to provide a major contribution to public health due to their accessibility, distribution, and available expertise. Pharmacists are also highly trusted health-care professionals and are ideally positioned to improve patient communication with respect to vaccine myths and hesitancy.

Influenza

Influenza (or the flu) is a common infectious respiratory disease that affects millions of people globally each year. In Canada, for example, there are up to 20,000 flu-related hospitalizations and 4000 deaths annually. Individuals with risk factors such as diabetes, cardiovascular disease, and respiratory conditions are even more susceptible to hospitalizations and complications. Influenza epidemics of variable extent and severity occur almost every winter. They impose an enormous burden in terms of morbidity, mortality, economic, and social costs.

Immunization remains the most cost-effective method in reducing influenza and influenza-related complications. The National Advisory Committee on Immunization recommends influenza vaccination for all Canadians aged 6 months and older. Despite this recommendation and the universal availability of the vaccine, Statistics Canada reports that only 28.9% of Canadians were vaccinated against the flu in 2012 (Papastergiou et al., 2014).

Pharmacists are highly trained and accessible health-care providers who are ideally positioned to provide flu vaccinations to the public. Their services are widely available and they typically do not require an appointment for consultation. Despite the benefits of immunization, scepticism about vaccination and general inconvenience continue to deter people from getting vaccinated. Pharmacists are a well-respected educational resource for patients with the potential to positively influence immunization rates. They are able to advocate for the importance of immunization, dispel common misconceptions, and screen for high-risk patients. As early as 1996, the American Pharmacists Association (APhA) had begun its training program for pharmacist-administered vaccinations. As a result, US pharmacists have increasingly become recognized as the vaccine experts. In Canada, this expansion in scope has also been received very positively. As of 2016, all pharmacists are authorized to administer influenza vaccinations, and all provinces have publicly funded compensation programs except for Quebec (Canadian Pharmacists Association, 2016). By the end of the 2012–13 flu season, more than 250,000 Ontarians were vaccinated by pharmacists, far exceeding the provincial government's initial target of 100,000. During the 2016–17 flu season, pharmacists provided over 2 million vaccinations nationally.

Overall feedback from patients regarding pharmacist-directed vaccination has been overwhelmingly positive. A 2014 study found that 92% of patients indicated they were very satisfied with the pharmacist's injection technique, and 98% of patients would recommend a friend or family to receive the same service (Papastergiou et al., 2014). Additionally, 28% of the respondents indicated that they would not have received a flu shot if the pharmacy program was not available, and 8% of the survey respondents received their first flu shot by a pharmacist (Papastergiou et al., 2014).

The impact of pharmacists on overall vaccination rates has also been positive. According to data from a US study in 1997, pharmacy-based influenza programs yielded a higher state level vaccination rate compared to states without programs in place in adults aged ≥65 years; 68.4% versus 64.7%, respectively ($P < 0.01$) (Steyer et al., 2004). A 2016 Canadian study produced similar results and showed a higher proportion of residents received flu shot in provinces where pharmacists provide them (30% vs. 28%).

In 2008, Posser and colleagues compared costs associated with administering influenza vaccinations in nontraditional settings and concluded that savings were significant when provided in pharmacies over traditional administration sites. In addition, Houle et al. reviewed 34 international pharmacy-based vaccination programs and their funding models. Remuneration ranged from $4.14 to $21.21 CAN (currencies converted in 2013), with an average of $13.12 CAN (SD $4.63) per injection. The availability of public reimbursement as well as the fee varied greatly between jurisdictions.

Vaccination Beyond Influenza

Pharmacists can play a major role in improving overall public health by becoming involved in immunization beyond influenza. The accessibility and distribution of community pharmacies make them a first point of contact with patients, providing an excellent opportunity to expand and increase access to immunization services. Convenient operating hours can be very attractive to busy patients and is particularly important in rural, isolated, and medically underserved areas, where access to vaccination can be challenging.

Unfortunately, vaccination policies vary dramatically across the globe, and the legal authority to immunize can differ significantly between jurisdictional regions, even within the same country.

In 2016, the International Pharmaceutical Federation (FIP) published a global report on immunization. The aim of the survey was to better understand the role of pharmacists in immunization across the world and the impact of these activities. FIP surveyed 137 member organizations and received responses from 45 countries and territories (33% response rate; 33% of FIP Member Organisations; 23% of WHO Member States). From all respondents, 71% (32 countries and territories) reported some level of engagement in support and advocacy activities connected with immunization service provision. The administration of vaccines was less common, with 29% (13) of respondents stating that pharmacist-administration was possible. Interestingly, 44% (20) stated that using pharmacies (as accessible health-care premises), including both pharmacists and other health-care professionals administering vaccines, was possible in their countries. There was also a clear association between advocacy and support for vaccination activities and being able to legally provide administration in pharmacy premises (by either pharmacists or other health-care professionals).

The integration of community pharmacies and pharmacists in national vaccination policies tends to develop as a gradual process over time. Several countries authorize vaccination in pharmacies and/or by pharmacists (e.g., in Argentina, Australia, Philippines, South Africa, UK, and USA); this practice has been initiated, in the majority of the cases, with pharmacy-based vaccinations against influenza and then expanded to include other vaccines from the immunization schedule. In most cases, it is associated with specific requirements such as pharmacist training, management of vaccination records, and specifications on premises, equipment, and waste management.

Pharmacist-Directed Travel Clinics

Pharmacy clinics that offer travel vaccinations have emerged as a recent but growing trend. These clinics offer yet another opportunity to expand pharmacist practice and generate an alternative revenue stream for pharmacies. Like other vaccination policies, state and provincial scopes of practice regarding travel vaccination vary greatly depending on the jurisdiction.

Travel vaccination services are highly personalized, and each visit requires an individual pharmacist consultation. Generally, these sessions involve (1) assessment of location of travel and patient's health status, (2) vaccine and other recommendations, and (3) physical administration of vaccine. That being said, depending on state and provincial laws, it is uncommon for all of the above steps to be covered under the pharmacist scope (Stewart et al., 2016). This has provided some challenges in the implementation of these programs. First, patient assessment requires health record access including access to immunization history if the patient cannot reliably provide the health information. This is limited in many settings. Second, vaccine prescribing and administration authority is often molecule dependent; pharmacist's may be able to provide some vaccinations without a prescription, but others will require a prescription from an authorized prescriber. These varying regulations can be problematic from the standpoint of being able to offer a "one-stop shopping" experience. For example, in Ontario, pharmacists have been authorized to administer vaccines for 13 preventable diseases including most travel diseases. Unfortunately, authority to prescribe these vaccines was not universal. In order to address these challenges, many pharmacies have adopted a collaborative approach with local physicians when offering travel consultation services. Standing order programs in the United States and medical delegation in Canada have been tried with some success.

Pharmacist confidence/competency in the area of travel has been identified as a possible area of education opportunity. Bascom and colleagues investigated community pharmacist knowledge on traveler's health (2015). Only 21% of interviewed pharmacists felt comfortable to effectively educate patients on travel-related topics (Bascom et al., 2015). Comfort levels increased to 66% with access to resources (Bascom et al., 2015). Bascom and colleagues suggested that further specialized education may be required for pharmacists to fully engage this opportunity (2015). The International Society of Travel Medicine offers a Certificate in Travel Health (CTH) that assists HCPs to build competency in this area. It is recommended that pharmacists considering offering a travel consultation service pursue this additional education.

In 2017, Houle et al. published a prospective cohort study among patients-seeking care from a pharmacist-managed travel health clinic in Alberta to identify (1) specific needs of travelers (e.g., demographics, health status, destination(s), itinerary), (2) acceptance of recommended vaccines, prescribed drugs, and nonprescription drugs, and (3) health status during travel and satisfaction with care and advice provided. In total, 103 participants were enrolled in the study. Pharmacists recommended 270 vaccinations, and acceptance was reported at 80%. Rabies was the most commonly declined vaccine (high cost, low perceived risk of exposure). About 14 participants reported a health concern during travel (traveler's diarrhea ($n = 8$), respiratory illness ($n = 4$), vomiting ($n = 2$), and allergic rhinitis, strep throat, altitude sickness, and eye infection ($n = 1$ for each). Five participants consulted a physician while traveling, and 2 consulted a physician upon return. Most patients visiting the travel clinic have some complicating factors affecting clinical decisions. While this may not be representative of all travelers, highlights the benefits of completing training in travel medicine to ensure optimal care. In the end, the authors concluded high patient satisfaction and adherence to vaccine recommendations in the pharmacist-directed clinics.

Point-of-Care Testing

Point-of-Care Testing (POCT) is defined as diagnostic testing performed outside the clinical laboratory in close proximity to where the patient is receiving care. POCT is typically performed by nonlaboratory personnel, and the results are used for clinical decision making. In recent years, advances in POCT testing have dramatically reduced the cost of the technology and made it available to a larger number of clinical care settings. Pharmacists, as the most accessible health-care provider, are ideally suited to offer POCT services. As such, many community pharmacy sites have embraced the concept and implemented testing into their daily practice. Most point-of-care tests do not require more than a finger prick and a couple of drops of blood or a throat or nasal swab; results are typically available within a couple of minutes and are easy to interpret. The goal of pharmacist-directed POCT is to improve chronic disease state monitoring, enhance patient education, and optimize medication adherence and patient outcomes. These tests allow pharmacists to have rapid access to laboratory quality results at the time of the patient interaction and are particularly useful to patients requiring more frequent monitoring as well as those living in remote areas without easily accessible laboratory services. Novel point-of-care testing technologies are available for both chronic disease monitoring and acute care diagnosis. The most common point-of-care tests conducted in community pharmacies include: HbA1C for diabetic patients, blood pressure monitoring for hypertensive patients, lipid screening and risk assessment for cardiovascular patients, and INR testing for patients requiring anticoagulation. Commonly utilized acute care tests include Influenza A/B screening and Group A Strep testing.

A1C Testing

Diabetes continues to affect an increasing number of Canadians each year and threatens the sustainability of our health-care system. There are currently 2.7 million Canadians (7.6%) living with diabetes. The annual cost of the disease to our economy is $11.7 billion and is projected to reach $16 billion annually by 2020. Many of these patients will develop diabetes-related complications including heart attack, stroke, kidney failure, blindness, limb amputation, and depression. These complications account for greater than 80% of overall diabetes costs. Besides its financial burden, diabetes can dramatically impact the patient's quality of life and can be a great stressor on family members and caregivers. One-third of those affected with type 2 diabetes are unaware that they have the disease (Papastergiou et al., 2012). More than half of Canadians with type-2 diabetes fail to achieve their A1c target or have their A1c regularly tested.

Historically, the testing of A1C required a visit to the physician and was limited to a laboratory blood test. With the introduction of point-of-care devices, patients can be tested by their community pharmacist without a laboratory requisition and A1C results can

be made available within 5 min. Meters have demonstrated an accuracy of 99% in three independent evaluation studies (Holmes et al., 2008).

A Canadian study described the impact of A1C screening by pharmacists. A total of 1111 patients (871 of which were included in the analysis) were screened in over 1200 pharmacies across Canada. The study found that the majority of patients (59.1%) did not have their blood glucose levels optimally controlled, 43.3% were hyperglycemic, and 15.8% had marked hyperglycemia. In fact, 59.1% had A1C levels above the target of 7%. Patients using insulin only (70%) or a combination of insulin and oral therapy (72.3%) were much more likely to be above A1c targets than those using oral therapy alone (54.3%).

In terms of clinical interventions, 1711 were conducted by pharmacists. Overall, there was an average of two interventions per person. The three most common interventions were lifestyle counseling (29% of all interventions), referral of patients to their doctor for follow-up (16.5%), and discussion of the A1C result with the pharmacist (13.7%). The prevalence of specific types of interventions showed an apparent shift from predominantly pharmacist-directed interventions in patients with better glycemic control toward an increased prevalence of physician-directed interventions in patients with poorer glycemic control. Pharmacists performed an average of 2.0 interventions, ranging from 1.4 in patients with optimal glycemic control to 2.8 in patients with marked hyperglycemia. Better technology and an expanded scope of practice have opened the door for pharmacists to play a far greater role in diabetes management support—and that door can open wide, based on the data from community pharmacies from across Canada.

Blood Pressure Monitoring and Management

It is estimated that 4.1 million Canadians are affected by hypertension. Hypertension is a chronic disease that requires long-term medication management and monitoring. If inadequately controlled, hypertension increases a patient's risk of cardiovascular events (such as stroke, myocardial infarction, angina, and heart failure) and mortality. Recent evidence has suggested that hypertension managed in collaboration with the community pharmacist can result in improved patient outcomes. Pharmacists can provide education to patients, help to prompt and monitor patients' blood pressure, and encourage patients to adhere to their medication regimen.

A 2014 study investigated the impact of community pharmacist managed hypertension on both patient outcomes and potential medication cost savings. Twenty-seven pharmacies across Ontario participated. In total, 118 patients with hypertension were randomly assigned to receive standard care or comprehensive care. In the comprehensive care group, pharmacists were trained to provide three components of patient-centered services: review and optimization of medications, education on lifestyle modification, and also promotion of adherence. After the 6-month study period, the intervention group had a 13.5 mmHg systolic blood pressure reduction while the control group had a 5 mmHg reduction. In addition, there was a 15% increase in patients' adherence to antihypertensive therapy, 4.6% decrease in patients' body mass index (BMI), and 31.2% decrease in average cost of antihypertensive therapy. These results provide the best evidence to date of the positive impact that pharmacist-directed POC blood pressure management can have on patient outcomes and cost savings. The current reimbursement offered to community pharmacists as part of the Greenshield Cardiovascular Health Coaching Program was a consequence of this study.

Lipid Screening and Cardiovascular Risk Assessment

Similar to hypertension, hypercholesterolemia is a condition that requires long-term medication management. With elevation of lipid levels, patients are at an increased risk for cardiovascular events and mortality. Hypercholesterolemia is also a common comorbid condition in patients with diabetes, hypertension, and other cardiovascular conditions. As frontline health-care providers, pharmacists are ideally positioned to calculate cardiovascular risk and empower patients to make lifestyle changes and improve adherence to their medication.

There are a number of POC cholesterol devices available for use by pharmacists. With a sample of blood, these devices are able to generate lipid profiles. Examples include CardioChek, Cholestech LDX, and Accu-chek Instant Plus. These devices are all validated against Abell–Kendall venous reference, a recommended cholesterol standard by the National Cholesterol Education Program (Haggerty and Tran, 2016).

Pilot studies that have shown the value of lipid screening and cardiovascular risk assessment programs. Most of these programs provide patients with a Framingham Risk Score (FRS). Interventions such as drug therapy changes and lifestyle modifications are made as required. Follow-up screening is also typically offered to those patients identified as moderate or high risk. Anecdotal results from pilot studies have showed a trend toward increased mean HDL and decreased mean LDL, total cholesterol (TC), TC/HDL ratio, systolic blood pressure, and 10-year CVD risk.

Chronic Kidney Disease Screening

Chronic kidney disease (CKD) is defined by reduced glomerular filtration rate of <60 mL/min or presence of kidney damage markers for longer than 3 months. CKD is a common comorbidity of patients with preexisting diabetes or cardiovascular diseases and is a progressive condition that may ultimately require dialysis for end-stage management. Although current therapies may help to slow and prevent rate of progression of CKD, CKD patients are still at elevated risk of cardiovascular events and death. With the prevalence rate of 10%, more than 2 million Canadian adults are affected by CKD. Due to the asymptomatic nature of early-stage CKD, it can be expected that CKD is underdiagnosed and undertreated. With early diagnosis and intervention, CKD progression can be slowed and prevented, reducing the need of dialysis, which requires intensive health-care services and resources. Early intervention can also help to improve patients' quality of life and reduce patients' cardiovascular and mortality

risks. It has been hypothesized that community pharmacists armed with novel POC technologies can play an active role in the early detection of CKD.

A recent study investigated the implementation of the CKD clinical pathway online tool in community pharmacies to screen targeted patients for CKD. Since patients with diabetes or cardiovascular conditions require extensive medication management through pharmacy services, community pharmacies are appropriate locations to explore implementation of targeted screening tools. Across 55 community pharmacies in Alberta, pharmacists identified 720 potential patients for targeted screening based on medications, including oral hypoglycemic, antihypertensive, lipid-lowering, antiplatelet, and anticoagulant agents. Of the 720 patients, 281 (39%) patients were found to have CKD, where 113 (40%) patients were previously not diagnosed with CKD. These finding are among the first to demonstrate the potential impact that pharmacists can have on patient outcomes using POC screening technologies or access to lab values.

Atrial Fibrillation Screening

Undiagnosed arrhythmias such as atrial fibrillation (AF) and drug-induced QT prolongation can lead to increased morbidity and mortality. However, despite the potential of catastrophic consequences, these conditions are asymptomatic, and patients' conditions are often undetected in routine physician visits.

Atrial fibrillation is the most common cardiac rhythm disturbances with an estimated prevalence of 350,000 Canadians. In addition, the prevalence of AF increases substantially with advancing age, from 0.5% at age 40 to 5% at age 50 and up to 15% at age 80. AF leads to electrical disturbances in the atrium introducing a loss of heart rate control, diminished atria contraction, and propensity for thrombogenesis. Combined, the pathogenesis of AF can cause ischemic stroke and systemic thromboembolism leading to impaired quality of life and frequent prolonged hospitalizations. An individual with AF has an increased risk of 3–5 times of stroke compared to individuals without AF. Consequently, AF is a large economic burden in the health-care system with an estimated annual spending of $815 million from emergency visits, hospitalizations, and same day surgical procedures, which can be largely preventable with early screening and proper treatment.

The high traffic of community pharmacies makes them the ideal location to screen for patients at high-risk AF. A number of devices are currently available for use by pharmacists. AliveCor is a smartphone electrocardiogram (iECG) device with an algorithm that detects AF from the two leads that connect to the back of the phone. The device was validated to have a 98% sensitivity and 97% specificity when used in the community pharmacy setting (Lowres et al., 2015). The HeartCheck PEN handheld ECG is a device that sends the reading to a center where it is read by experts and a report is returned to the pharmacy.

Screening high-risk patients with a handheld device at a community pharmacy can potentially result in improved detection, implementation of treatments, prevention of stroke, and improved health outcomes of patients. The International Pharmacist for Anticoagulation Care Taskforce (iPACT) created a partnership with the Atrial Fibrillation Association (AF Assoc) to promote the involvement of pharmacists actively participating in awareness campaigns. During the global 2017 Arrhythmia Alliance World Heart Rhythm Week, pharmacists from ten countries embraced this initiative and contributed primarily to raise the awareness of AF. In addition, active participants used pulse taking as recommended by the latest ESC guidelines to identify and refer people suspected of having AF. Whenever possible, pulse taking was confirmed using mobile technology. The use of mobile technology depended largely on the availability of mobile ECG technologies in that country and financial considerations.

Strep Testing

Acute bacterial pharyngitis, also referred to as "strep throat," is most commonly caused by *Streptococcus pyogenes*, or Group A streptococcus (GAS)—beta hemolytic, gram-positive cocci. GAS is responsible for approximately 2 million visits to family physicians annually with additional visits to walk-in clinics and the ER. Signs and symptoms of acute pharyngitis include sore throat, pain upon swallowing, tonsillar exudate, and tender or swollen anterior cervical lymph nodes, which may be accompanied by fever, nausea, and/or vomiting. Nonetheless, these symptoms are nonspecific and can be caused by a variety of bacteria and viruses. In fact, only 5%–15% of cases of sore throat in adults and 20%–30% of cases in children are caused by GAS. This poses a challenge for the treatment of acute pharyngitis and, if bacterial, for appropriate antibiotic selection. Inappropriate antibiotic use contributes to increasing antibiotic resistance as only 10% of sore throats require antibiotics, while 60% of patients receive antibiotic treatment.

The Infectious Diseases Society of America (IDSA) recommends swabbing the throat and testing for GAS via rapid antigen detection test (RADT) and/or throat culture to identify the causative agent. Throat culture on a sheep blood agar is the gold standard for the diagnosis of GAS. While the gold standard is 90%–95% sensitive for detecting GAS, it requires 18–24 h of incubation time, which can significantly delay the time to treatment. RADTs can obtain results within 15 min. One example of a RADT, the BD Veritor system, is a rapid chromatographic immunoassay for the direct and qualitative detection of the GAS antigen. It has 95.4% sensitivity (95% CI 90.3%, 97.9%) and 95.7% specificity (95% CI 93.7%, 97.1%), and results are available within 5 min.

As the most accessible health-care professional, pharmacists are well-positioned to provide RADT point-of-care testing (POCT) for GAS. Adoption of RADT by community pharmacists can lead to appropriate selection of treatment, health economic benefits via antimicrobial stewardship, and reduction in use of health-care resources. There have been some studies in both the United States and the United Kingdom that have evaluated POCT for GAS in the community pharmacy setting. These studies have been able to demonstrate feasibility of the service as well value for patient care.

In a recent Canadian study, a retrospective analysis of aggregate billing data was conducted to evaluate the effectiveness of a community pharmacist-directed strep testing program to 7050 patients across 204 Shoppers Drug Mart pharmacies in British

Columbia, Alberta, and Nova Scotia. Pharmacists trained in sample collection offered the screening to patients with symptoms suggestive of strep throat. The average age of patients presenting symptoms was 27.3 years with children (5–14) representing 30.7% of those screened. Throat swabs were collected and analyzed using the BD Veritor system for rapid detection of GAS. About 25.5% of patients tested positive for GAS. Same-day initiation of antibiotic therapy for strep-positive patients occurred in 68.7% of cases but varied by province. In Alberta, where pharmacists have advanced prescribing authority, same day initiation was 73.8% compared to a rate of 40.5% ($P < 0.0001$) in the other jurisdictions. These results highlight both the public readiness to access point-of-care services in community pharmacies and the ability of pharmacists to conveniently expedite management of patients with GAS.

Influenza Screening

Influenza (or the "flu") is a common infectious respiratory disease that affects millions of patients each year. During the 2013–14 influenza season, 5457 hospitalizations and 344 influenza-associated deaths were reported in Canada. Individuals with risk factors such as diabetes, cardiovascular disease, and respiratory conditions are particularly susceptible to hospitalizations and complications. Influenza epidemics of variable extent and severity occur almost every winter. They impose an enormous burden in terms of morbidity, mortality, economic and social costs. Early detection and management of influenza infections are key in controlling the extent and severity of annual influenza epidemics.

Influenza viruses are transmitted via respiratory droplets or from contact transmission of contaminated surfaces. Symptoms of infection typically include fever, nonproductive cough, chills, headache, and myalgia. Untreated patients with influenza exhibit peak viral shedding on the first day of symptom onset, with a steady decline in viral load over the following 7 days. This period of viral shedding has been shown to be prolonged in immunocompromized individuals. Successful treatment with antiviral agents has been demonstrated to significantly decrease both the period of viral shedding and viral load when compared to placebo. Ideally, antiviral treatment for influenza should be initiated as early as possible and is most likely to provide benefit when started within the 48 h of symptom onset. As such, early identification of influenza infection is instrumental in decreasing the duration of symptoms of illness, reducing the risk of influenza-related complications in high-risk individuals, and decreasing the risk of contact transmission as a result of decreased viral shedding.

The BD Veritor System for the detection of influenza is a rapid, point-of-care test used to detect influenza A and B viral antigens from the nasal and nasopharyngeal passages of symptomatic patients. The system uses a chromatographic immunoassay to differentiate between influenza A and B viral antigens. When the respiratory specimen is added to the test device, influenza A and influenza B antigens bind to the anti-influenza antibodies. The anti-influenza antibodies are conjugated to detector particles. The antigen–conjugate complex then migrates across the test strip to the reaction area where the membrane captures the antibody–-conjugate complex. A positive test for influenza A and or influenza B is determined by the BD Veritor System Reader when the antigen–conjugate complex is deposited on the corresponding position. The sensitivity of the BD Veritor System is 89.6%, and the specificity is 98.8% in comparison to real-time RT-PCR of nasal swabs.

Historically, patients that visit a pharmacy with fever, cough, and malaise are given recommendations for over-the-counter products and offered nonpharmacological supportive care. Often, patients are referred to a physician for further investigation. Additionally, many patients indiscriminately visit physicians' offices seeking antibiotics as a result of upper respiratory tract infections. These visits tie up physicians' time, result in inappropriate antibiotic use, and utilize public resources unnecessarily. For those influenza-positive patients that are not referred, delayed antiviral therapy can lead to prolonged recovery, transmission of disease, and/or disease complications. The availability of this new point-of-care technology will provide pharmacists with the ability to more effectively screen and triage patients and, ultimately, expedite access to care for those influenza-positive individuals.

During the 2014/15 flu season, a group of frontline community pharmacists investigated the impact of community pharmacy-based influenza screening. They recruited 59 patients, of whom 44% had at least one risk factor for influenza complications. Thirty-four percent tested positive for influenza, and 40 percent of these patients were prescribed antiviral therapy. All patients who tested negative had their symptoms managed with supportive care measures. It was concluded that community pharmacy-based influenza screening may facilitate prompt access to pharmacologic treatment for patients with influenza as well as decrease the burden on the health-care system. Timely physician communication remains a barrier for access to treatment, suggesting a potential key role for advanced pharmacist prescribing.

Helicobacter pylori Testing

Helicobacter pylori is a gram negative bacterium found on the surface of the gastric epithelium. The World Health Organization (WHO) has identified *H. pylori* as a major risk factor of gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric lymphomas. Almost 25% of Canadians with uninvestigated dyspepsia have evidence of an active *H. pylori* infection.

Pharmacists, as the most accessible health-care practitioners, are ideally positioned to improve access to *H. pylori* screening and increase the awareness of the potential consequences of untreated disease. The development of point-of-care screening devices, in combination with the expanding scope of pharmacy practice, has allowed pharmacists to become more actively involved in the screening and management of various chronic diseases. Specific to *H. pylori* infection, a few studies have demonstrated that early screening and treatment of *H. pylori* may be beneficial in both reducing health-care costs and decreasing morbidity and mortality. Furthermore, screening in the community setting has been shown to reduce resource use and may be linked to health gain in quality adjusted life years and cost savings pertaining to gastric cancers.

Recently, three pharmacies in Toronto, Ontario, offered *H. pylori* screening as part of their clinical programs. Pharmacists facilitated subject enrolment among patients who they believed would benefit from screening and met inclusion criteria. Decision to screen was based on the Canadian Helicobacter Study Group Consensus (CHSG). Patients were screened using the *Rapid Response H. pylori* test. In total, 65 patients were recruited with a mean age of 46.9 years. Patients were ethnically diverse with a significant proportion (61.5%) identified as being born outside of North America including Asia 26.1%, Africa 9.2%, Middle East 7.7%, Europe 12.3%, and South and Central America 6.2%. Overall, the detection rate of *H. pylori* infection was 21.5%. North Americans had the lowest incidence of an undiagnosed *H. pylori* infection 8%. Europeans 25%, Middle Eastern 20%, and Asians 23.5% had a moderate incidence followed by the highest prevalence for those of African 66.7% descent. These results highlight the readiness of community pharmacists to adopt *H. pylori* screening into practice and to leverage this novel technology to positively identify and treat undiagnosed *H. pylori* infection.

Pharmacogenomics

The field of pharmacogenomics (PGx) was established in the 1950s, but physicians and pharmacists have long been aware of the subtle differences in drug response between patients. Interpatient variability in drug response can result in lack of efficacy, intolerance, or even serious adverse reactions. It is routine for physicians and pharmacists to consider factors such as age, body mass, renal function, and drug interactions in an attempt to avoid unintentional drug consequences. Nonetheless, genetic factors alone can account for anywhere between 20% and 95% of the variability in drug response, yet these often go unrecognized. In recent years, clinical PGx research has made significant progress in defining which genetic variations are important for influencing interpatient variability in drug response. Historically, there has been no easy way for clinicians to screen or assess patients for these differences. It was not until very recently that the technology for PGx testing has been made available to practitioners in frontline clinical settings. This availability, in combination with the pharmacist's expertise in pharmacology and kinetics, make them ideally suited to champion implementation of this novel technology in order to optimize therapy.

In a survey conducted in the United States, 101 pharmacists were asked to assess their interest and readiness in providing personalized medicine care to patients. A total of 75% of the pharmacists expressed interest in providing such services to their patients, but 50% of the interested pharmacists felt uncomfortable making recommendations to physicians or counseling patients without further training in this field. As this important technology continues to evolve, comprehensive training programs must be developed to prepare pharmacists to provide this service at the point of care.

Recently, two community pharmacies in Toronto, Ontario, offered pharmacogenomic screening as part of their professional services program. Pharmacists facilitated voluntary subject enrolment among 100 patients who they believed would benefit from screening. Pharmacists cited the most common reasons for testing as ineffective therapy (44.6%), to address an adverse reaction (35.5%), and to guide initiation of therapy (11.8%). Patients were 57.4 years of age on average and taking a mean of 5.6 chronic medications. Eligible patients received a simple buccal swab followed by DNA analysis using PillCheck; a proprietary genotyping assay that translates genomic data and generates a personalized, evidence-based, report that provides insight into patients' inherited drug metabolic profile. Upon receiving the report, pharmacists invited patients back to the clinic for interpretation of the results. An average of 1.3 clinically significant drug therapy problems were identified per patient. Recommendations for medication optimization were then forwarded to the primary care physician, which included change in therapy (57.1%), dose adjustment (14.3%), discontinuation of a drug (7.1%), and increased monitoring (19.6%).

Generally, physician feedback was positive but did reveal an opportunity for a broader understanding of the technology. The results of this study highlight the readiness of community pharmacists to adopt pharmacogenomic testing into practice and their ability to leverage the results to positively impact medication management.

Conclusion

The evidence supporting the value of pharmacist-directed point-of-care screening continues to mount. That being said, implementation of these programs is not without its challenges. Pharmacists engaged in these activities have reported difficulties balancing time and resources, a lack of support from stakeholders, and concerns surrounding pharmacist training and confidence. As utilization of these technologies becomes more common, models will be developed to help overcome these barriers.

In the end, point-of-care screening initiatives provide an effective mechanism for improving patient education, enhancing disease management, and increasing pharmacist––physician communication. As we evolve our practice, the accessibility of the community pharmacist places them in a unique position to actively screen and monitor patients with both chronic and acute disease states. The wave of technology and innovation will arm pharmacists with the tools required to help meet these health-care needs.

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Hospital Pharmacy Practice: A Case Study from Canada

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Mission

Hospital pharmacy professionals—pharmacists and pharmacy technicians—strive to optimize the safety, the effectiveness, and the appropriateness of drug therapy through patient-centered care in collaboration with patients and their health-care teams. Pharmacists practicing in the hospital setting have therefore much in common with their colleagues from the community setting. Their role in medication management is to:

- Assess patients and their medication-related needs and identify actual or potential drug therapy problems;
- Formulate and implement care plans to prevent and/or resolve drug therapy problems;
- Recommend, adapt, or initiate drug therapy where appropriate;
- Monitor, evaluate, and document patients' response to therapy;
- Collaborate and communicate with other health-care providers, in partnership with patients.

What typically differentiates the responsibilities of hospital pharmacists from those of their community colleagues is the provision of complex medication services, such as preparation of centralized intravenous admixtures, parenteral nutrition, and chemotherapy. However, hospital pharmacists are also distinctive in their contributions to medication management in that they routinely collaborate in the care of the most acute and complex cases for a broad range of health conditions across a wide variety of patients (e.g., in critical care) or in a specific patient group (e.g., in pediatrics) or for a limited range of health conditions across a wider variety of patient groups (e.g., in oncology).

Hospital pharmacy practice "is designed so that patients receive the most clinically appropriate, safe, and cost-effective therapy, supported by the best available evidence, to optimally meet the patient's needs on the basis of indication and effectiveness" (Canadian Society of Hospital Pharmacists, 2016). With their precise knowledge about drug therapy, hospital pharmacists can contribute effectively to better patient care in collaborative health-care settings.

Hospital Pharmacy Setting

The hospital setting itself offers unique conditions for the practice of pharmacy:

- The focus of the pharmacist can be solely professional in nature if health services provided at a hospital are insured publicly; strictly speaking, there is then no business obligation apart from the expectation of fiscal responsibility.
- The environment can facilitate the optimal integration of the pharmacist within the interprofessional health-care team.
- Patient care information, including treatment indications and laboratory test results, can be readily available to pharmacists in health records.
- Drug procurement and distribution can be extensively delegated to pharmacy technicians.

Governance

Many professional pharmacy associations around the world advocate a pharmacist with advanced training in hospital pharmacy be accountable for managing the medication use system in hospitals (American Society of Health-System Pharmacists, 2016; Canadian Society of Hospital Pharmacists, 2005; Vermeulen et al., 2016). Furthermore, many pharmacy regulatory authorities stipulate that the head of hospital pharmacy services must be a pharmacist. Given the complexity of hospital medication use systems and the specialized nature of hospital pharmacy practice, pharmacists are deemed most knowledgeable and best trained to lead the safe, effective, and efficient management of the medication use system with the ultimate goal of optimizing patient outcomes.

Basel Statements on the Future of Hospital Pharmacy

In 2008, more than 340 hospital pharmacists from 98 nations met at the inaugural Global Conference on the Future of Hospital Pharmacy in Basel, Switzerland, part of the 68th World Congress of Pharmacy and Pharmaceutical Sciences of the International Pharmaceutical Federation (FIP) (2009). At the close of this momentous conference, the participants had developed and endorsed 75 consensus statements reflecting the profession's preferred vision of practice in the hospital setting, a global roadmap that should lead to improvements in patient outcomes around the world. Responses to an earlier survey determined the 6 themes, which covered all areas of the medicine use process in hospitals (procurement, influences on prescribing, preparation and delivery, administration, and monitoring of medication practice) and human resources and training. Medication safety was also an important consideration in developing the consensus statements.

In late 2013, a revision process of the Basel statements was undertaken and involved a global online survey (334 survey responses received from 62 countries), a review through an online forum (by individuals from 28 countries, representing all 6 of the World Health Organization regions), and a "World Café" workshop (80 participants from 20 countries) at the 2014 FIP Congress in Bangkok (Vermeulen et al., 2016). The process resulted in the final 65 revised Basel statements, arranged under an overarching category and the 6 original main themes, which reflect new aspirational goals for the future of hospital pharmacy.

Patient Safety

The World Health Organization (WHO) (2009) defines a patient safety incident as an event or circumstance within the health-care system that could have resulted, or did result, in unnecessary harm to a patient. Unsafe health care is an alarming global concern. A working paper published by the Organization for Economic Co-Operation and Development (Slawomirski et al., 2017) concludes that patient harm is the 14th leading cause of the global disease burden, that up to 17% of all hospitalizations are affected by one or more patient safety incidents, with 30%–70% potentially preventable, and that as many as one in ten patients are harmed during hospital care. Not only does unsafe health care inflict unnecessary morbidity and premature mortality on patients, but it imposes exorbitant financial and resource costs on the health-care system owing to additional diagnostic and therapeutic services, emergency

room visits, hospital admissions or readmissions, and extended length of inpatient stay. Patient safety incidents most commonly relate to surgical procedures, health care-associated infections, and medications.

Medication Safety

Unsafe medication use systems are a leading cause of preventable patient harm in health care across the world. Medication incidents can occur along the whole continuum of the medication use system: prescribing, transcribing, communicating, procuring, manipulating and compounding, labeling and packaging, dispensing, administering, monitoring, educating, and using. Compared to the primary and long-term care settings, available evidence suggests that medication incidents in hospitals tend to cause more serious patient harm, most likely because of the more acute clinical situations and the more complex medication regimens.

Given the magnitude of the problem, WHO (2017) has initiated its "Global Patient Safety Challenge: Medication Without Harm" with the goal of reducing the level of severe, preventable patient harm related to medications by 50% over 5 years, globally. The Challenge aims to achieve improvements at each stage of the medication use system and focuses firstly on three priority actions to improve medication safety: high-risk situations, polypharmacy, and transitions of care.

Influence of Hospital Pharmacists and Pharmacy Technicians on Medication Safety

Hospital pharmacists and pharmacy technicians play pivotal roles in the prevention and review of medication incidents and in the improvement of medication use systems. Together they strive toward patient safety by reducing the risk of unnecessary patient harm to an acceptable minimum throughout the medication use system, such as removing hazardous medications from hospital wards, educating patients about their medications, and reconciling medications at transitions of care. Furthermore, compelling evidence shows that the inclusion of pharmacists in interprofessional care teams results in lower mortality rates, fewer medication incidents, decreased health-care costs, shorter lengths of stay, and reduced emergency visits and hospital readmissions.

Antimicrobial Stewardship

Antimicrobial-resistant infections increasingly threaten public health and the economy around the globe. Patients infected with microorganisms resistant to antimicrobial drugs undergo additional diagnostic tests, receive less effective and more expensive therapies, experience longer illnesses, and face higher risks of complications and premature death compared to patients infected with nonresistant strains of the same microorganism. In response to this threat, WHO (2015) has launched its *Global Action Plan on Antimicrobial Resistance*.

Misuse and overuse of antimicrobial drugs in human and veterinary medicine and in food production are known to accelerate the occurrence of antimicrobial-resistant infections. In hospitals, studies have revealed that 30%–50% of prescribed antibiotics are unnecessary or inappropriate. Resistance is already prevalent among bacteria that commonly cause serious health care-associated infections. Antimicrobial misprescribing and overprescribing are therefore reckoned patient safety and medication safety concerns.

Improving, monitoring, and evaluating antimicrobial prescribing practices in hospitals by means of stewardship programs can help curb resistant infections, improve individual patient outcomes, and reduce health-care costs. Hospital pharmacists should resolutely promote the judicious use of antimicrobial drugs and, where a formal antimicrobial stewardship program exists, they should play a prominent role in the interprofessional leadership team.

Drug Procurement and Distribution

Patients and staff deserve to benefit from a drug distribution system that safely, reliably, and effectively procures, stores, prepares, and distributes high quality medicines, in a timely manner. It is the responsibility of the pharmacy department to develop and oversee such a system.

Safety is never to be assumed: it must be deliberately built into the system from the point of procurement, through to storage, preparation, distribution, and administration to the patient. People must be adequately trained to execute their responsibilities; procedures must be set to guide and direct personnel (PIC/S Secretariat, 2014). The physical environment should be designed and used to safely support the drug distribution activities performed therein (PIC/S Secretariat, 2014). The movement of all medications and critical supplies used in the drug distribution system should be traceable from the point of purchase to the point of use or disposal (Clark, 2012). And, a quality management system should be established to assess whether the drug distribution system is functioning as intended—to ensure access to essential medicines in a timely, safe, and effective manner—and continues to improve.

People

Collectively, pharmacists and pharmacy technicians possess the knowledge and understanding of which medicines are available, how to store and prepare them, as well as the clinical condition under which the medicines should be used. They have a leadership role in the hospital regarding decisions about how drugs are acquired, stored, and used within the organization. Other persons such as pharmacy assistants and clerical staff may also have a role in the drug distribution system. In the end, the decision to assign

responsibilities related to drug distribution to different cadres of personnel must consider the legislated scope of practice, who is best equipped to perform the task at hand, and the human resources available.

The design of the drug distribution system should also draw on the expertise of other persons, as needed. For example, accountants and information technology specialists should be consulted to assist in developing processes to ensure that the drug inventory is adequately controlled to prevent or detect theft or pilferage of inventory.

Procurement

All medicines used in the hospital should be purchased, stored, and distributed under the direction of the pharmacy department. Adequate segregation of critical duties should be maintained throughout purchasing, receiving, and inventory management to strengthen internal controls against theft and fraud.

The medicines purchased should be those that are required to meet the needs of the community of people served by the hospital: typically the decision to purchase a drug is directed by the hospital's formulary system. Resources should not be squandered by obtaining medicines that are of poor quality or are not needed by the hospital's patients, or holding unnecessarily high volumes or purchasing at frequencies that unnecessarily compromise the hospital's capital available for other purchases (Chalker, 2012; Dias, 2012; Layloff, 2012; Olson, 2012).

Medications should be purchased only from vendors who can assure that the medicines are of high quality and pedigree. Drugs that could be counterfeit or whose quality is suspicious or compromised can cause harm (Alliance for Safe Online Pharmacies (2018)) and should never be purchased for administration to patients. The pharmacist should understand how counterfeit drugs enter the country, how to avoid purchasing counterfeit drugs, and what suppliers are legitimate.

The quantities of medicines purchased should reflect the usage patterns in the hospital for at least the period required to procure the drugs without lowering the stock levels below the minimum safety stock level (Dias, 2012). In many hospitals, just-in-time inventory practices are used, which are supported by a reliable computerized inventory management system.

For safety reasons, purchasing multiple strengths and sizes of the same product should be avoided, because they can result in selection errors and could introduce sound-alike, look-alike errors. If it is not possible to avoid such purchases, extra care and attentions should be given to reduce the likelihood of a medication error with these products.

Ideally, drugs that are purchased by the hospital are shipped directly to the pharmacy. If the drugs must be first delivered to the hospital's receiving area, the receiving personnel should check the outer packaging for signs of damage and compare the number of packages received against the shipping order. Any discrepancies should be reported immediately to pharmacy for follow up. (The shipping packages are only opened in the pharmacy department.) The shipment should then to be delivered to pharmacy without delay. The pharmacy staff should carefully inspect the contents of the shipment. Any errors in the order (e.g., wrong drug, damaged goods, wrong quantities) should be followed up with the organization that shipped the order. The quantity and identity of all drugs that will be added to the pharmacy's stock should be recorded in the pharmacy's inventory system.

Throughout the purchasing system, adequate segregation of duties should be maintained to prevent having one person with sole control over purchasing, receiving, and inventory management.

Drug Shortages

Drug shortages can have serious consequences on patient care and the drug distribution system. They can occur for a variety of reasons such as discontinuation of product, unanticipated high demand for drug, disruption in supply of ingredients or packaging components, regulatory decisions, compromised quality of the drug product, or natural disasters (Multi-Stakeholder Steering Committee on Drug Shortages in Canada, 2017a). The hospital should have a contingency plan in the event of a drug shortage: such a plan typically assesses the nature, extent, anticipated duration of the shortage, identifies alternatives to cope with the shortage, and includes a communication plan to inform key stakeholders. Strategic steps are taken when establishing contracts to purchase drugs that could help mitigate the negative effects of drug shortages. Guidelines and toolkits are available to assist in developing these plans and strategies (Multi-Stakeholder Steering Committee on Drug Shortages in Canada, 2017b; Multi-Stakeholder Steering Committee on Drug Shortages in Canada, 2017c).

Dispensary and Storage Areas

Medicines should be stored in an area that encourages the segregation of certain products and the safe, secure accessibility of drugs, and under conditions that maintains the integrity of the medicine for the duration of its expected shelf life. The area is designed to prevent unauthorized access; to be climate-controlled, clean (and free of vermin or other pests), and well-lit; and to be organized and constructed of materials that can easily facilitate cleaning. The area also supports infection control and prevention practices and protects people and products from unnecessary exposure to hazardous substances.

The following list provides examples of safe medicine practices related to the storage of medicines, which should be used by everyone who handles or stores medicines:

- To avoid cross-contamination, food is not to be stored in the same area as medicines.
- High-alert medicines (Institute for Safe Medication Practices, 2018) are easily identified: they are segregated from other medicines, warning labels are affixed to the container, and forcing functions employed to prevent certain medication incidents from occurring.

- If sound-alike, look-alike medicines must be held in inventory, strategies should be employed to minimize the likelihood of a selection error or name confusion (e.g., they are not stored adjacent to each other) (WHO Collaborating Centre for Patient Safety Solutions, 2007).
- Medicines that are intended for external use only are stored in an area away from medicines that are for internal use.
- Drugs that have the potential for abuse should have controlled access, and not be stored with other drugs.
- Hazardous drugs require special handling and storage provisions. For example, they are not stored with other drugs. They are each assigned their own designated area that is adequately externally ventilated, and in a manner that promotes their safe handling (e.g., on shelves that have guards to prevent the container from falling) (Power and Coyne, 2018).
- The hospital has a safe medication handling system that ensures personnel are not directly exposed to medications through handling. The pharmacy department takes responsibility for identifying and labeling medications that have potential to cause effects to those who may exposed. Persons working with hazardous drugs don personal protective equipment and follow safe handling procedures to avoid exposure to the drug. The National Institute for Occupational Safety and Health (NIOSH) is an agency that conducts research on work-related safety and recommends strategies to reduce these exposures. NIOSH has a list of hazardous drugs, which can be used as a starting point for pharmacies and health-care environments (NIOSH, 2016).

Wardstock

Drugs that are used in urgent or emergency situations should be readily available on the care unit. The decision to store a medication as wardstock should take into account the safety profile of the drug, the degree of urgency to access the drug, and the cost of the drug. Work practices should be set to mitigate the risks of medication incidents commensurate with the level of risk exposure. Concentrated electrolytes (e.g., potassium chloride 2 mmol/mL) should not be stored as wardstock. The quantity of drug supplied as wardstock should be small enough to reduce wastage due to the passing of the expiry date, yet large enough to meet the needs of patients. Access to the wardstock storage area should facilitate timely access to the hospital personnel who need to prepare the drugs, yet be inaccessible to the general public or patients.

Automated Processes and Dispensing Devices

Automated drug preparation and distribution systems and processes should be considered and adopted based on, and evaluated against, principles of safety. Advances in drug distribution and preparation technologies are rapidly changing. The pharmacy department should consider adopting technologies that improve the responsible use of resources, reduce overall costs to the health system, and improve medication safety within the system.

Automated dispensing devices (or cabinets) offer an alternative to storing medicines in a medication supply/preparation room in patient care areas. These devices are capable of storing wardstock supplies of medicine and medicines for specific patients. Ideally, such devices are integrated with the pharmacy information system and a bar-coding system to maintain an accurate record of the drugs dispensed to and withdrawn from the device, at both the patient and care unit level of enquiry. Furthermore, a stronger, safer distribution system can result when the automated dispensing device is coupled with a formulary system that places restrictions on the variety of strengths supplied in the device.

The use of automated processes and dispensing devices throughout the medication use system can produce efficiencies and other benefits, particularly when human resources are scarce. However, it is important to not become too reliant on them and assume that they are free of errors (Institute for Safe Medication Practices Canada, 2016). These devices and systems can introduce new, unanticipated, or different root causes of medication incidents and care should be taken to be mindful of such incidents and take corrective, preventive action (Grissinger et al., 2007; Institute for Safe Medication Practices, 2009; Institute for Safe Medication Practices Canada, 2016). Guidance to assist hospitals prevent medication incidents associated with automated processes and dispensing devices is available (Institute for Safe Medication Practices, 2009; Institute for Safe Medication Practices Canada, 2016).

Unusable Stock and Disposal of Drugs

Stock that is expired, damaged, or otherwise not usable should not be comingled with other stock to avoid being used or dispensed. It should be quarantined until it is removed for proper disposal. The hospital's waste management system and process should include provisions for the safe disposal of drugs. The pharmacist should be involved in the development of waste management procedures to ensure that drugs are properly disposed of (Vermeulen et al., 2016).

Access to Pharmacy

For safety and security reasons, the hospital should limit access to the pharmacy to pharmacy professionals only. However the pharmacy's hours of operations should not be an impediment to timely access of medications. A risk management strategy should be in place to give access to medications in an urgent or emergency situation (Canadian Society of Hospital Pharmacists, 2016). Such strategies may include an on-call system to bring a pharmacist (or pharmacy technician) to the hospital, or a night cupboard/dispensary, which contains urgently needed medications not found elsewhere in the hospital and which can be accessed by other health professionals (Olson, 2012). Records of all stock removed should be maintained.

Preparation

Under ideal circumstances, the medicines dispensed to patient care areas are supplied in ready-to-use, unit-of-use packaging, for a specific patient. The quantity supplied is usually for a 24-h period (Olson, 2012), knowing that medication orders can change quickly. This form of dispensing is considered the safest distribution method. It may require additional front-end expenses (Olson, 2012), but is usually associated with lower rates of wastage (because unused drugs returned to pharmacy can usually be safely returned to stock) and nursing invests less time in preparing the drug for administration.

Compounding and Repackaging

Medications that require compounding or repackaging are prepared in the pharmacy, unless doing so would compromise patient care in an urgent or emergent situation.

The medications that must be dispensed in a sterile formulation and require compounding or repackaging should be aseptically prepared in a clean room that is properly outfitted for that purpose (PIC/S Secretariat, 2014). Only specially trained personnel should be involved in aseptic compounding or repackaging activities. The clean room and the primary engineering control (or clean air device) must reliably provide air of a quality sufficient for the activities undertaken in the clean room: these specifications are laid out in pharmaceutical standards or guidelines such as the United States Pharmacopeia and other resources (Beaney, 2016; Canadian Society of Hospital Pharmacists, 2014a; Society of Hospital Pharmacists of Australia, 2010). Equipment and supplies used for aseptic compounding remain dedicated to the purpose of aseptic compounding. Supplies used in sterile compounding should be used as per the manufacturer's instructions. Sharps should be safety engineered to reduce workplace injuries, wherever possible single-use only sterile supplies should be used.

Medications that require compounding or repackaging but do not have the requirement of being sterile should be prepared in a dedicated area or room that is separate from the controlled work environment, and not in the immediate area where other pharmacy activities are undertaken. Only persons who are specially trained in nonsterile compounding are involved in such activities. Equipment and supplies used for nonsterile compounding remain dedicated to the purpose of compounding.

If a drug must be removed from its original primary container (that which comes in contact with the medicine) for repackaging, the new primary container must be fit for purpose (Jackson and Lowey, 2010) suitable for the dosage form, dose, and storage requirements for the medicine. It must not interfere with the medicine (i.e., it must not cause adsorption, absorption, or chemical reactions), rather it must maintain the integrity of the medicine to the point of administration to the patient. Furthermore, the method of repackaging must not damage the drug, introduce harm to the persons handling the drug, or contaminate other drugs that will be repackaged using the same equipment. Some drugs will leave a residue in the equipment or be hazardous: these drugs should not be repackaged using an automated repackager.

Labeling

The primary package must always be labeled to allow for accurate identification of the contents of the package, up to the point of administration of the drug. The use of abbreviations on labels should be minimized to avoid the risk of misinterpretation or miscommunication of the abbreviation (Institute for Safe Medication Practices Canada, 2017).

Information about the safe storage and handling of the drug should be provided to anyone who will handle or administer the product.

Safety Checks

At key stages in preparing certain high alert medicines for dispensing, independent, double checks should be employed to ensure that the correct medicine (identity, dose, formulation, and quantity) is selected and dispensed. Despite the value of independent double checks, processes should not rely solely on them to reduce medication incidents. The system should be bolstered with other strategies. Refer to recommendations from a variety of organizations that disseminate such information (such as the Institute for Safe Medication Practices and the Institute for Safe Medication Practices Canada).

Procedures

The hospital should have a robust set of procedures to guide every key step in the drug distribution system. At a minimum, procedures should be written for the following topics, describing the roles and responsibilities of personnel involved in the activity and the standard operating procedure:

- initial and ongoing training of staff
- selection of vendor
- receipt and storage of drugs
- conducting inventory counts (comparing physical stock-on-hand records to expected stock-on-hand records)
- traceability of drugs through the drug distribution system
- receipt of medicines through unconventional methods such as patient's own medicines, samples, donated medicines
- inspection of drugs at every stage of handling, to ensure the product is of high quality and safe for use
- distribution of medicines to patient care areas
- handling of special categories of medicines

- controlled substances such as narcotics, benzodiazepines
- hazardous medicines, such as chemotherapy
- investigational medicines
- high-alert medicines
- disposal of drugs that are deemed unusable (e.g., expired, damaged)
- compounding and repackaging of medications
- monitoring the safety of the drug distribution system

Staff should be encouraged and supported to "stop the line" whenever a product, service, or procedure is not correct. This step is critical to prevent an incident from occurring in the moment. And, if proper follow-up is conducted, it prompts people to learn from what contributed to the "near miss" and make changes to reduce the likelihood of an incident occurring in the future.

The people who perform drug distribution activities need to know about the importance of the activities, and the outcomes that can occur to patients or persons handling a drug if an activity is not performed correctly. To that end, it is important that personnel be informed of changes to policies and procedures and continue to develop their knowledge and skills.

Quality

The hospital's processes should be supported by a robust quality management system to help ensure the drug distribution system is functioning as intended. The quality system should include the following topics.

- Quality control
- Quality assurance
- Quality improvement
- Contingency planning

Key activities (such as compounding or repackaging) should have quality control measures in place to ensure that the product meets the required specifications. At a systems level, key performance indicators such as turn-around time regarding dispensing medications, medication incidents (including near-misses) should be regularly measured; looking for trends that serve as alerts of how well the system is working and where attention to make improvements is warranted.

Pharmacy departments should subscribe to medication safety bulletins to keep informed and up to date about risks or how to mitigate them or their effects. Such publications and alerts are available from the Institute for Safe Medication Practices or similar organizations (e.g., the Institute for Safe Medication Practices Canada).

Clinical Pharmacy Services

Evidence supporting the provision of clinical pharmacy services in hospitals has shown that increasing both the number of clinical pharmacists in hospitals and their involvement in patient medication management is associated with lower mortality rates. In the largest datamining study published to date, the observed mortality reduction was associated with seven specific clinical pharmacy services: management of drug protocols, participation in medical rounds, provision of in-service education, execution of drug-use evaluation, collection of admission drug histories, management of adverse drug reactions, and participation on the cardiopulmonary resuscitation team (Bond and Raehl, 2007). Another study, which evaluated the inpatient care provided by clinical pharmacists, confirmed that there were improvements in patients' outcomes in association with the following pharmacist activities: interacting with the health-care team during rounds, interviewing patients, reconciling medications, and providing medication counseling and follow-up to patients at the time of discharge and beyond (Kaboli et al., 2006). A more recent study found that the provision of direct patient care by hospital pharmacists was associated with numerous improvements in patients' outcomes, including mortality, length of stay, hospital readmissions, and emergency department visits, as well as improvements in various clinical parameters, such as low-density lipoprotein cholesterol, glycosylated hemoglobin, and blood pressure (Chisholm-Burns et al., 2010b). Evidence has also demonstrated that providing these clinical pharmacy services results in economic benefits (Chisholm-Burns et al., 2010a).

Education of Other Health-Care Professionals about Pharmacotherapy

In addition to their roles in providing direct patient care, hospital pharmacists play an integral role in educating physicians, nurses, and other health-care professionals about the rational and appropriate use of drugs. The increasing complexity and importance of medications in the health care system underscore the need for pharmacists to share their unique pharmacotherapeutic knowledge and expertise with other health-care providers. Arising from their collaborative and interprofessional practice exposure to physicians, nurses, and other health-care practitioners, hospital pharmacists are well positioned to educate and advise these professionals about various aspects of pharmacotherapy, including appropriate indications, safety profiles, and potential interactions with drugs and other consumed products, such as food and alcohol, as well as the expected therapeutic and potential adverse responses. Working in collaborative practices, hospital pharmacists can directly influence medication therapy decisions and optimize patient outcomes by sharing their medication knowledge and educating other team members.

Education of Patients about their Medications

Part of the direct patient care role fulfilled by hospital pharmacists is the provision of medication education to patients. Educating patients about their medications helps them to become active participants in their own health care by ensuring safer medication use, improved adherence, and better identification and appropriate management of adverse drug effects. This interactive educational exchange between the pharmacist and the patient occurs at various times throughout the hospital stay. Additionally, hospital pharmacists provide comprehensive education at the time of discharge, to help patients become further informed about their medications and to ensure that they are able to adhere to and receive the intended benefits of the accepted treatment plan after they have transitioned out of the institutional setting. Typically, discharge education includes the provision of a schedule for medications that are to be taken at home (with details of each drug's name, dose, frequency, and indication), a summary of changes from the patient's preadmission medication regimen, and education about any new medications. Commonly, medication education and discharge medication counseling can be provided in the same face-to-face encounter, depending on the pharmacist's clinical workload and the complexity of the patient's medication regimen (Fernandes et al., 2015). It is expected that this patient education will continue and be reinforced by other health-care professionals (e.g., the community pharmacist), as the patient transitions through the health-care system.

Education of Pharmacists

Entry-to-practice Education

To provide the quality of pharmacy care that is expected in modern health-care systems, professional educational programs must be designed to ensure that graduates are trained to fulfill the changing expectations of the patients and communities that they serve. In Canada, the Association of Faculties of Pharmacy of Canada (2017) has specifically defined the educational outcomes for graduates from programs leading to a first professional (i.e., entry-to-practice) degree in pharmacy. These educational outcomes are designed to ensure that graduates are grounded in a professional identity as a care provider and are able to approach pharmacy practice by skillfully integrating the roles of communicator, collaborator, leader-manager, scholar, and health advocate into their overall care provider role. Formal accreditation of these professional degree programs provides public recognition and assurance that they meet the established professional qualifications and educational standards needed to produce graduates capable of becoming licensed pharmacists (Canadian Council for Accreditation of Pharmacy Programs, 2018).

As regulated health-care professionals, pharmacists are responsible for and accountable to patients through legislation and through the standards and bylaws of the professional regulatory authority of the jurisdiction they practice. In Canada, the National Association of Pharmacy Regulatory Authorities (NAPRA) (2009) has set out model standards of practice for pharmacists, with the goal of specifying the standards against which a pharmacist's performance can be judged in practice by an individual regulatory authority. Although the requirements for licensure to practice are set out by legislation and standards, one additional requirement for initial registration and licensure is certification of an applicant's knowledge, skills, and abilities at entry to practice. This certification is granted by the Pharmacy Examining Board of Canada to those who successfully complete the organization's qualifying examination.

Training in Hospital Pharmacy Practice

Specialized training in hospital pharmacy practice after getting the entry-to-practice degree provides pharmacists with experience in a variety of roles. In Canada, a pharmacy residency program is a 12-month directed postgraduate learning experience in a hospital or collaborative health care setting. Through structured rotations in pharmacy practice, education, research, and administration, the residency program prepares pharmacists for challenging and innovative hospital pharmacy practices. The key objective of hospital pharmacy residency programs is to provide experiential learning under skilled practitioner role models. The necessary skills, knowledge, and values required to practice effectively as a hospital pharmacist can be acquired and applied by the resident in the promotion of exemplary patient care (Canadian Hospital Pharmacy Residency Board, 2009). The designation "Accredited Canadian Pharmacy Residency" (abbreviated as ACPR) is conferred on residents upon their graduation. These residencies are an important source of highly qualified pharmacists trained in institutional practice.

Standards for a year 2 residency in advanced pharmacy practice have recently been defined by the Canadian Pharmacy Residency Board of the Canadian Society of Hospital Pharmacists (CSHP) (2016). The advanced (year 2) pharmacy residency focuses on additional training in direct patient care, teaching, and research. It is intended to increase or refine pharmacists' knowledge, skills, and attitudes, to ensure they are equipped for the interprofessional management of patients with more complex clinical needs, by focusing on a specific therapeutic area (e.g., cardiology, oncology, infectious diseases), a specific patient population (e.g., pediatrics, geriatrics), or a specific type of practice (e.g., primary care, ambulatory care, critical care). As these advanced residency programs evolve, it is anticipated that pharmacy practitioners will be able to provide increasingly complex pharmacy care to patients in hospitals and other collaborative health-care settings.

Provision of Expertise

In addition to core functions of drug distribution and patient care, hospital pharmacists provide crucial infrastructure to support the appropriate use of drugs. They may provide drug information services in their hospital or region or manage the hospital formulary.

They may also participate in clinical trials or practice research, serve on research ethics boards, champion medication safety or quality improvement programs, lead the development of treatment protocols or preprinted orders, or deliver in-services and other educational materials.

Pharmacists who work in these areas require a specialized skill set. They must have skills in critical appraisal and evidence-based medicine. They must have the ability to find and critique scientific literature, relying on a thorough understanding of study design, statistics, and common sources of bias. They must be able to interpret and apply the evidence to clinical practice, both at a patient level and a population level. Importantly, they must also have the ability to synthesize and communicate their findings in a clear and timely manner.

Drug Information

Standards of practice for pharmacists commonly include the provision of medication information as a core competency. Standards from FIP (Vermeulen et al., 2016), Canada's NAPRA (2009), Great Britain's Royal Pharmaceutical Society (2017), and the Society of Hospital Pharmacists of Australia (2013) all include expectations that pharmacists critically evaluate drug information and present it in a manner that is tailored for the recipient. American Society of Health-System Pharmacists (ASHP) guidelines (Ghaibi et al., 2015) place the provision of drug information "among the fundamental professional responsibilities of all pharmacists."

In hospitals, a specialized drug information service is often available. Guidelines from CSHP (2015) describe this as a formal unit of the pharmacy department, with dedicated staff and resources providing information on drug therapy. The service is often housed in a drug information center, physically separated from the pharmacy dispensary. The goal of a drug information service should be to support evidence-based care and discourage unproven therapies.

The drug information service is generally available to all health professionals in the hospital, with drug information pharmacists available by phone, fax, or email. There is occasionally a call center for patients as well. Such a service complements the day-to-day work of hospital pharmacists by assisting with urgent questions or questions requiring extensive research.

Dedicated financial resources are required to develop and maintain a library of high-quality resources. This may include print textbooks, but services are increasingly dependent on subscriptions to electronic databases, websites, and list-servers. Drug information pharmacists should also have the resources to join relevant societies and participate in continuing education events.

Key aspects of any drug information service are a systematic approach and thorough documentation. A systematic approach was first proposed by Watanabe et al. (1975). The approach has been modified over the years, but still includes the basic steps of gathering information to understand the true question, classifying the question, conducting a systematic search, analyzing and disseminating the results, and documenting the response.

A comprehensive documentation system is crucial for a drug information service. Documenting every request in a database that allows for easy retrieval by keyword or drug class prevents duplicating effort for similar requests. This information also allows for the provision of consistent information, particularly when the response makes reference to guidelines, policies, or protocols within the local health system. A documentation system allows for quality assurance because responses can be reviewed as needed. Finally, such a system can also provide important data trends to help inform the work of the drug information pharmacist.

The work of drug information pharmacists can be categorized as in-coming (reactive) or out-going (proactive). Reactive tasks are focused on responding to in-coming requests received through the drug information service. Proactive tasks are those that aim to disseminate information in advance of when it is needed, perhaps by creating patient information sheets and making them available on the hospital's website, or publishing a monthly newsletter for health professionals explaining new drugs or treatment protocols. Reactive tasks should inform proactive tasks. Pharmacists should be alert for trends in-coming requests. Many questions on the same topic may indicate that information is lacking on that topic and a more proactive approach is required to push information out across the organization, perhaps in the form of an in-service, newsletter, practice tool, or preprinted order set.

Formulary Management

Hospital pharmacists promote the optimal use of drugs through a formulary, a list of medications that have been approved for use in the hospital. The formulary lists approved drugs, along with dosage forms, dosage strengths, unit-of-use quantities, and unit cost for each drug product. CSHP (2008) calls the formulary a "dynamic compilation" of approved medications, emphasizing that the formulary should be constantly reviewed for potential additions and deletions.

Hospitals should have a clear policy on formulary governance, including the composition of the committee responsible for formulary decisions, and procedures for making changes, additions, and deletions. The formulary should be available to anyone who prescribes, dispenses, or administers medications in the hospital.

More than simply a list of medications, the formulary includes relevant policies and information to support appropriate drug use. Formularies may include helpful tools such as dosage charts or equivalency tables, criteria for the use of restricted drugs, or institutional policies on generic substitution.

Most formularies include information on the hospital's approved therapeutic interchanges. Therapeutic interchange is the automatic substitution (or "auto-sub") of one chemical entity for another, when the formulary management committee has deemed these different drugs to be therapeutically equivalent (CSHP (2008)). This often occurs within a class of drugs. By including only one of the drugs on formulary and automatically substituting that drug whenever any of the equivalent drugs are ordered, hospital pharmacies can simplify their inventory and distribution systems, and decrease costs by purchasing the preferred drug in bulk. There

may also be patient safety benefits in avoiding therapeutic duplication within the formulary. Standards for hospital accreditation in Canada (Accreditation Canada, 2017) mandate designing the formulary so as to minimize the number of medications that health professionals need to be familiar with.

Formularies can also prevent duplication and confusion by limiting the number of dosage forms available for each drug and standardizing the doses available. FIP (Vermeulen et al., 2016) recommends that hospital pharmacies stock only standardized concentrations of high-risk medications such as electrolytes, and that this standardization is guided by the hospital formulary.

A formulary system may facilitate the development of standardized treatment protocols and pre-printed orders. Such protocols may be managed by a separate committee, but they are excellent companions of the hospital formulary as both have the goal of promoting evidence-based, safe, and equitable care. Olson (2012) recommends that the hospital formulary align with any regional or national guidelines that have formally adopted as standards of care.

Olson (2012) calls the hospital formulary "the cornerstone of medication management in the hospital" and offers suggestions to promote formulary adherence, such as monitoring and acting on all nonformulary drug use, prohibiting the distribution of samples, providing easy access to the formulary, communicating changes to the formulary, and involving medical staff in formulary decisions.

Pharmacy and Therapeutics Committee

The committee responsible for formulary management is usually called the Pharmacy and Therapeutics Committee (P&T). P&T should have an official mandate and should be multidisciplinary (WHO, 2003a), including representatives from pharmacy, medicine, nursing, administration, and other disciplines. P&T should oversee all policies related to the use of drugs in the hospital (ASHP (2008); CSHP (2008)).

P&T should have a rigorous process in place for considering additions or changes to the formulary. Committee deliberations should cover therapeutics, safety, economics, access, and equity. Submissions to the committee should include evidence for the potential benefits and harms of the drug, reasons for adding it to the formulary, a comparison with other drugs already on formulary and whether these other drugs could be replaced, any special training or restrictions that should be required, and a pharmacoeconomic analysis (CSHP (2008)).

It is important to consider the overall budget impact of formulary changes. Some drugs may add new costs to the drug budget, but reduce complexity of care, nursing time, or length of stay. Some drugs may reduce drug costs, but add lab monitoring or nursing time.

P&T may also oversee a formal program of medication use evaluation (MUE). Also called drug use evaluation or drug use review, this is an ongoing, systematic evaluation of drug use (CSHP, 2014b) that looks at pattern of use, quality of use, determinants of use, and outcomes of use (WHO, 2003b). Such a program may include benchmarking levels of drug use, monitoring usage trends and costs, evaluating effectiveness, creating guidelines or criteria for drug use, and evaluating where additional education may be required (CSHP, 2014b). ASHP (1996) MUE guidelines offer criteria for choosing which drugs to review, such as drugs that are known to cause adverse reactions, are used in high-risk patients, are used in a large number of patients, are a critical component of care for a specific condition or procedure, or are expensive.

Conclusion

The evolving health-care landscape provides new opportunities for pharmacists and pharmacy technicians to deliver services that will enhance medication use and engage patients in improving their overall health. These services span the entire scope of pharmacy practice. As evidence about pharmacists' impact on clinical and economic outcomes continues to expand, the demand for and expectations of hospital pharmacists to help improve patient-specific therapeutic outcomes and reduce health-care costs will increase. Pharmacist and pharmacy technician education, training, and certification systems and processes must keep pace with these demands and expectations, to ensure that future pharmacy professionals can fulfill their roles and responsibilities for improving patients' mediation-related outcomes.

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List of Relevant Websites

'AAFH Modelo de prática profesional en farmacia hospitalaria' at http://www.aafhospitalaria.org.ar/index.php
'ACCP Papers' at https://www.accp.com/govt/positionPapers.aspx
'AHRQ Right place, right drug, wrong strength' at https://psnet.ahrq.gov/webmm/case/436
'ASHP Drug shortages' at https://www.ashp.org/drug-shortages
'ASHP Policy positions and guidelines' at https://www.ashp.org/Pharmacy-Practice/Policy-Positions-and-Guidelines
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'Board of Pharmacy Specialties' at https://www.bpsweb.org/
'CDC Antibiotic prescribing and use in hospitals and long term-care' at https://www.cdc.gov/antibiotic-use/healthcare/index.html
'CPSI Intravenous potassium chloride can be fatal if given inappropriately' at http://www.patientsafetyinstitute.ca/en/NewsAlerts/Alerts/pages/alertdetail.aspx?alertid=PC71)
'CSHP Advocacy' at https://cshp.ca/advocacy
'CSHP Canadian Pharmacy Residency Board' at https://cshp.ca/cprb
'CSHP Excellence in hospital pharmacy' at https://cshp.ca/excellence
'CSHP Hospital pharmacy in Canada' at http://www.hospitalpharmacysurvey.ca
'CSHP Official publications' at https://cshp.ca/official-publications
'EAHP Hospital pharmacists and combatting antimicrobial resistance' at http://www.eahp.eu/practice-and-policy/antimicrobial-resistance
'EAHP Hospital pharmacy specialisation' at http://www.eahp.eu/practice-and-policy/hospital-pharmacy-specialisation
'EAHP Policy and advocacy' at http://www.eahp.eu/practice-and-policy/advocacy
'EAHP Positions papers' at http://www.eahp.eu/practice-and-policy/EAHP-statements
'FIP addressing global medicines shortages' at https://www.fip.org/Medicines-shortages
'FIP Hospital Pharmacy Section' at http://www.fip.org/hospital_pharmacy
'FIP Patient safety is ensured by pharmacists' at http://www.fip.org/www/index.php?page=patient_safety
'IHI Changes: Eliminate or reduce the availability of multiple medication strengths' at http://www.ihi.org/resources/Pages/Changes/EliminateorReduceAvailabilityofMultipleMedicationStrengths.aspx
'ISMP Independent double checks: Undervalued and misused: Selective use of this strategy can play an important role in medication safety' at https://www.ismp.org/resources/independent-double-checks-undervalued-and-misused-selective-use-strategy-can-play
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'OECD Antimicrobial resistance' at http://www.oecd.org/health/antimicrobial-resistance.htm
'SHPA Fact sheets & position statements' at https://www.shpa.org.au/fact-sheets-position-statements
'SHPA Standards of practice' at https://www.shpa.org.au/standards-of-practice
'The Pharmacy Examining Board of Canada, Pharmacist Qualifying Examination' at http://www.pebc.ca/index.php/ci_id/3147/la_id/1.htm
'USP Compounding Compendium' at http://www.usp.org/products/usp-compounding-compendium'WHO Antibiotic resistance: Fact sheet' at http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/
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'WHO Essential medicines' at http://www.who.int/topics/essential_medicines/en/
'WHO Patient safety – Medication without harm: WHO's third global patient safety challenge' at http://www.who.int/patientsafety/medication-safety/en/
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Expanded and Evolving Roles for Pharmacists

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Scope of Practice and the Pharmacist's Professional Role

The scope of practice by pharmacists has experienced, and continues to undergo, a substantial shift to meet the evolving needs of patients and health systems. Prior to large-scale pharmaceutical manufacturing, the pharmacist's primary role was the preparation of medicinal products for individual patients. The commercial manufacturing of drug products significantly reduced the need for pharmaceutical compounding, shifting the responsibility of pharmacists' knowledge and practice toward patient education and advice on self-care. In hospital pharmacies, pharmacists were increasingly adopting roles in pharmacokinetic drug monitoring—beginning to blur the boundary between drug dispensing and direct patient care. In 1990, Hepler and Strand defined the pharmacist's role in pharmaceutical care as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Strand, 1990). This was instrumental in assigning responsibility to pharmacists for optimizing drug therapy outcomes of their patients, largely through the identification and management of drug-related problems. Their classification system for types of drug-related problems has been utilized in countless quality assurance measures, standards of practice and guideline documents, and research endeavors advancing pharmacy practice.

While the widespread definition of pharmaceutical care has not been revised since, the roles and responsibilities of pharmacists have continued to evolve. A number of factors can be credited with influencing this change. For example, growth in the number of approved pharmaceutical compounds has contributed to greater complexity in medication selection and use, creating the opportunity for pharmacists' drug therapy expertise to take on increased value within the multidisciplinary provision of patient care. Revised pharmacy curricula in many countries with greater emphasis on pharmacotherapeutic knowledge and clinical rotations—including the development of entry-level PharmD programs whereby new pharmacy graduates have the PharmD credential (Romanelli and Tracy, 2015)—have sought to produce pharmacy graduates with the knowledge and skills to be frontline healthcare professionals. Finally, an aging population and increasing prevalence of chronic disease (Prince et al., 2015) have placed financial and capacity burdens on many health systems, requiring consideration of how nonphysician health professionals can improve chronic disease management outcomes and improve medication use.

The scope of practice by pharmacists has therefore grown to accommodate these increasing demands and better utilize pharmacists' expertise in drug therapy. Often termed *expanded scope*, activities such as renewing and adapting prescription orders, prescribing drug therapy, ordering and interpreting laboratory tests, and administering drugs and vaccines by injection have been generally defined as services provided by pharmacists beyond those involved in routine dispensing and medication profile/chart reviews. In contrast to providing therapeutic recommendations to patients and other healthcare providers, expanded scope activities generally require decision-making and action on identified patient care needs by the pharmacist.

As other chapters of this resource specifically address the pharmacist' role related to a number of the services considered to be within the purview of expanded scope, this chapter will discuss broader considerations related to the enactment, uptake, and provision of expanded scope services as a whole, and the impact of this evolving role on the future of pharmacy practice.

Enacting Scope Expansion in Pharmacy

As a regulated health profession serving both the public and private sectors, enacting scope expansion in pharmacy is complex. At the highest levels in the organizational structure of the profession, scope expansion is pursued by pharmacy advocacy associations and regulatory bodies to meet identified care gaps in the health system and advance the profession. As a highly accessible profession with pharmacies located in many communities, expanded scope services are often intended to improve the timely and convenient access to health services for patients. As such, pharmacy regulatory bodies, with mandates to represent the needs of the public, play a key role in identifying expanded scope activities likely to be of greatest benefit to residents of their province/state/country, and establishing and enforcing standards related to the quality and safety of those services. Depending on the legislation of health professions in different countries, amendments to regulations at the state/provincial and/or national level may be required for pharmacists to legally provide these services. Additional information on the regulation of the pharmacy profession can be found in Chapter 710 of this resource. Consultations with the public, other health professionals, policy-makers, and payers further inform the specific design of the services introduced. These factors therefore lead to high variation internationally in services offered, patient eligibility for services, and payment (Houle et al., 2013, 2014a; Law et al., 2012; Taylor and Joubert, 2016).

As expanded scope activities involve pharmacists taking responsibility for any outcomes or risks associated with these decisions, standards of practice which may include required education or credentialing in order to provide the service, documentation and communication requirements, safety considerations and restrictions, and requirements for liability insurance may be mandated by regulators. Pharmacy advocacy organizations, universities, and continuing education providers commonly play a role in supporting pharmacists and pharmacy students to meet these requirements. Insurance companies and employers must ensure pharmacists and pharmacies are adequately insured for any potential losses or damages that may occur. Patients, institutions, and other health professionals must also be informed of the change in scope to ensure recognition of, and collaboration with, pharmacists as they adopt these new responsibilities. At the level of individual clinicians and practices, additional training or education may be required, modifications to workspaces and workflow are often necessary (Houle et al., 2017), and standard operating procedures may need to be developed. This complexity related to enacting practice change and scope expansion can result in great variation in uptake among jurisdictions—and individual practitioners within those jurisdictions (Guirguis et al., 2017; Rosenthal et al., 2015)—related to the uptake and provision of these services in practice.

Barriers to Expanded and Evolving Roles for Pharmacists and Potential Strategies to Overcome These Barriers

The enactment of legislation and standards of practice to enable expanded scope activities is a foundational step toward adoption by pharmacists, but does not ensure it. Indeed, pioneers of expanded scope activities worldwide have regularly reported hesitation to provide these services and suboptimal uptake by pharmacists and patients when initially introduced for a number of reasons. Those wishing to pursue similar opportunities are therefore strongly encouraged to both anticipate and proactively address the commonly reported barriers summarized below. While not an exhaustive list of all potential challenges, these represent barriers frequently reported in the pharmacy practice literature.

Time, Workflow, and Space

While the traditional activities of pharmacists as providers of medications is shifting, they will unlikely be eliminated entirely from a pharmacist's professional responsibilities. One cannot undervalue the importance of the safe preparation and dispensing of medications, as this process includes reviewing the patient's medical history and medication profile for potential interactions or contraindications, monitoring medication adherence and effectiveness, and providing patient counseling—all of which require the clinical expertise of a pharmacist. It is indeed during the dispensing process when many prescribing errors and drug-related problems are identified. As pharmacists introduce expanded scope activities in their practices, they must often be performed in addition to existing responsibilities rather than in place of them.

As a result, the impact of these additional services on pharmacists' time and workload cannot be underestimated. Due to the high level of individualization required to conduct most expanded scope services, considerable time is required to identify the patient's chief concern and goals of therapy, consult references to guide clinical decision-making, document care provided (McCann et al., 2011; Penm et al., 2017), and communicate these actions to other health professionals involved in that patient's care to ensure continuity and safety across care providers. Standardized documentation forms may also need to be completed to comply with legislative requirements and/or to receive remuneration for the activity.

Furthermore, the physical layout of many pharmacies has been designed to optimize the efficiency of the dispensing process. Additional requirements for the introduction of expanded scope activities may include private patient counseling or examination rooms with medical equipment for patient assessment (e.g., a blood pressure monitor), a waiting area for patients to complete forms for history-taking or remain for monitoring following the administration of an injection, and additional computer terminals where pharmacists can complete clinical documentation with minimal interruptions. Subscriptions to additional drug information resources may also be required to support clinical decision-making.

Pharmacies must also consider how expanded scope activities will be integrated into the existing workflow of processing prescription orders and providing advice on nonpharmacologic products (Houle et al., 2017; Penm et al., 2017). As a commonly

cited advantage of pharmacies as a primary care setting is their accessibility—often allowing patients to see a pharmacist without an appointment and across broader operating hours than many medical clinics—many pharmacies have opted to provide some expanded scope services on a walk-in basis. While optimizing patient accessibility to these services, walk-in availability introduces unpredictable disruption to the existing workflow of the pharmacy, which may require reexamination of staffing levels throughout the day to consider when walk-in requests appear to be most frequent. More time-intensive services, such as chronic disease monitoring/management or travel consultations, may be better suited to an appointment model, where additional staff can be present to minimize workflow disruption. This also allows the pharmacist the opportunity to prepare for the appointment in advance by collecting necessary background information or ensuring the required equipment is readily available for the interaction.

The corresponding expansion to the scope of practice of pharmacy technicians in some regions can further enable greater integration of these activities into existing workflow (Houle et al., 2014b). With technicians adopting larger roles in product ordering and inventory management, patient education on certain medical devices such as blood pressure and blood glucose monitors, and performing final checks on the dispensing of prescription products (following a review of its safety and clinical appropriateness by the pharmacist), these tasks may be potentially reduced from the pharmacist's workload, with the freed time now able to be allocated to expanded scope services. Additional information on pharmacy technician education and training is provided in Chapter 103 of this resource.

Education and Confidence

The addition of expanded scope services into a pharmacist's repertoire has largely been an occurrence of the 2000s—especially the past decade. While pharmacy schools in jurisdictions authorizing expanded scope services have integrated teaching and practice with these activities into their curricula for new graduates, such training was largely excluded from the education received by experienced pharmacists. As previously mentioned, expanded scope services often require the pharmacist to ultimately make a decision regarding a patient's pharmacotherapeutic needs, and act upon that decision. This is in contrast to the traditional role of pharmacists as information providers, trained to provide evidence-based recommendations on drug therapy which were ultimately decided and acted upon by physicians and other prescribers.

Pharmacists have therefore had to adapt professionally and personally to this added responsibility (Maddox et al., 2016; Penm et al., 2017; Rosenthal et al., 2010, 2015). Learning needs identified by practicing pharmacists to meet these responsibilities have included additional clinical education in physical assessment and laboratory test interpretation (Hoti et al., 2014), and documentation of care plans and actions for both clinical and legal purposes. As can be expected, competence or legislative ability to perform a particular service does not imply confidence (Teixeira et al., 2017), as the latter is generally achieved through practice and repetition. Pharmacists who do not feel confident in these skills may therefore not promote the availability of these services widely to patients, or may refer patients back to traditional prescribers for decision-making under situations of uncertainty. While referral of patients to other health professionals for concerns beyond the scope of pharmacists is encouraged and expected, the subjective interpretation of when referral is the preferred action for a given scenario is highly variable among pharmacists, and largely associated with their confidence in providing the service. This hesitation to perform a service due to lack of confidence may contribute to a cycle whereby attaining sufficient experience to achieve confidence is significantly delayed or not achieved.

Professional education and socialization is often highly reliant on the mentorship of new members of the profession by experienced practitioners. The challenge created by an expanding and evolving role for pharmacists is that newer practitioners may be more informed of legislative requirements and drug information resources specific to expanded scope services, and may have had more opportunities to practice expanded scope activities with standardized patients as part of their formal training, compared to experienced colleagues. Seasoned practitioners, on the other hand, have likely developed greater confidence in skills such as shared decision-making with patients, and communication with other health professionals than newer practitioners. This splitting of areas of confidence between new and experienced practitioners often becomes evident during practical education experiences or internships, when both generations must work together as part of the student's formal education. Conflict may arise if the new graduate feels discouraged from practicing to their full scope due to hesitation from the mentor, or if the mentor feels the value of their experience has been eclipsed by the expanded scope knowledge instilled into new clinicians. Experiential education must therefore consider the distinction between learner and teacher to be fluid when related to expanded scope services, with each party serving as both the learner and teacher depending on their areas of proficiency.

Continuing education programs for pharmacists must also consider and account for the potential for learners to lack confidence in multiple potential aspects of expanded scope service provision. The traditional approach to continuing education, focusing on improving learners' knowledge of a particular disease and associated drug therapy options, fails to address barriers in practice such as decision-making under clinical uncertainty, seamless care across health professionals and care settings, effective documentation of actions taken, and monitoring the patient's response to therapy. Case-based and interactive learning strategies are often employed to prepare pharmacists to apply their scientific knowledge to patient care decisions.

Support From Other Health Professionals and Patients

The expansion of the role of any professional contributes to a blurring of the roles in patient care, historically solely performed by specific health professionals. For example, prescribing and adapting drug orders is now a shared activity in some jurisdictions across physicians, nurse practitioners, physician assistants, and pharmacists. The administration of vaccines by injection is now largely

shared between public health nurses and community pharmacists in regions where this authorization has been granted to pharmacists. This shared scope has introduced complexity related to payment for services through government or third-party payers, concerns over the potential for unnecessary duplication of services by multiple health professionals caring for a mutual patient, and collaboration (Donald et al., 2017; McCann et al., 2012; Penm et al., 2017), as each profession is now struggling to maintain a unique professional identity and position of relevance in the health system. Efforts to contain growing healthcare costs due to an aging population has also created tension among professions who may now be competing for a share of the same market, negatively impacting the market value related to remuneration offered for these services. Codes of ethics for most professions include a focus on the best interest of the patient or client at all times; however, concerns over one's professional position and the sustainability of their practice cannot be ignored. Furthermore, pharmacists who anticipate or experience a negative reaction to their expanded scope activities by other health professionals may hesitate to provide such services to patients, to avoid disrupting established professional relationships.

Support for expanded scope services by pharmacists among members of the public has been mixed. Patients value the convenience and accessibility of community pharmacies as primary care sites (Hutchings et al., 1998; Mansell et al., 2015). Patients who have received care from a pharmacist are generally highly satisfied with the experience (Gardner et al., 2008; Hale et al., 2016; Houle et al., 2018; Mansell et al., 2015; Stewart et al., 2011; Tinelli et al., 2015), and view their pharmacist as a knowledgeable member of their healthcare team specifically related to drug therapy knowledge (Bishop et al., 2015). Concerns have been raised, however, related to the lack of private space for consultations in many community pharmacies (Famiyeh and McCarthy, 2017; Stewart et al., 2011), the need to ensure all members of the patient's healthcare team are made aware of any actions made by the pharmacist to ensure safety and continuity of care, and the impact that seeking care from a pharmacist may have on the patient's relationship with their other healthcare providers (Donald et al., 2017). Research has also reported low awareness among the public of expanded scope services available to them from their pharmacist (Feehan et al., 2016), which may be partly due to pharmacists' hesitation to advertise these services due to lack of confidence as mentioned above.

As such, changes to the scope of practice for pharmacists must be accompanied by awareness campaigns for other health professionals and the public by pharmacy regulatory bodies, advocacy associations, and individual pharmacists and pharmacies. Pharmacists are often legally required to document and communicate care they provide to patients to other health professionals also involved in that patient's care; however, this communication generally occurs after the care has been provided. Pharmacists are encouraged to meet with local health professionals that they share mutual patients with in advance, to inform them of new services being introduced, address any questions or concerns, and agree on how communication and collaboration will occur. Case-finding efforts should also be employed by pharmacists and pharmacy team members to proactively identify patients who may benefit from a service, as it cannot be assumed that members of the public will be aware of, and request, these services from their pharmacist.

Remuneration/Payment for Services

Community pharmacy revenues have traditionally been linked to the sale of prescription and nonprescription drugs, and other product purchases by patients and customers. As a result, the traditional focus of pharmacists' efforts on dispensing prescription drugs and counseling patients on nonprescription drug products have been congruent with the financial viability of the pharmacy business. As pharmacists increasingly adopt nondispensing patient care responsibilities, the business model of pharmacy practice must follow suit. To date, remuneration for clinical pharmacy care services by government and/or third-party payers beyond the dispensing of medications has been slow to develop, and inconsistent across services and jurisdictions (Houle et al., 2013, 2014a; Law et al., 2012). Fee amounts offered, when available, are set rather arbitrarily, as evidence to estimate actual costs incurred by pharmacies to provide these services, and to examine the cost-effectiveness of expanded scope interventions at the societal and individual patient levels, is generally lacking.

Remuneration decisions must consider not only the fee amount to be offered, but also: (1) whether fees should be based on the provision of the service regardless of actual time spent or outcome(s) achieved; or (2) if fees should be reflective of the time invested to provide care for each patient and/or the clinical effectiveness of the intervention in achieving health-related goals. Research comparing the effectiveness of different payment models such as fee-for-service, capitation, or pay-for-performance among physicians has produced mixed results (Houle et al., 2012), further complicating these decisions within the pharmacy profession. Initial research of performance-based payment for pharmacists suggests no impact (Houle et al., 2016). Furthermore, as many pharmacists are employed by licensed pharmacy businesses who provide the overhead within which the pharmacist operates, there is also debate around whether payments should be issued to the individual pharmacist(s) providing care, or the employer/company. Proponents for payment issued to individual providers feel this may reduce perceived pressure to perform services for the sake of profitability rather than patient need, and incentivize and reward individual pharmacists who provide these services. Proponents for payment issued to the employing organization feel this reduces competition among individual pharmacists and promotes collaboration, and is more consistent with business structures where staff pharmacists providing care are not owners of the business and therefore do not bear any of the operating expenses. As of the time of publication of this resource, the vast majority of programs currently provide remuneration for expanded scope services to the pharmacy/company, although some employers have enacted agreements where a proportion of each fee is redistributed to the individual who provided that service.

The introduction of payment for pharmacists' nondispensing services has also led to concerns about the potential conflict of interest associated with being both the prescriber and dispenser of a product, and receiving remuneration for each of these actions.

While not unique to pharmacy—it can be argued that a dentist prescribing an orthodontic appliance, for example, practices under the same potential conflict—the retail setting many pharmacists practice within may make this appear more pronounced. To reduce concerns about this conflict, it can be legislated that remuneration offered is for the assessment of the patient rather than the prescribing of a product (hence, payment is also received for the assessment even if it results in a decision to not use drug therapy or to refer to another health professional), and that patients issued a prescription by a pharmacist must have the ability to have that prescription dispensed from the pharmacy of their choice, even if it is not the same pharmacy where the expanded scope assessment was performed.

Access to, and Sharing of, Medical Records

While pharmacies have long maintained records of patients' medication histories, allergies, and other information relevant to the safe dispensing of medications, the documentation of detailed care plans, prescribing decisions by pharmacists, and the administration of injections is a recent addition to many pharmacy software programs. The added time required to complete this documentation related to expanded scope activities has already been addressed above.

The professional responsibility taken by the pharmacist associated with their decision to provide an expanded scope service requires more detailed patient information than standard dispensing records, in many cases. Unlike pharmacists who may practice in medical clinic or hospital settings, most community pharmacists lack direct access to the patient's complete medical chart. Information on diagnoses, laboratory test results, and goals of therapy established by the patient's physician or other primary care provider(s) may have to be requested directly from the other professional and communicated verbally, electronically, or via fax. The availability of this information by shared electronic medical record would be ideal, but is often delayed due to technological challenges and security concerns related with the sharing of patients' personal health information. In the absence of readily available medical records, pharmacists may feel unable to perform a particular expanded scope service due to the inability to fully assess its safety and appropriateness for the patient. While referral of the patient back to their primary care provider for this care may be in the patient's best interest, this may create a delay in accessing care that could have been prevented if this information was easily accessible by the pharmacist.

As discussed above, patients and other health professionals have expressed a desire for all members of the patient's healthcare team to be informed of any expanded scope activities provided (Donald et al., 2017). Indeed, the communication of these activities is often a required condition within the legislation authorizing that service to be performed by pharmacists. Pharmacists must therefore maintain detailed clinical records that not only are available for the pharmacist's reference, but also describe the action taken, the rationale for the decision made, and any required monitoring by other health professionals. Similar time investment and privacy implication concerns related to accessing patients' medical records also apply to the communication of these documents by pharmacists to other health professionals following the provision of an expanded scope service.

Efforts to streamline documentation through the use of standardized forms and the electronic sharing of records can be expected to improve the efficiency of this added responsibility. Pharmacists should aim to keep documentation concise and action-focused, clearly indicating which aspects of care they are taking responsibility for (such as monitoring for side effects after initiating a new therapy) and which aspects they are requesting collaboration with (such as the ordering of laboratory tests when outside the pharmacist's scope of practice to do so), to reduce the risk of care fragmentation and unintentional omissions when care for a mutual patient is shared across multiple professionals.

Concerns Related to Professional Liability

As pharmacists transition from recommendation-based to decision-based practices, they also adopt the professional liability associated with those decisions. Surveys of pharmacists have identified that concerns about errors or adverse events and their personal responsibility for those outcomes may impede the provision of expanded scope activities when there is perceived uncertainty or risk involved (Feehan et al., 2016; Maddox et al., 2016). As a result, pharmacists may choose to only perform these services in scenarios where there is low possible risk of an adverse outcome. However, it is rare that a healthcare decision presents with little to no risk, so this hesitation may result in few patients receiving the service. Pharmacists must also document their assessments, care decisions, and rationale in a way that ensures not only continuity of care, but also satisfies medicolegal requirements should an adverse outcome result.

Historically, many pharmacists were insured by their employer for any consequences related to errors in the dispensing process; however, many jurisdictions authorizing expanded scope services by pharmacists also mandate that the pharmacist holds personal liability insurance in addition to any insurance provided by their employer. Insurance specific to expanded scope services by pharmacists is therefore a relatively new addition to many professional insurance providers, and is being continually refined as the pharmacist's scope continues to expand. Pharmacists are encouraged to carefully review their insurance policies to ensure the protected actions included are consistent with their current service provision, and obtain legal advice for clarification as required.

Misunderstandings by other health professionals related to who retains professional liability for pharmacists' expanded scope activities have also been reported. Physicians and other prescribers have historically held sole responsibility for the outcome of prescribing decisions. Even when delegation of prescribing authorization to other health professionals has occurred by protocol, they have retained some responsibility for the outcome of that delegated prescribing. Some physicians and other prescribers have

expressed concern about potentially assuming some professional responsibility for a pharmacist's decision to make a pharmacotherapeutic decision for one of their patients. However, many jurisdictions that have enacted expanded scope legislation for pharmacists to date have very clearly specified that the pharmacist retains sole responsibility for the outcome of their actions. As such, adapting, renewing, prescribing, and the administration of injections by pharmacists are consistent with independent prescribing rather than delegated prescribing from a liability perspective.

Pharmacy regulatory bodies, advocacy organizations, and members of the profession are encouraged to make this responsibility for the outcome of the expanded scope decision clear to other health providers when communicating that an expanded scope service was provided. As the individual responsible for the outcome of that action, pharmacists must also perform monitoring and follow-up of patients to ensure the safety and effectiveness of the action taken. This may present a challenge when activities such as laboratory test ordering and interpretation are outside of a pharmacist's current scope or if physical assessment is required; however, effective collaboration with the other health professionals involved in the patient's care can ensure such follow-up is completed.

Practice Facilitation and Other Quality Improvement Strategies

Challenges experienced related to providing expanded scope services in pharmacy practice are highly individualized to each pharmacist and practice setting. Identifying these barriers and strategies to most successfully mitigate them requires both personal reflection and an objective analysis of the practice's space and workflow. Practice facilitation, also referred to as outreach, involves introducing a facilitator trained in change management to a professional practice, to provide assistance with identifying areas for improvement and implementing strategies to address them. As an external consultant for the practice, this individual applies both personal observation and information collected from interviews with staff members to create an individualized action plan to achieve a desired goal. While practice facilitation is a relatively new occurrence within pharmacy practice (Houle et al., 2017), it has demonstrated moderate effects on improving the adoption of evidence-based care in primary care medical practices (Baskerville et al., 2012).

Other strategies have been considered to improve the uptake and quality of pharmacists' expanded scope services, including audit and feedback, and pay-for-performance remuneration; however, little literature exists to date on the comparative effectiveness of these strategies in pharmacy practice.

Evidence Related to Expanded Scope Activities

A robust body of evidence exists showing clinical, economic, and humanistic benefits of nondispensing activities by pharmacists across a number of patient populations and disease states. However, most studies have focused on activities such as patient education, recommendation-based disease state management, and education of other health professionals, which are generally not considered to be expanded scope activities.

As the administration of injections by pharmacists was first introduced in the United States in the mid-1990s, the body of evidence for this expanded scope activity is the most established to date. The uptake of this service by pharmacists appears to be more rapid and significant than uptake of other expanded scope services. A number of factors may have contributed to this observation, such as the relatively technical and low-risk nature of administering an injection versus initiating a drug therapy, for example, or corporate and employer pressures to offer vaccination services to remain competitive in the community pharmacy sector. The uptake of this service by patients has also been noteworthy (Gai and Feng, 2017), although only modest improvements in overall population vaccination rates against influenza have been realized in a number of US states and Canadian provinces since the introduction of pharmacist-administered vaccination programs (Buchan et al., 2017). It is hypothesized that the increasing number of vaccinations administered in community pharmacies without a corresponding increase in the population vaccination rate represents a shifting of vaccine provision from medical and public health clinic settings to community pharmacies. Challenges remain with engaging individuals with vaccine hesitancy to improve overall population vaccination rates. The evidence also reports that pharmacist-administered injections are safe (Hattingh et al., 2016), with adverse event rates comparable to other settings where vaccines are administered. Patient satisfaction with these services has been rated as consistently high, with convenience and availability without an appointment cited as benefits unique to pharmacy-based vaccination programs (Hattingh et al., 2016; Papastergiou et al., 2014; Poulose et al., 2015). Patients have expressed some concern related to the lack of privacy available in many community pharmacies, as noted previously.

Pharmacist assessment and prescribing for minor ailments has also been evaluated. Results of pharmacy-based minor ailment programs have been generally positive, noting high patient satisfaction (Mansell et al., 2015; Taylor and Joubert, 2016), and more timely access to consultations from pharmacies than from medical clinics. Concerns over the lack of private spaces for consultations in some pharmacies have been voiced, and many patients lack awareness of both the availability of these services from their community pharmacist, and the pharmacist's level of knowledge and training related to minor ailment assessment and management. Surveys of patients receiving minor ailment consultations from pharmacists have reported that a high proportion of those patients would have visited a medical clinic for care had the pharmacy not been available to provide the service (Baqir et al., 2011;

Mansell et al., 2015), suggesting cost-savings to the health system, as care provided in pharmacies is often less expensive than that provided in other primary care settings (Rafferty et al., 2017).

Research on protocol-based prescribing by pharmacists in areas such as travel medicine (Durham et al., 2011; Hess et al., 2010; Tran et al., 2015) and anticoagulation (Zhou et al., 2016) has also identified high patient satisfaction and adherence to therapy. High patient satisfaction was also reported following a pharmacist prescribing in surgical preadmission clinics and sexual health clinics (Hale et al., 2016). A pharmacist prescribing in a US pain clinic was also found to be clinically effective and cost-effective (Dole et al., 2007). However, most evidence on independent prescribing by pharmacists (in other words, prescribing without a protocol) has been generated for chronic disease management. Trials of pharmacist prescribing for the management of diabetes (Al Hamarneh et al., 2013), hypertension (Tsuyuki et al., 2015), and dyslipidemia (Tsuyuki et al., 2016) have been conducted in Canada with results showing improvement in surrogate outcome measures such as blood pressure, lipid levels, and hemoglobin A1c, and the proportion of patients on guideline-adherent drugs for primary and secondary prevention of cardiovascular disease. Research evaluating the effectiveness of pharmacist prescribing on hard outcomes such as heart attack, stroke, and heart failure incidence remains to be conducted.

Next Stages in the Evolving Roles for Pharmacists

Expanded scope activities such as the adaptation and renewal of prescriptions, initiation of therapy, and administration of injections are expected to solidify the pharmacist's position among healthcare professionals as the drug therapy expert—allowing them to take greater responsibility for timely and effective patient access to needed drugs and vaccines. This application of pharmacists' expertise in a way that is visible and tangible to patients can be expected to enhance the public's awareness of the pharmacist as a primary care provider, and increase public demand for these services. However, great variation in expanded scope legislation among countries and at the state/provincial level has led to an inconsistent definition of what a pharmacist does, and which services patients can expect to receive from their pharmacist. Restrictions currently in place in many regions limiting pharmacists' expanded scope activities to certain patient populations, disease states, or specific products create inequities regarding patient access to these services and hinder pharmacists' ability to provide holistic care for a patient considering all of their healthcare needs and comorbidities.

Evolution of these services should therefore aim to optimize the breadth and depth of care that can be provided under this expanded scope. Minimization of the use of protocol-restricted prescribing and expansion in the use of electronic medical records that can be easily shared among clinicians will allow pharmacists to best tailor medication therapy to an individual patient's needs. The ability to order and interpret laboratory tests and perform basic physical assessment should be integrated into the scope of practice for pharmacists, and into pharmacy training (for both new graduates and as continuing education for current pharmacists), as required components to effectively monitor the safety and efficacy of expanded scope actions. It should be stressed that these physical assessment skills are not intended to replace assessment and diagnosis by physicians and other health professionals with diagnostic expertise, but should be focused on skills specific to monitoring a patient's response to a drug therapy after the diagnosis has been established. The ability to collaborate with, and refer patients to, physicians or other healthcare professionals for additional assessment and diagnosis will remain an important part of pharmacy practice.

Consistent with the ability to order and interpret laboratory tests, the greater adoption of point-of-care testing technologies is expected to occur in the pharmacy profession. These technologies, which allow for physical assessment measures to be taken, or blood or urine samples to be collected at the pharmacy and rapidly analyzed for screening and monitoring purposes, are described in Chapter 414 of this encyclopedia. Pharmacies will increasingly employ point-of-care testing to perform population screening for chronic and acute diseases for further assessment and diagnosis, or to monitor and subsequently adapt prescription drug orders (for example, performing point-of-care international normalized ratio (INR) testing and warfarin dose adjustment). The accessibility of pharmacies both geographically and due to extended operating hours enables pharmacists to interact with individuals who may otherwise not regularly access the health system. Building upon the success of pharmacy-based influenza vaccination programs, other pharmacy-based public health outreach initiatives such as needle exchange programs, safe medication disposal drop-off, smoking cessation clinics, and the distribution of at-home screening kits for colon cancer and HIV can be expected to increase in popularity.

Developments in the field of pharmacogenomics/pharmacogenetics (discussed in Chapter 417) are also expected to further expand the role of pharmacists related to the tailoring of drug therapy based on a patient's genetic profile. Finally, as pharmacists seek to further their knowledge and skills related to therapeutic areas of personal interest and of relevance to their patient population, the future of pharmacy is likely to demonstrate increased specialization in pharmacy practice, where some pharmacists practice to their fullest scope including patient assessment and prescribing but in a limited field that they possess specialized knowledge in. Menopause symptom management, pretravel consultations, and anticoagulation are examples of specialized pharmacist-led practices achievable under an expanded scope. Ultimately, collaboration between pharmacists and other health professionals is expected to be enhanced as pharmacists increasingly demonstrate their added value to the multidisciplinary team. Further experience with, and evidence to support, expanded scope activities will create countless additional opportunities for pharmacists to improve health outcomes through optimizing medication use, as this professional evolution continues.

Glossary

Adapt The decision, by a pharmacist, to modify an existing order for a prescription drug from a prescriber to account for patient-specific considerations or to correct prescribing errors. Examples of adapting may include modification of the dosage of the medication due to a patient's impaired hepatic or renal function or age, or modification of the route of administration of a drug from an oral to parenteral route due to swallowing difficulties. Adapting may also consider modifying the dosing regimen or duration of therapy for improved patient adherence or consistency with clinical practice guideline recommendations for a certain indication.

Capitation Payment model where the provider is paid a set amount per patient to provide care over a specified time. Patients are usually allocated to only 1 practitioner or clinic that must provide all necessary care out of the set payment provided for that patient.

Case finding The proactive consideration of patient demographics, risk factors, or symptoms to identify individuals who may benefit from a specific test or intervention.

Expanded scope Activities performed by pharmacists in the patient care process beyond those involved in routine dispensing and medication profile/chart review, often requiring decision-making and action by the pharmacist. These activities may include, but are not limited to, renewing and adapting prescription orders, prescribing drug therapy, ordering and interpreting laboratory tests, and administering drugs and vaccines by injection.

Fee-for-service Payment model where the provider is paid a set fee amount for each service delivered, with different services reimbursed at different rates depending on their complexity, time investment generally required, or other factors.

Pay-for-performance Any compensation system that links pay amounts for providers to the quality of care provided and/or outcomes achieved as a result.

Practice facilitation The involvement of a skilled individual to assist practices with identifying areas for improvement, implementing strategies, and monitoring the impact of these strategies toward attaining a particular goal.

Renew The decision, by a pharmacist, to extend an existing order for a prescription drug from a prescriber for an additional duration of time beyond what was specified in the order. This is done to ensure continuity of therapy until the patient is able to see the prescriber for further assessment and renewal of the order, as appropriate.

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Professional Pharmacy Services

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Learning Objectives

By the end of this chapter, the reader will be able to:

1. Define professional pharmacy services.
2. Discuss the origin of related terms including:
   a. Clinical pharmacy
   b. Pharmaceutical care
   c. Cognitive pharmacy services
3. Describe seven categories of professional pharmacy services and list examples within each category.
4. Highlight factors impacting implementation of professional pharmacy services in community pharmacies.

Introduction

Pharmacists in diverse practice settings across the world use a variety of terms to describe their approach to practice, as well as their daily activities. Readers have likely encountered terms, including clinical pharmacy, pharmaceutical care, and cognitive (pharmacy)

services, to describe this concept, yet each of these terms has its own origin and particular nuances. Starting from what we hope is shared common ground, as a profession, pharmacists strive to partner with patients and other health providers to optimize medication therapy, and their patient's health in a broader sense, in pursuit of the best possible outcomes for patients while stewarding the use of health system resources.

Defining Professional Pharmacy Services

In this chapter, we focus on professional pharmacy services (PPS), a term that describes services offered by pharmacists and their teams in community settings. PPS are "an action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population or other health professional, to optimize the process of care with the aim to improve health outcomes and the value of health care (Moullin et al., 2013)." Drawn from Donebedian's framework, the definition includes the structure, process, and outcome of pharmacy services. The term was developed to fill an important gap. Prior to its introduction, there was no consensus term to describe the entire package of health-focused services offered in community pharmacies.

Highlighted below are some of the fundamental components of the definition of PPS (Moullin et al., 2013):

1. Unlike other terms, which limit their scope to services offered by pharmacists, this definition focuses on all services provided by pharmacies. PPS can be provided by pharmacists but also by other care providers who possess unique health expertise, including regulated pharmacy technicians, nurses, or dietitians.
2. PPS may involve provision of care to patients directly or indirectly. For example, medication information provided to another health provider or participation in interprofessional discussions about patient care both fall within the definition.
3. The term applies exclusively to services conducted in community settings, that is, within or in partnership with a community pharmacy.

For further discussion about the rationale for all components of the definition of PPS, readers are encouraged to review the publication by Moullin et al. (Moullin et al., 2013).

Three criteria guide whether a service is considered PPS or its counterpart, a nonprofessional service. These are:

1. PPS require the use of specialized health knowledge possessed by health care professionals.
2. PPS focus on optimizing the processes of patient care.
3. PPS are concerned with "improving health outcomes and the value of health care (Moullin et al., 2013)."

To better elucidate the difference between PPS and a nonprofessional service, consider the following examples. Evaluating the therapeutic appropriateness of a prescription order and dispensing this medication to a particular patient satisfies these criteria and would be considered a PPS. Conversely, delivering a prescription medication to a patient's home does not involve the application of a health care professional's specialized health knowledge and, as such, would be considered a nonprofessional service.

Summary

PPS are "an action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population, or other health professional, to optimize the process of care with the aim to improve health outcomes and the value of health care (Moullin et al., 2013)." The term professional pharmacy service will be used throughout the remainder of this chapter and shapes the content herein.

Related Terminology

Several terms exist to describe similar phenomena with respect to pharmacy services. Many have multiple definitions as they have been developed iteratively and some have origins within particular jurisdictions (e.g., medication therapy management in the United States). In this section of this chapter, we highlight three additional terms with which we believe "professional pharmacy services" are most closely linked. Readers are encouraged to review **Table 1** for a more comprehensive list of other associated terms.

To understand how these terms are linked, it is useful to briefly explain their origins. Historically, the role of pharmacists focused on using their expert knowledge about how best to combine drug ingredients to prepare and fill prescriptions for patients. In many jurisdictions (e.g., North America, the United Kingdom, Australia) by the 1960s, due to the growth of the pharmaceutical industry and industrial manufacturing of medications, it had become evident that pharmacists would need to expand their practices to find new ways to contribute their expertise to enhance care and add value for patients and the health care system. Thought leaders called for the reprofessionalization of pharmacy: "a process of occupational reconstruction and self-renewal (Hepler, 1988)." These tensions were not confined to pharmacists practicing in a particular setting (e.g., community, institutions, and so on) but rather rippled across the profession.

Table 1 Related terms

Terms	*Definition(s)*	*Comments*
Clinical pharmacy services	American College of Clinical Pharmacy: Services in which "pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention" in all health care settings. Emphasizes direct patient care (American College of Clinical Pharmacy, 2008) European Society of Clinical Pharmacy: Services of the "clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices." Encompasses all services performed by pharmacists practicing in any setting; applicable to direct patient, as well as population health care (Hepler, 2004)	A broad term that can be used to describe all functions of a pharmacist in all practice environments. Key differences noted between jurisdictions.
Cognitive (pharmacy/ pharmaceutical) services	"Any activity in which pharmacists would use their professional knowledge and abilities to improve pharmacotherapy and disease management by means of interacting with the patient or other health care professionals (Cipolle et al., 1998)" "Those services provided by a pharmacist or for a patient or health care professional that are either judgmental or educational in nature, rather than technical or informational (Cognitive Services Working Group, 1989)"	Nondispensing functions performed by pharmacists, including those that do not directly involve the patient.
Medication therapy management	"A service or group of services that optimize therapeutic outcomes for individual patients. Medication therapy management services include medication therapy reviews, pharmacotherapy consults, anticoagulation management, immunizations, health and wellness programs, and many other clinical services. Pharmacists provide medication therapy management to help patients get the best benefits from their medications by actively managing drug therapy and by identifying, preventing, and resolving medication-related problems (American Pharmacists Association, 2012)"	Term originates from the United States.
Medicines optimization	"A person-centered approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines. Medicines optimization applies to people who may or may not take their medicines effectively. Shared decision-making is an essential part of evidence-based medicine, seeking to use the best available evidence to guide decisions about the care of the individual patient, taking into account their needs, preferences, and values (Cutler et al., 2011)"	Term originates from the United Kingdom.
Pharmaceutical care	"The Pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes (Allemann et al., 2014)" "A professional patient care practice, which, when provided as an organized service, is experienced, documented, evaluated, and paid for as medication management services (Cipolle et al., 2012)" "Specialized knowledge [provided] by pharmacists for the patient or health care professionals for purpose of promoting effective and safe drug therapy (Cipolle et al., 1998)" "Includes the determination of the drug needs for a given individual and the provision not only of the drugs required but also of the necessary services (before, during, or after treatment) to assure optimally safe and effective therapy. It includes a feedback mechanism of care by those who provide it (Brodie et al., 1980)"	This term is used to describe nondispensing, direct patient care roles performed by pharmacists.
Professional pharmacy services	"An action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population, or other health professional, to optimize the process of care with the aim to improve health outcomes and the value of health care (Moullin et al., 2013)"	Similar in scope to cognitive services, but includes health professionals other than pharmacists and is limited to the functions that are performed in association with community pharmacies.

Clinical Pharmacy

Over time, the pharmacist profession was reenvisioned as a clinically focused health specialty, commonly referred to as clinical pharmacy. Throughout the 1980s and 1990s, many pharmacists, particularly in institutional settings, adopted the term to describe their activities. The European Society of Clinical Pharmacy defines clinical pharmacy as a "health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices." It encompasses "all services performed by pharmacists practicing in hospitals, community pharmacies, nursing homes, home-based care services, clinics, and any other setting where medicines are prescribed and used." The term "clinical" refers to activities that impact the health of patients at both an individual and population level. Some argue that this definition is unnecessarily limiting in its focus on medication use. Another definition, from the American College of Clinical Pharmacy, defines clinical pharmacy as "a health science discipline in which pharmacists provide direct patient care that optimizes medication therapy and promotes health, wellness, and disease prevention (American College of Clinical Pharmacy, 2008)" in all health care settings. Some contend that this definition's focus on direct patient care is too limited because it precludes population level services.

Pharmaceutical Care

A chapter about professional pharmacy services would be incomplete without mention of pharmaceutical care. The earliest use of the term described pharmaceutical care as: "the care that a given patient requires and receives, which assures safe and rational drug usage (Mikeal et al., 1975)." Another definition was introduced in 1980, pharmaceutical care: "includes the determination of the drugs needs for a given individual and the provision not only of the drug required but also the necessary services to assure optimally safe and effective therapy (Brodie et al., 1980)." While other refinements to the definition were proposed through the 1970–80s the most notable revision appeared in 1990, as put forward by Hepler and Strand: "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life (Hepler and Strand, 1990)." The concept included both "drug-product control and clinical pharmacy services (Hepler, 1988)." The International Pharmaceutical Federation endorsed the Hepler and Strand definition in 1998 though amended the definition to emphasize that outcomes should improve or maintain a patient's quality of life (Wiedenmayer et al., 2006).

Further refinements and clarifications about pharmaceutical care have been put forward by both American and European groups. Most recently, the Pharmaceutical Care Network of Europe in 2013 defined pharmaceutical care as "the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes (Allemann et al., 2014)." Common across all of the definitions, pharmaceutical care refers to pharmacist services provided to individual patients that seek to optimize health outcomes related to medication therapy. Readers interested in a more in-depth exploration of the many definitions of pharmaceutical care are referred to resources created by the Pharmaceutical Care Network of Europe (Allemann et al., 2014).

Cognitive Services

Cognitive services are closely linked with those provided as a part of pharmaceutical care. In 1998, within the first edition of their foundational textbook about pharmaceutical care, Cipolle et al. defined cognitive services as "any activity in which the pharmacists would use their professional knowledge and abilities to improve pharmacotherapy and disease management by means of interacting with the patient or with other health professionals (Cipolle et al., 1998)." Interestingly, the term does not appear in subsequent editions of the text, which is consistent with the trend toward its declining use in the United States by the late 2000s.

"Cognitive service" was coined by D'Achille and coworkers (1989) as "those services provided by a pharmacist or for a patient or health care professional that are either judgmental or educational in nature, rather than technical or informational (Cognitive Pharmacy Services Working Group, 1989)." A revised definition was soon presented that explicitly included the provision of technical information as part of cognitive services (Martin, 1990). Examples of services included under the umbrella of cognitive services were patient education programs, counseling about medical conditions, and monitoring drug levels. Note that these early definitions of cognitive services did not link them to a particular practice setting, such as community pharmacies, as pharmacists in many settings were being called upon to transform their roles. Additionally, while both of these early definitions detail the actions or activities with patients or other health providers as the recipients, they lack a description of the intended outcomes of the services.

The list of services that could be described as cognitive services continued to evolve throughout the 1990s, as did efforts to articulate target outcomes of the services. Further complicating efforts to define the term, some authors refer to cognitive services as cognitive pharmacy or pharmaceutical or pharmacist services (Roberts et al., 2006).

The breadth of the definition is noteworthy. Cognitive services are neither constrained to interventions regarding medications nor are they solely concerned with outcomes involving medications (e.g., adherence or side effects). Instead, the term was intended to be more holistic, such that cognitive services encompassed all activities performed by pharmacists (and pharmacy teams) that focused on improving health outcomes for patients.

We appreciate the need for a term to describe emerging services offered by pharmacists and their teams beyond those connected with providing medications to patients. However, we feel that wide-scale use of the "cognitive pharmaceutical/pharmacy/pharmacist services" may be considered suboptimal for at least two reasons.

First, some argue that use of the word "cognitive" inadvertently denigrates services excluded from its definition. It implies that other services rendered by pharmacists or in pharmacies, such as dispensing or compounding of medications, do not require cognitive ability or effort. We know this to be untrue, as processes involved in these services, for example, verifying filled prescriptions for therapeutic appropriateness, are not only vital for patient safety, but are cognitively demanding as well.

Second, there is controversy about whether the term 'pharmacy', 'pharmacist', or 'pharmaceutical' should be used. While seemingly subtle in their differences at the outset, consider the following: "pharmaceutical," in the eyes of some, ties the services unnecessarily to a product. "Pharmacist" may be too limiting as it excludes the contributions of pharmacy team members like pharmacy technicians who provide patient care services (e.g., glucometer teaching, best possible medication history gathering) in some countries. "Pharmacy" may not be optimal either. Advocates for "pharmacy" contend that this is the broadest and thus most inclusive term. However, others are concerned that pharmacy will be interpreted by some to mean "pharmacy" as a physical location, such as a community pharmacy, and may not be inclusive of coworkers practicing in other sites, including hospitals and clinics. The authors of this chapter do not have a resolution for these controversies. As such, our leaning is to instead endorse the term "professional pharmacy service" (Moullin et al., 2013).

Summary

Clinical pharmacy, pharmaceutical care, and cognitive services are terms that have been presented in pharmacy discourse as synonyms for professional pharmacy services. Each term has its own origins, evolution, and finer points of distinction with respect to definitions. A globally accepted consensus-based lexicon for the profession would be useful in many applications. However, we expect that all of these terms will continue to be used within different countries. Our hope is that by articulating these nuances, readers will be better equipped to choose terms that best match their intentions.

Examples of Professional Pharmacy Services

Let us now turn our attention to further appreciating the breadth of professional pharmacy services offered by community pharmacists and their teams across the world. One could quickly become overwhelmed trying to list every service that could fall within this umbrella. Instead, we present categories of services that fall under the PPS umbrella and provide examples within them.

In their paper introducing PPS, Moulin et al. propose two broad categories for PPS, including pharmaceutical services (i.e., those relating to medication therapy) and other health care services (i.e., services not considered directly medication-related, e.g., health promotion). For readers new to the topic of PPS, we felt that a more detailed schema would be helpful. However, when preparing this chapter, we did not identify a single unifying taxonomy for the services that provided the depth we sought. Closest was a scheme proposed by Rotta and coworkers (2015) in their review of systematic reviews of clinical pharmacy services which featured seven categories that we adapted to fit the community pharmacy lens of professional pharmacy services. Most of these categories are consistent with the pharmaceutical services subtype of PPS in the model proposed by Moullin et al. Admittedly, these "categories" may not be comprehensive or all inclusive. As the profession continues to evolve into new avenues, so too will the categories and examples of services within each category.

Patient Education and Counseling (With or Without Medication Dispensing)

Educating patients about their health conditions and the roles for medication as part of their management is a central component of clinical pharmacy practice. Many jurisdictions mandate that pharmacists "counsel" patients (i.e., provide them with information about how a medication works, its intended benefits and potential risks) when a new prescription is dispensed. There are countless studies exploring the nuances of the optimal content, context, and setting in which these interactions between patients and pharmacists are ideally situated. Just as the nature of these interactions with patients are highly valued, so too are the outcomes associated with these activities.

In a systematic review of pharmacy services in low to middle income countries, Pande et al. (2013) found that low to moderate quality evidence from middle income countries suggested many benefits when pharmacists provided education and counseling to people living with chronic conditions (Pande et al., 2013). These included small improvements in health outcomes (including blood pressure and glycemic control) and quality of life, reduced use of health services, and potentially lower medication costs.

Medication Reconciliation

Medication reconciliation is a structured process that begins with interviewing patients and their caregivers to gather a comprehensive medication history. The information gathered through the history-taking process is then verified against other information sources (e.g., prescription vials, pharmacy dispensing records). The health care professional conducting medication reconciliation then takes responsibility for identifying and resolving any discrepancies between information sources. Lastly, a best possible medication history (i.e., a list of reconciled medications) is compiled and shared with the patient and other care providers.

In the institutional setting, medication reconciliation reduces medication discrepancies, adverse drug events, and can lead to detection of drug-therapy problems but impact on readmissions following hospital discharge, length of stay, and mortality is less clear (Kwan et al., 2013; Lehnbom et al., 2014; Mueller et al., 2012). When medication reconciliation is conducted by pharmacists at the time of discharge, reductions in emergency room visits and readmissions are reported (Mekonnen et al., 2016). Improved identification and resolution of discrepancies has also been found when community pharmacists conduct medication reconciliation following hospital discharge, though studies are generally found to be at moderate to high risk of bias and have not examined clinical or health system outcomes (McNab et al., 2018).

Medication Therapy Assessment

Coupled with medication monitoring, assessment services are best envisioned as those aligned with the provision of pharmaceutical care. After medication reconciliation is conducted, pharmacists use their knowledge and skills to assess patients' medications (as they appear on the best possible medication history) to ensure all are indicated, effective, safe and convenient (includes adherence and cost considerations). The names for these services and their exact components vary by jurisdiction and evolve over time. For example, in the United States, medication therapy management is commonly discussed. In Australia, pharmacists are remunerated for conducting home medicines reviews and in New Zealand Medication Use Review (MUR) and

Adherence Support services are offered (Jokanovic et al., 2016). Within the United Kingdom, community pharmacies in England and Wales are remunerated for medicines use reviews while a similar service, the chronic medication service, is remunerated in Scotland (Blenkinsopp et al., 2012).

A detailed review of the evidence at the level of primary studies exploring the impact of medication therapy assessment conducted in community settings on outcomes is beyond the scope of this chapter. An overview of systematic reviews explored clinical, humanistic, and economic outcomes associated with medication review services based on 31 prior systematic reviews of moderate to high quality (Jokanovic et al., 2016). Clinical outcomes (including those associated with medication management; blood pressure, glycemic, and lipid control) were most commonly reported across the reviews and on the whole, reported favorable outcomes. Humanistic outcomes, including medication adherence, quality of life, and patient satisfaction were reported by at least half of the reviews, also with generally favorable outcomes. The impact of medication therapy assessment and monitoring by pharmacists on health care costs were least well explored.

Medication Therapy Monitoring and Follow Up

Monitoring patient outcomes associated with medication therapy recommendations is a key responsibility of pharmacists who accept responsibility for providing pharmaceutical care to patients. Following up with patients about their experiences with changes to their medication therapy allows pharmacists to determine whether their recommendations had the intended positive impact on their patients. This may occur by monitoring therapeutic drug levels, laboratory tests, or discussing expected improvements in signs and symptoms associated with underlying health conditions.

Prescribing

Prescribing is "an iterative process involving the steps of information gathering, clinical decision making, communication, and evaluation, which results in the initiation, continuation, or cessation of a medicine (Weeks et al., 2016)." Pharmacists currently have the legal authority to prescribe medications in a number of jurisdictions, including the United Kingdom, New Zealand, Israel, the United States, and Canada (Hoti et al., 2011; Tonna et al., 2007; Yariv, 2015).

A more fulsome discussion about models of pharmacist prescribing (i.e., independent, dependent, supplementary models, and so on) can be found in Chapter 708: Prescribing. For this discussion, as outlined in the definition provided above, pharmacist prescribing can be thought of as pertaining to three key areas: initiation, management, and cessation of medications.

Initiation of Medications

The decision to prescribe a medication generally follows completion of an assessment by the prescribing health provider. Initiation occurs when a new medication (or one not currently being taken by a patient) is ordered to treat signs and symptoms associated with a particular diagnosis, slow or avoid the progression of a medical condition, or prevent sequelae related to a clinical indication.

Management of Medications

This involves prescribing to ensure continuity of therapy (i.e., renewing or refilling a medication) or changing the dose, route, or formulation of an already prescribed medication (known in some jurisdictions as adapting a prescription).

Cessation

The importance of deprescribing, "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes (Reeve et al., 2015)" is gaining attention globally as one strategy for addressing the complex problem of harm related to use of potentially inappropriate medications. Given their expertise in medication management, many argue that pharmacists are well suited to help patients and other health professionals deprescribe medications.

As the number of jurisdictions with pharmacist prescriptive authority continues to grow, so does the need to evaluate the impact of these services on health outcomes. A Cochrane systematic review included pharmacist prescribing when examining the outcomes associated with medical and nonmedical prescribing on acute and chronic disease management across 46 studies, most of which focused on ambulatory settings (defined by the authors as primary care clinics, medical centers, general practices, hospital outpatient clinics, and community pharmacies) (Weeks et al., 2016). The authors concluded that nonmedical prescribers were comparable to medical prescribers for the management of high blood pressure, hemoglobin A1c for diabetes, high levels of low density lipoprotein cholesterol, adverse drug events, patient adherence to medication regimens, patient satisfaction with care, and health-related quality of life. Note though that the certainty of evidence for all outcomes, except hemoglobin A1c, was rated as moderate or low for varying reasons. For example, the certainty of evidence for blood pressure and lipids outcomes was downgraded to moderate due to considerable statistical heterogeneity and differences in prescribing models, settings (community pharmacies versus primary care settings), and scope of prescribing (initiating versus changing doses). Also, the review did not differentiate between studies featuring nurse and pharmacist prescribing for the purposes of reporting outcomes. As such, the impact of community pharmacist prescribing on outcomes, outside the context of individual randomized controlled trials, is still to be determined.

Randomized controlled trials (RCTs) of interventions featuring prescribing by pharmacists in community settings in Alberta, Canada suggest favorable impacts on glycemic and blood pressure control, achievement of lipid targets, and cardiovascular risk

reduction (Al Hamarneh et al., 2013; Tsuyuki et al., 2015, 2016). How well these interventions translate into real-world practice without the ongoing supports offered in the context of RCTs and whether these interventions lead to long-term impacts on outcomes, including mortality and health system use, are yet to be determined.

Information Provision

Rotta et al. (2015) describes this service as provision of information about medication or medical conditions by the pharmacist to other members of the health care team. In certain jurisdictions, this happens routinely in institutional settings through activities such as interprofessional team discussions and development of clinical protocols. There are examples, though, of health care professionals connected to community pharmacies participating in these activities while providing clients, for example, those receiving home care services or residing in hospices, with health and pharmaceutical information. Another opportunity in this realm involves academic detailing (Jin et al., 2012).

Detection, Prevention, or Control of Risk Factors

Increasing global attention is focusing upon opportunities for pharmacists' roles as public health providers. For those keeping track, this category of PPS services would fall into "other health care services" in the context of Moulin's model.

Health Promotion and Preventative Care

Health promotion occurs when pharmacists partner with patients to modify their health behavior to minimize the risk of disease and promote healthy living. Examples of associated services include (but are not limited to) supporting patients with smoking cessation, body weight management, and cardiovascular risk reduction. A 2016 systematic review explored the effectiveness of community pharmacy-delivered interventions in reduction of alcohol consumption, smoking cessation, and weight management (Brown et al., 2016). There was insufficient evidence to draw conclusions about alcohol reduction but the authors did find that community pharmacy-delivered interventions for smoking cessation are effective and cost-effective when compared with usual care. Despite heterogeneity across interventions types, community pharmacy interventions were reported to be as effective as other short-term primary care-based interventions for weight management with similar costs to comparators.

Immunization

Another public health role for pharmacists is connected with immunization. Pharmacists in Canada, Ireland, Portugal, the United Kingdom, and the United States can administer vaccines as a part of their scope of practice. In other countries, pharmacists may not administer vaccines themselves but serve as facilitators (i.e., by hosting other health professionals authorized to administer vaccines with the goal of enhancing patient access) or educators (i.e., providing education or recommending vaccination) about the importance of vaccination. Based on a systematic review of 36 studies, pharmacist involvement with vaccination, regardless of their role (as facilitators, educators, or administrators) or vaccination involved (influenza, pneumococcal), increased uptake of immunizations (Isenor et al., 2016).

Screening, Detecting, or Monitoring Disease

Another area of expansion for pharmacists' roles in community pharmacies involves screening for detecting and monitoring disease. Well known examples involve screening for hypertension (Kaczorowski et al., 2011), osteoporosis (Goode et al., 2004; Yuksel et al., 2010), cardiovascular disease, and diabetes (Willis et al., 2014). This may involve the use of point of care testing (laboratory testing done within the pharmacy), for example, glycemic control (blood glucose or hemoglobin A1c) (Saldarriaga et al., 2017), lipids (Haggerty and Tran, 2017), or rapid diagnostic testing for infectious diseases including HIV (Weidle et al., 2014), influenza, and group A streptococcus (Klepser et al., 2018). It may also involve use of evolving technology, for example, handheld ECG-devices for detection of atrial fibrillation (Sandhu et al., 2016).

Summary

Professional pharmacy services can be envisioned as consisting of seven categories beyond medication dispensing. Within Moullin's model of PPS, six of these (i.e., patient education and counseling, medication reconciliation, medication therapy assessment, monitoring and follow-up, prescribing, information provision) would be considered pharmaceutical services and one (i.e., services associated with detecting, screening for and preventing risk factors) would fall within other health services.

Implementation of Professional Pharmacy Services

Despite policy changes in recent years that have allowed pharmacists in numerous countries to start offering their patients a variety of professional pharmacy services (PPS), uptake of these services by pharmacists has been slower than expected in most jurisdictions. Implementation of these types of services is an intricate process—one that is often overlooked after new regulations allow them to be delivered by pharmacies. This oversight stems from an assumption that by granting expansions to

pharmacists' scopes of practice and providing general guidelines for their delivery, a practice change and widespread uptake of these services will be observable shortly thereafter (Roberts et al., 2006). This assumption disregards the manifold factors that govern pharmacy's position within the health care system and hold influence over the implementation of change to the profession's practice.

Considerable research has been conducted, primarily through semistructured interviews and focus groups with various stakeholders in community pharmacy, to tease out ways in which the implementation of PPS are enabled or inhibited (Luetsch, 2017). These "enablers and inhibitors of practice change" are frequently referred to in the literature as barriers and facilitators, but as many of these factors exist on continua (e.g., a community pharmacy can be oriented as a profitable business, a health care organization, or anywhere in between) or are binary in nature (e.g., presence or absence of private counseling area within pharmacy), this chapter will refer to each as a determinant of practice (Flottorp et al., 2013).

It is useful to categorize determinants of practice to further describe and conceptualize the magnitude and location of their impact on implementation of change in pharmacy practice. Again, several frameworks have been proposed to guide this categorization, but this chapter has chosen to ascribe each determinant of practice to one of the following levels: individual, interpersonal, organizational, or health care system. These categories are an adaptation of those first presented by Hossain et al. (2017), and best describe both the determinants of practice and where to target interventions aimed at addressing them (Hossain et al., 2017a). Of course, real world application of such organized thinking rarely allows for tidy categorization. Thus, some of the determinants of practice discussed in this chapter are connected to, and influenced by, one another across levels of our framework.

Individual Determinants

Determinants of practice that exist on an individual level are those that involve the beliefs, abilities, and characteristics of any person-possessing agency in the implementation of PPS in practice. These focus primarily on the characteristics of individual pharmacists, but also extend to those of patients, physicians, and other health care providers, and people involved in shaping health care policy. One of the most commonly identified individual-level determinants of practice is a pharmacist's attitude toward a particular PPS (Luetsch, 2017; Roberts et al., 2006). This has been demonstrated in both positive and negative capacities. Some pharmacists sincerely believe in the benefit that a PPS is providing to their patients or to the health care system, and are more likely to incorporate it into their practice; other pharmacists harbor doubt surrounding the PPS's value and are therefore less likely to invest the effort required to offer it to their patients. Identifying at least one staff pharmacist who is enthusiastic about the utility of a PPS to help lead its implementation in a pharmacy has been suggested as a potential way to overcome apathy and negative perceptions of it among other pharmacy staff (Roberts et al., 2006). Of course, having pharmacists who wish to provide the PPS under their own volition will likely result in more sustained and engaged participation, which is why demonstrating the benefits of a PPS can also be a useful intervention to improve the attitudes of pharmacists while implementing a PPS (Gastelurrutia et al., 2009). Typically, prior to initiation of a PPS on a large scale there are pilot studies and controlled trials that investigate the PPS's value and generate objective data supporting its utility. This information can be leveraged to persuade pharmacists and other frontline staff of the quality of a PPS and the importance of its uptake.

Two related determinants of practice also attributed to an individual pharmacist are the pharmacist's competence in providing a given PPS, as well as their confidence in doing so (Hopp et al., 2005; Luetsch, 2017; Roberts et al., 2006). If pharmacists lack the ability to competently provide a PPS then the service may not achieve its desired effect even if it is performed (e.g., a pharmacist conducting an incomplete medication review may overlook crucial drug therapy problems). If pharmacists lack confidence in their own ability to provide a PPS, then they may be unwilling to offer a potentially beneficial service to their patients. Similarly, the attitudes of physicians and patients about the service, as well as their opinions of pharmacists' competency, influence their willingness to refer to or participate in the service being offered (Hossain et al., 2017a; Hossain et al., 2017b). Qualitative interviews conducted with community pharmacists and physicians in Indonesia, for example, revealed discordance between the two groups of health care providers: all pharmacists included in the interviews believed that they should offer additional services beyond medication dispensing, while the majority of physicians interviewed felt that pharmacists' roles should extend no further into patient care (Wibowo et al., 2016). Interestingly, there was more agreement between the pharmacists and physicians regarding the competence of the pharmacists in providing patient care: neither group exhibited confidence in pharmacists possessing the requisite clinical knowledge for a greater role in health care delivery. This phenomenon is demonstrative of the fact that pharmacists often have the attitudes required to support the delivery of PPS in that they are willing. However, a positive attitude is sometimes not enough to overcome some of the other barriers that may impede the uptake of a PPS.

Pharmacist training, then, can be an important part of the implementation process for PPS (Feletto et al., 2010; Hopp et al., 2005; Hossain et al., 2017a; Luetsch, 2017; Wibowo et al., 2016). Numerous studies involving didactic and interactive educational sessions delivered to pharmacists in preparation for their positions in the delivery of a PPS suggest that this training helps to improve the uptake and implementation of the PPS. These educational sessions often focus on the diagnosis and treatment of specific disease states, up-to-date treatment guidelines, and clinical skills such as problem solving and communication (Patwardhan et al., 2014). Continuing education credits or other incentives were sometimes awarded to increase participation in these sessions, which were most effective when facilitated by clinical pharmacists who were not affiliated with the practice sites where the PPS was being implemented. The need for ongoing support and training was highlighted in a number of studies as an integral feature of interventions that resulted in more sustained uptake and implementation of the PPS (Roberts et al., 2006).

These individual-level determinants of practice are closely tied in with both physicians' and patients' perceptions of the role of pharmacists within the health care system, which are related to how the scope of practice for pharmacists has evolved over time. Some physicians and patients may be acutely aware of the expanding role of pharmacists in the delivery of health care—expansion that has seen them become a more integral player in optimizing patient outcomes and health care system usage—and these physicians and patients may be more likely to become actively engaged in various PPS than those that think of community pharmacies as medication dispensing-oriented retail businesses. These perceptions may even be accurate in the context of one pharmacy, but inaccurate about another a short distance away, as the professional orientation of the pharmacy owner largely determines whether the pharmacy is organized as a retail destination or as a destination for the delivery of health care (Hopp et al., 2005). This illustrates a distinction between pharmacists' positive attitudes toward PPS and sometimes the fixed attitudes that many pharmacists and pharmacy owners have about making changes to the way they practice. Despite evident enthusiasm from pharmacists for expanded clinical involvement, as in Indonesia and many other parts of the world, qualitative interviews with community pharmacists and pharmacy strategists in Spain demonstrated that pharmacists' negative attitudes about changing roles in health care are a determinant of practice that is currently impeding pharmacist uptake of PPS (Gastelurrutia et al., 2009). Practice change is not an easy or quick process. When imperatives from pharmacy owners are incongruent with the enthusiasm that staff pharmacists hold for PPS delivery, pharmacists may look for ways to increase efficiency in other areas of their practice so that they can undertake new PPS (Luetsch, 2017). An important tension arises when additional operational efficiencies are not easily identified or implemented which preclude pharmacists providing services they wish to offer.

Interpersonal Determinants

Interpersonal-level determinants of practice describe the relationships and interactions between all of the individuals mentioned previously. These determinants of practice are often intricately intertwined with those at the individual level. An example is how a nurse's perception of a pharmacist's competence would impact (either positively or negatively) the level of trust, communication, and collaboration between the nurse and pharmacist, likely influencing the nurse's perception of the pharmacist's role in the health care system and engagement in a PPS (Roberts et al., 2006). The existing relationship and the amount of trust between pharmacists and patients, again largely influenced by how their shared experiences in the past have shaped their perceptions of one another, are other common interpersonal-level determinants of practice (Hossain et al., 2017a; Hossain et al., 2017b). In countries, such as Indonesia or India, where the introduction of PPS is in its infancy and community pharmacies are very much medication dispensing- and retail-oriented businesses, neither physicians nor patients perceive them as health care destinations, but rather as storefronts attempting to turn a profit (Wibowo et al., 2016). These perceptions can become self-fulfilling prophecies that impede practice change and make it difficult for pharmacies to create demand for PPS.

Even interactions between patients and health care providers outside of the pharmacy setting can affect engagement in a PPS, such as when poor communication between a prescriber and patient results in inappropriately prescribed medications that necessitate a pharmacist's intervention (Hossain et al., 2017a). Communication is integral to any interpersonal relationship, which is why having formalized systems in place for communication between health care providers is another commonly cited interpersonal-level determinant of practice. Having systems in place that encourage both verbal and written communication between pharmacies and their local network of health care providers can enhance collaboration and engagement in a pharmacy's provision of a PPS, including referral into a PPS program and feedback from the pharmacy to the referrer about its impacts on the patient's health (Hopp et al., 2005; Hossain et al., 2017b). Established examples of systems to enhance collaboration between pharmacies and prescribers include both supplementary prescribing in the United Kingdom and collaborative practice agreements in the United States (Patient Access to Pharmacist's Care Coalition, 2015; Pharmacist Prescribing Task Force, 2010). These programs involve formalized agreements between pharmacists and physicians that use their respective medication and diagnostic expertise. Physicians assess the patient and formulate a care plan that is then implemented and managed by the pharmacist, possibly including the prescribing and monitoring of medication therapy. The enhanced clinical involvement in patient care that is afforded to community pharmacists by programs such as these both facilitate, and are facilitated by, strong lines of communication between health care providers. A similarly collaboration-centric model was used by Chen et al. (1999a,b) where a multidisciplinary group of pharmacists and physicians was formed to guide the implementation process for a PPS, from development to practice (Chen et al., 1999a,b). This group remained active even after the study ended, and led to the sustained implementation and delivery of the PPS.

Standardized communication mechanisms between health care providers would also help ensure at least some degree of accessibility of each health care provider to the other. The availability of prescribers to pharmacies, which is a concern given frequently heavy workloads, can be a deciding factor in the ease and amount of collaboration between them. Similarly, the degree of accessibility of patients to pharmacies also plays a role in governing the uptake of a PPS. Frequent, in-person patient visits (rather than by telephone, or through caregivers) help increase use of PPS. So too does being the sole provider of pharmacy services to a patient, rather than being one of several pharmacies caring for them.

Education and training that focuses on multidisciplinary collaboration and communication skills are commonly suggested interventions for improving performance in interpersonal determinants of practice (Hossain et al., 2017a; Luetsch, 2017). This can be done by including interprofessional elements into training sessions for delivery of the PPS, continuing professional development events, or within undergraduate curricula. Similar initiatives that emphasize a patient-centered approach to health care and communication are useful for enhancing pharmacist–patient relationships and the ability of pharmacists to provide care.

Organizational Determinants

Aspects of the pharmacy setting, such as its physical environment, organizational structure, policies and procedures comprise the organizational-level determinants of practice. Of these, staffing levels and pharmacist workload are among the most commonly described factors that either hinder or enhance the uptake of a PPS at a particular pharmacy. A key determinant of practice, then, is the degree to which a pharmacist is permitted to delegate PPS duties including compounding and dispensing medications to pharmacy assistants and technicians. In certain countries, such as Germany and Canada, pharmacy technicians must complete formalized training and licensure programs before becoming eligible to perform delegated acts in a pharmacy. This extensive preparation positions pharmacy technicians as heavily-relied upon contributors to the operations of a community pharmacy—coworkers to whom pharmacists can delegate a variety of tasks to free themselves for provision of certain PPS that require pharmacists' unique knowledge and skills. An example of successful delegation from the institutional setting is the involvement of pharmacy technicians in medication review and reconciliation programs in hospitals. When performed by technicians, these tasks, traditionally the responsibility of pharmacists, reduce medication discrepancies during transitions of care to the same degree as pharmacist-led programs (Mekonnen et al., 2016).

This is not limited to technicians practicing in institutions. Delegation is used advantageously in community pharmacies in the United Kingdom and parts of the United States where pharmacy technicians can become certified to check the technical accuracy of dispensed prescriptions before they are released to the patient, thereby providing the pharmacist with more time to participate in the PPS that require their unique skill sets and clinical knowledge. A pharmacy that has only a few staff members present at a time, however, may rely heavily on the pharmacist playing a part in the functions of medication dispensing (i.e., preparing packaging, confirming accurate dispensing) that could otherwise be delegated, leaving minimal remaining time for PPS that require pharmacists' expertise. In this scenario, it is evident that distribution of duties within a pharmacy is a major organizational-level determinant of practice. Noteworthy, though, is that delegation is imperfect in many settings: even if a pharmacy has numerous technicians and assistants who are capable of handling all dispensing-focused PPS, many jurisdictions (e.g., Australia, Canada, UK, and many other countries with established health care systems) require pharmacists to perform the final clinical check of a prescription before it can be dispensed to a patient (Koehler and Brown, 2017; Moleschi et al., 2009; Pharmacy Board of Australia, 2015; Quaye, in press). If this pharmacy processes a high number of prescriptions per day then it may still be difficult for the pharmacist to devote time to nondispensing PPS despite adequate staffing levels. A solution to this problem, then, may be to shift to a pharmacy model that employs proportionately more pharmacists to engage in the provision of clinical care, increasing the likelihood of successful implementation of nondispensing PPS. The operating costs associated with paying pharmacists wages would undoubtedly be higher, but could be offset by an increase in sales and patronage due to greater involvement of pharmacists with patients and an improved public image (Feletto et al., 2010).

While usually somewhat regulated across a country or territory, small differences in the physical layouts of pharmacies, including immunization booths and private areas for patient interviews or counseling, can facilitate or impede the provision of certain PPS. This was another common theme that emerged from the interviews conducted by Gastelurrutia et al. (2009), with both pharmacists and pharmacy strategists identifying a "need to change the structure of pharmacies (larger in size, having more pharmacists per pharmacy, and private areas for patient care)" to facilitate the implementation of nondispensing PPS (Gastelurrutia et al., 2009). The same is true about the technology and automated systems used in pharmacies; how the increased efficiency that is afforded by this technology is used (i.e., to free up more time for the provision of clinical PPS or to increase the number of prescriptions filled) is a related organizational-level determinant of practice. The way technology is used may also say a lot about the orientation and setup of the pharmacy, positioning itself somewhere on a spectrum between a profitable business that focuses on dispensing and front shop merchandising, to a health care destination that offers a comprehensive suite of health services. This organizational-level determinant, of course, will largely be influenced by the individual-level professional orientation of the pharmacy owner, but will also be shaped by local health care policy and regulations, the orientation of the pharmacy staff, and demand from the community.

Given that community pharmacies in most health systems are retail stores, the financial resources available to a pharmacy are a major organizational-level determinant of its ability to provide a PPS. A large pharmacy, or a banner group or chain of stores, will typically have far greater financial resources at their disposal than smaller, single location (sometimes called "independent") pharmacies. This provides larger pharmacies with added adaptability to change scopes of practice for pharmacists, such as by hiring additional staff or purchasing the equipment required to provide a new PPS. These resources can also be used to market or advertise a new service to the public, increasing community engagement, demand, and utilization of a PPS. Marketing a PPS differs from marketing other products in that pharmacists must be able to educate patients, as well as other members of the supply chain (i.e., prescribers and other health professionals) about the value of the PPS (Roberts et al., 2006). Engaging both stakeholder groups is necessary for optimal uptake of the PPS, however focus should be toward the general public so that a demand for the service is cultivated and the public's new expectations of pharmacists stimulate a change in pharmacy practice.

Health Care System Determinants

The influences of the jurisdiction in which the PPS is being delivered, that is, the broad political and social norms and regulations that impact the context of the PPS, are referred to as the health care system-level determinants of practice. These are overtly reflected in a jurisdiction's existing health care policies and health system structure.

One of the more common high-level factors affecting implementation of PPS that pharmacists discuss in the qualitative literature, understandably, is the reimbursement schedule for various PPS. Given that reimbursement often lags behind provision of the services, this is often touted as a major barrier for PPS implementation. There is a considerable geographical variability in the amount of compensation pharmacists receive for their services, with full reimbursement schedules established in certain regions and then others where pharmacists receive little or no pay for services beyond medication distribution (Wibowo et al., 2016). In Spain, there is a common feeling among community pharmacists that their reimbursement system requires substantial overhaul that decreases the revenue that pharmacies can generate through dispensing and increases the income from the delivery of other, clinically-focused PPS (Gastelurrutia et al., 2009). This is especially true when the administrative workload associated with PPS delivery that is required by some pharmacy regulatory agencies results in a decreased capacity for pharmacists to engage in other revenue-generating tasks for the pharmacy.

The dichotomy between how existing reimbursement schedules benefit individual pharmacists versus how they benefit the pharmacy owners must also be considered. A payment scheme that reflects the actual work being done (i.e., that favors the pharmacist providing the PPS) in the delivery of a service may be a greater impetus for the implementation and uptake of PPS (Roberts et al., 2006).

However, despite what pharmacists divulge in interview-based studies, numerous reviews of the literature have demonstrated that reimbursement alone does not result in sustainable uptake of newly implemented PPS (Hersberger and Messerli, 2016; Patwardhan et al., 2014). Contributing to this, perhaps, is that even when reimbursement schedules are established for nondispensing PPS, they often still lag behind the profitability of dispensing medications.

Australia took a dramatic approach to level the reimbursement for the two groups of pharmacy services: markups on prescription products were eliminated at the same time that the funding available for PPS was doubled (The Commonwealth of Australia and The Pharmacy Guild of Australia, 2015). In New Zealand, a new community pharmacy reimbursement schedule combines the existing fee-for-service payment structure with a funding model that rewards pharmacist involvement in the care of complex patients, incentivizing the use of their pharmaceutical expertise and their participation in PPS (Napier et al., 2018).

As reimbursement alone does not appear to drive successful implementation of PPS, other health care system-level determinants of practice must be considered. Public, health care authority, and overall health care professional awareness of the PPS and its benefits has a dramatic impact on its implementation and success. Of course, the quality of the PPS itself, both in terms of its impact on clinical outcomes and its cost-effectiveness, play a role in raising awareness of the service and obtaining buy-in to its uptake. How these costs are covered, that is, by third party payers or as out-of-pocket expenses paid by patients, partially determines public engagement. The same is true of whether a newly implemented PPS addresses a gap in health care, or if it merely presents an alternative method for a preexisting process.

The ideal PPS, then, provides an innovative way to efficiently improve patient health at little or no cost to patients; the ideal PPS creates its own publicity and demand and easily overcomes any health care system-level barriers to its implementation. The ideal PPS also does not exist. For this reason, another hugely important health care system-level determinant of practice is support for the PPS and its implementation from professional pharmacy advocacy bodies. The power that these professional organizations possess is often vital for fostering collaboration in a PPS from health care authorities and other health care professionals and their respective advocacy groups. Some contend that collaboration is best negotiated through professional organizations rather than by individual practitioners (Luetsch, 2017). Using these relationships, agreements form that lead to the development of useful tools for expanding pharmacy's involvement in clinical care, such as sharing of patient information and laboratory values with community pharmacists.

Through such partnerships between governing bodies and pharmacy professional organizations, regulatory frameworks are formed that facilitate greater involvement of pharmacists in health care and delivery of PPS. An example of such collaboration exists between the federal government of India and pharmacy professional groups, who have partnered on clinical pharmacy pilot programs that draw on the skills that pharmacists have learned in the Doctor of Pharmacy program introduced in 2008 (Cipolle et al., 2012).

Education is another way in which pharmacy advocacy groups can support the enhancement of the profession. After identifying a lack of clinical education for community pharmacists as a barrier for the successful implementation of PPS, the Swiss Association of Pharmacists sponsored professorships in the pharmacy programs at universities in Basel and Geneva for 5 years to increase the quality and amount of clinical, patient-oriented teaching that pharmacy students received (Hersberger and Messerli, 2016).

Lack of clinical education is not isolated to Switzerland, however, as pharmacy education appears to lag behind the evolution of the profession, and often does not reflect the increasing international emphasis on the benefits of clinically oriented PPS. Pharmacists in Vietnam, Egypt, and China, for example, all receive an education that focuses on basic sciences and the traditional compounding and dispensing roles of pharmacists (Cipolle et al., 2012; Vo et al., 2013). Further impeding the implementation of PPS in China, it is forecasted that, due to the success of their pharmaceutical industry, pharmacy curriculum will begin to feature manufacturing and marketing components rather than shifting to a focus on patient-centered care and clinical skills (Hu et al., 2014).

As in Switzerland, pharmacy professional organizations in these countries will likely have to play a role in reshaping the undergraduate education that pharmacists receive to better prepare them for the increasing clinical expectations of pharmacies around the world. This reconfiguration would benefit from an emphasis on multidisciplinary education sessions and practical rotations that place pharmacy trainees into the collaborative and patient-centered situations they will face upon becoming a member of the profession (Gastelurrutia et al., 2009; Luetsch, 2017; Vo et al., 2013).

University curriculum, however, is not the only way in which pharmacists receive instructional support for the delivery of PPS; in-practice training and clinical coaching are other commonly employed methods for improving these skills. Again, these programs are often facilitated by pharmacy professional groups. The availability of both pregraduate and continuing professional development that equips pharmacists with the practical skills they need to provide PPS is a key health care system-level determinant of practice.

Summary

Enabling and inhibiting factors that influence the uptake of professional pharmacy services by pharmacies, pharmacists, other health care professionals and members of the public are frequently referred to in the literature as barriers and facilitators. However, as many of these factors exist on continua or are binary in nature, we opted to refer to each as a determinant of practice. Four levels of determinants of practice were discussed including individual, interpersonal, organizational, and health care system.

Conclusions

Professional pharmacy services describes services for individual patients or populations that require health care professionals connected to community pharmacies to apply specialized health knowledge with the aim of optimizing health outcomes and values in the health system. Related terms that are commonly used in the literature, including clinical pharmacy services, pharmaceutical care, and cognitive services have relative merits and drawbacks. To enhance the readers understanding of the breadth of services encompassed under the umbrella of professional pharmacy services, seven categories of services were presented and associated evidence of their impact discussed when it was available. Lastly, factors impacting the implementation of professional pharmacy services at the individual, interpersonal, organizational, and health system levels were presented to illustrate the complexity of implementation.

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Prescribing: Practices, Standards, Ethics, Behaviors, and Competencies: A Case Study in Alberta

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Introduction

"The doctor knows that it is the prescription slip itself, even more than what is written on it, that is often the vital ingredient for enabling a patient to get rid of whatever is ailing him" (Cousins, 1979).

The ability to prescribe has a powerful place in medical practice" (Cousins, 1979). In some countries, prescribing has been restricted primarily to physicians. In other parts of the world, citizens are able to select their own medication therapies using healthcare practitioners to guide choices at the citizen's discretion (Erku et al., 2016; Sakeena et al., 2018). Overall, citizens' access to prescription medication has been expanding (Bennadi, 2013). First, an increasing number of medications that were once prescription have been designated as non-prescription, allowing for citizen self-selection (Mahecha, 2006). Secondly, non-physician prescribers such as nurses, physiotherapists, chiropodists/podiatrists, radiographers, optometrists, and physician assistants have been granted prescribing privileges (Cope et al. 2016). Considering the elderly population, scarcity of physicians in some locations, increased healthcare cost, inflexibility of the healthcare system, and the challenge of chronic disease management, governments have expanded prescribing for non-medical healthcare providers so that they can use their expertise to address the increased demand for healthcare services. As a result, pharmacists around the world have obtained prescribing privileges (Emmerton et al., 2005).

Pharmacists have unique medication knowledge that should be harnessed to improve patients' access to medications and improve health system efficiency. Health care systems are not only striving for efficiencies but striving for ways to enhance the patient experiences. Enabling patients to choose where they access their prescribing needs can improve that patient experience. A recent systematic review found that non-medication prescribers including pharmacists, were as effective as usual care medical prescribers (Weeks et al., 2016). In this chapter, pharmacist prescribing will be characterized including prescribing practices, standards, ethics, behaviors, and competencies with a focus on the experience in Alberta, Canada. Alberta has a broad range of prescribing privileges that are unique in North America.

Pharmacy Prescribing Practices

The varying forms of pharmacist prescribing practices can be characterized by the level of autonomy and the type of prescribing activity.

Prescribing Autonomy: Independent or Dependent

The autonomy of pharmacist prescribing is broadly characterized by independent and dependent models. Independent prescribing is recognized by a regulatory authority and requires a prescriber to assess and manage the patient without the supervision of another healthcare professional. Independent prescribing does not require the pharmacist to diagnosis a patient (Emmerton et al., 2005). Note, this does not preclude collaboration with other prescribers in order to ensure pharmacists have complete information and are acting in the patient's best interest. Independent refers to the authority to prescribe and does not require care be provided in the absence of other providers. Collaboration has been recognized as a key component in independent prescribing models (Yuksel et al., 2008). The second form is dependent prescribing which requires the supervision of another healthcare professional. This

supervision could be at the individual or jurisdictional level. The authority to prescribe is granted by another prescriber. There are many forms of dependent prescribing that vary depending on the level of supervision and reliance on a formal protocol (Emmerton et al., 2005).

The most common forms of dependent prescribing are supplementary, collaborative, and protocol prescribing where pharmacists are allowed to prescribe a medication subject to a protocol and supervision of a prescriber such as a physician (Emmerton et al., 2005; Tonna et al., 2008). In supplementary prescribing, the agreement is generally limited to a patient-specific clinical management plan that is agreed by the prescriber and patient. Collaborative prescribing models require a relationship between a pharmacist or group of pharmacists and a prescriber group. Pharmacists are allowed to prescribe for a group of patients in collaboration with an individual prescriber or group of prescribers. Collaborative drug therapy management has been defined as "a collaborative practice agreement between one or more physicians and pharmacists wherein qualified pharmacists working within the context of a defined protocol are permitted to assume professional responsibility for a variety of functions, including patient assessment; ordering drug therapy-related laboratory tests; and selecting, initiating, monitoring, continuing and adjusting drug regimens" (Hammond et al., 2003). In prescribing by protocol, pharmacists provides care following a detailed protocol outlining the process of prescribing. A typical example is pharmacist management of aminoglycosides by a standing order in a hospital.

Prescribing Activities

A second way to categorize pharmacist prescribing is by activity which include: extending a prescription, adapting or modifying a prescription, prescribing for minor ailments, and initial access prescribing. In prescribing for refills or extension, pharmacists prescribe to continue or extend an existing prescription without altering the original prescription or directions.

A second form of prescribing is adapting or modifying a prescription initiated by another prescriber based on pharmacists' patient assessment. For example, a pharmacist may alter the dose of a prescription based on a patient's organ function, substitute dosage forms based on patients' preference or availability, or make a therapeutic substitution. The intent of the prescription remains the same, but the prescription is modified and signed in the pharmacist's name.

The third activity is prescribing for common or minor ailments which are conditions that do not require laboratory tests for diagnosis and do not mask more serious conditions (Lee and McCarthy, 2015). While prescribing for minor ailments is the internationally used term, some believe minor is demeaning as it implies less important conditions or patient's issues are of lesser concern (Taylor and Joubert, 2016). In place, pharmacists may prescribe medications which commonly have evidence for efficacy, a wide safety margin, self-diagnosed or self-limiting disease conditions, and straightforward self-care management (Taylor and Joubert, 2016). Lab tests and long-term follow-up are not required to prescribe (University of Saskatchewan, 2015).

Common examples where a pharmacist prescribes for common ailments are cold sores, allergic rhinitis, and oral thrush.

Finally, pharmacists can prescribe for initial access or to manage ongoing therapy without delegation (Law et al., 2012). This form best mirrors typical physician prescribing activities. This may include narcotics and controlled substances as designated by justification.

The Intersection of Autonomy and Activities

The level of prescribing autonomy and type of activities overlap (Fig. 1). Different pharmacists may perform the same activity with different levels of autonomy. For example, a pharmacist may have either independent or dependent authority to renew a medication refill. The act of writing the pharmacist's name on the physical prescription for the refill is the same, and the pharmacist may provide

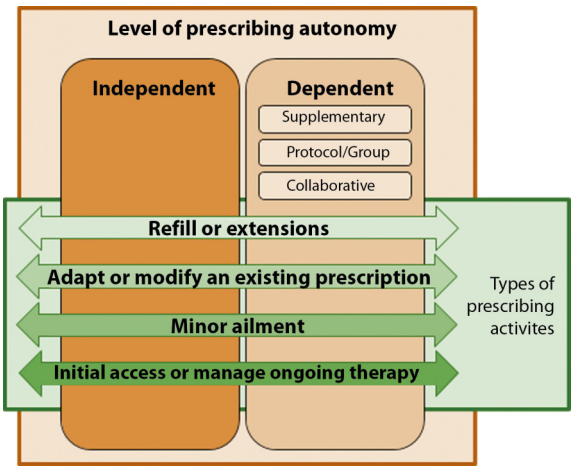

Figure 1 Intersection of pharmacist prescribing activities and degree of autonomy.

similar care to the patient, but the regulations that enable the pharmacist to require different levels of oversight. Conversely, a pharmacist may have a collaborative working agreement with a physician which allows them to initiate a new prescription and authorize refills. The complexity of the prescribing activity may vary, but both activities required a physician's protocol. Further examples on the intersection of autonomy and activities will be provided on the next section on the evolution of prescribing.

Evolution of Prescribing Standards

Pharmacist prescribing has been described as an evolution, not a revolution (Pearson, 2007). The practice of pharmacy has evolved from the initial compounding of medications for individual patients. With the advent of medication manufacturing in the 1950s, the pharmacist role moved to focus on medication distribution. Starting in the 1960s, Brodie documented the rise of clinical pharmacy with a focus on therapeutic drug monitoring and clinical services, predominating in hospital pharmacies. In the 1990s, pharmaceutical care characterized a practice that placed patients at the center of care. In the early 21st century, patient centered-care became the most common term to describe ideal pharmacist practice. The shared language with other professions highlights the inherent overlap in patient care activities. Pharmacists, nurse, and physicians all practice patient care activities around the selection, provision, and monitoring of medication therapy. Prescribing is a natural extension of these care activities and allows for a nimble health care system that can respond to patient needs.

Internationally, pharmacist's scope of practice has been expanding during the last two decades (Latter and Blenkinsopp, 2011; McBane et al., 2015; Raghunandan et al., 2017; Stewart et al., 2017). Pharmacist prescribing was first documented and operationalized in England and the US. England was the forerunner in this area and implemented supplementary prescribing rights in 2003 and independent prescribing rights in 2006 (Latter and Blenkinsopp, 2011). Independent nurse prescribing was sanctioned in several pilot sites in England, and eventually, the success of the pilot project enabled expansion to all nurses in England in 2001 (Cooper et al., 2008). In 2003, further changes in policy approved supplementary prescribing by trained nurses and pharmacists which allowed them to prescribe under the supervision of an independent prescriber, typically a physician. Physiotherapists, chiropodists/podiatrists, radiographers, and optometrists received similar prescribing authority in 2005. Legislation approved independent prescribing for both nurses and pharmacists in 2006 (Cooper et al., 2008). Pharmacists who prescribe independently are solely responsible to assess, initiate and manage medical conditions in different settings. In Scotland, pharmacist prescribing rules are similar to England (Stewart et al., 2017).

In the United States, pharmacist prescribing has been part of collaborative drug therapy management (CDTM) since 1979 (McBane et al., 2015). Pharmacists are allowed to prescribe drug therapy under the delegated authority of a physician (Hill et al., 2016). As a part of CDTM, pharmacists may order laboratory tests, assess patients, initiate and modify drug therapy, monitor patients, and administer drugs (Carmichael et al., 1997). Approximately 48 states permit some type of pharmacist prescribing, though the level of authority varies in each state's CDTM legislation (Centers for Disease Control and Prevention, 2017). The independent prescribing model was first introduced in a Florida Veterans Affairs' outpatient clinic and is found predominantly in the Veteran Affairs system (Ukens, 1997).

Pharmacists in New Zealand are also involved in collaborative prescribing (Pharmacy Council of New Zealand, 2013). Pharmacists are allowed to modify and initiate therapy associated with assessment and interventions in a collaborative health team environment. Australian pharmacists are eligible to prescribe specific over the counter medications and ensure a continuous medication supply by prescribing an "emergency prescription" or "repeat prescription" (Hoti et al., 2011). Australian pharmacists can prescribe medicines for minor ailments (e.g., non-sedative antihistamine, nasal spray containing steroids) as well as pharmacist only medicines (e.g., pseudoephedrine, salbutamol) which require a pharmacists' advice and follow-up. Finally, Australian pharmacists prescribe to extend a prescription provided by an authorized prescriber for up to one year.

In the last ten years, provinces in Canada have introduced different policies regarding the extended scope of pharmacy practice, mainly focused on prescribing activities (Emmerton et al., 2005). As pharmacists' scope of practice falls under provincial jurisdiction, prescribing authorities vary across Canada. Pharmacists can prescribe schedule 1 drugs (i.e., prescription only medications), except narcotic and controlled drug (i.e., opioids and its derivatives, barbiturates, and benzodiazepines) with a few provincial exceptions for seizure medications (Law et al., 2012). A summary of these evolving policies is maintained by the Canadian Pharmacists Association at: https://www.pharmacists.ca/pharmacy-in-canada/scope-of-practice-canada/. The following prescribing activities are considered independent prescribing unless otherwise noted.

Renewing prescriptions: Pharmacists in all ten provinces and one territory (i.e., Northwest Territory) can renew or extend it for continuity for up to three months as per provincial regulations (Canadian Pharmacists Association, 2017).

Modify or adapt an existing prescription: Pharmacists in all provinces are allowed to adapt a prescription by changing the dosage, formulation or regimen if needed (Canadian Pharmacists Association, 2017). Pharmacists can make therapeutic substitutions in all the provinces except three (i.e., Ontario, Manitoba, and Quebec) (Canadian Pharmacists Association, 2017).

Prescribing for minor ailments: Pharmacists prescribe for minor ailments and smoking cessation in all provinces except two (i.e., Ontario and British Columbia) (Canadian Pharmacists Association, 2017). Pharmacists in two provinces required additional training or authorization.

Initiating new prescription: There are two forms of independent prescribing—initiating a prescription and emergency prescribing. Pharmacists in four out of ten provinces can initiate a new prescription within a collaborative agreement (i.e., Saskatchewan, Manitoba, New Brunswick, and Nova Scotia) (Canadian Pharmacists Association, 2017). Albertan pharmacists with additional

prescribing authority can initiate a new prescription independently (Yuksel et al., 2008). Pharmacists in three provinces require additional training or authorization (Canadian Pharmacists Association, 2017). In six out of ten provinces (i.e., Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island) pharmacists can provide emergency supplies of prescribed medication when the patient does not have access to medical care but requires immediate attention (Canadian Pharmacists Association, 2017).

In Canada, pharmacist prescribing is guided by several professional components. Pharmacists must maintain a professional relationship with both patients and other healthcare providers. Pharmacist prescribing should be in the patient's best interest and not for their (i.e., pharmacists') own family members. Pharmacists need to maintain competence, have sufficient clinical knowledge, apply practice evidence, and prescribe for approved indications (Canadian Pharmacists Association, 2017). Prescribing decisions and their rationale should be documented and conveyed to other healthcare professionals involved in a patient's care (Yuksel et al., 2008).

Alberta was the first jurisdiction in Canada, to authorize pharmacist prescribing (MacLeod-Glover, 2011). Albertan pharmacists acquired this approval in 2007 under several timely and positive influences which included re-designation of scope of practice for all healthcare providers, support from the Alberta College of Pharmacists, a robust platform of pharmacists' knowledge and skill supported by the pharmacy education program, independent research support, and a requirement for timely and fair access to health care services (MacLeod-Glover, 2011). Pharmacists with additional prescribing authorization can initiate a new prescription independently or in collaboration with another health care provider after appropriate assessment within their limit of competency at the point of access (MacLeod-Glover, 2011). To receive this special authorization of prescribing, pharmacists have to submit a comprehensive application to the ACP providing evidence of quality patient care (Alberta College of Pharmacists, 2017b). In this application, pharmacists must demonstrate the ability to build a relationship with a patient, assess patients' needs, develop a care plan with appropriate follow-up, collaborate with other healthcare professionals, document patient care, and apply sound judgment.

Prescribing Ethics

The act of prescribing is an extension of the care pharmacists already provide to their patients. In Alberta, the Code of Ethics states that pharmacists must act in the best interests of the patient, maintain a professional relationship, and practice within their own competence (Alberta College of Pharmacists, 2009). The act of recommending non-prescription medications would require the same ethical duty of care as prescribing a new therapy. As such, the ethics of pharmacist prescribing are not explicitly raised in documents such as the Code of Ethics in Alberta (Alberta College of Pharmacists, 2009) or Standards for Pharmacy Professionals in the UK (General Pharmaceutical Council, 2017). Despite this, three issues around the ethics of pharmacist prescribing commonly arise: 1) ensuring patient consent for pharmacist prescribing, 2) separation of pharmacist prescribing and dispensing activities, and 3) perception of prescribing for financial gain.

Prescribing is a medical intervention, and as such, pharmacists must clearly seek the patient's voluntary consent. The patient must be informed and have the capacity to consent. Patients are often unaware of pharmacist practice beyond filling a prescription and may not be familiar with pharmacists' scope of practice (Faruquee and Guirguis, 2015; Perepelkin, 2011). Thus, pharmacists must use clear and specific language to explain pharmacist prescribing and ensure the patient understands the options. In the case of prescribing in Alberta, pharmacists are required to obtain patients informed consent to prescribe, but documentation of consent is not required (Alberta College of Pharmacy, 2018).

The second issue is the separation of prescribing and dispensing. Many prescribing standards or guidelines suggest the same pharmacist should not prescribe and dispense a medication unless in urgent situations (General Pharmaceutical Council, 2017; Kaae et al., 2011; Pharmaceutical Society of Northern Ireland, 2013). The rationale being that a pharmacist's role at the time of dispensing is to complete a second check for the effectiveness and safety of medications for individual patients. Physicians typically do not dispense in North America. In other jurisdictions, legislation has been put in place to separate physician prescribing and dispensing to remove any monetary incentive to prescribe medications (Chou et al., 2003). Thus, it seems contrary for prescribing pharmacists to dispense a medication they prescribed. Yet, pharmacists have been navigating the space for decades. In the case of minor ailments, pharmacists have been making recommendations for nonprescription medications and then providing the product—the equivalent of prescribing and dispensing.

In Alberta, the standards for practice state that pharmacists who prescribe at initial access should not dispense the medication they prescribed unless it compromises patient health, or the patient chooses for the pharmacist to dispense the medication (Alberta College of Pharmacy, 2018). In the latter scenario, the pharmacist must advise the patient that they can have this dispensed by another pharmacist, ensure the patient has sufficient information to participate in decision making, and obtain informed consent to dispense the medication (Alberta College of Pharmacy, 2018). This does not apply to pharmacists who are extending or adapting a prescription, as these forms of prescribing arise from a prescription from another provider and typically occur during patient care activities at time of dispensing.

The third is the inherent conflict of interest in prescribing for financial gain. In Canada, physicians have raised concerns about conflict of interest arising with pharmacist prescribing (Faruqee et al., 2018; Lee and McCarthy, 2015). Pharmacy is practiced in a retail environment. As such, pharmacists sometimes are perceived to straddle a role between a business person and healthcare professional (Resnik et al., 2000). McCormack first described this in the academic literature (1956). This debate assumes that other

prescribers do not have inherent financial benefit in prescribing. However, physicians, physiotherapists, and dentists are all reimbursed for assessing the need for treatment as well as providing treatment (Lee and McCarthy, 2015). In the end, it may be difficult to conclude that prescribing has inherently more room for abuse than other activities in health care. Interestingly, the majority of community pharmacists in Canada practice in a pharmacy where they are paid a salary which is not dependent upon the quantity of prescribing or billing. The codes of ethics must be honored in all situations.

Prescribing Behaviors

Behavior refers to real-world prescribing activities. Standards and regulations are enabling tools which do not compel a pharmacist to prescribe. In fact, many pharmacists choose not to prescribe as they feel they can influence prescribing decisions in other ways (Guirguis et al., 2017; Makowsky et al., 2013). This section will describe prescribing behaviors in Alberta with a focus on (1) pharmacists' adoption of additional prescribing authority (i.e., prescribing to initiate a prescription) and (2) pharmacists use of other forms of prescribing.

When pharmacist prescribing was initiated in Alberta in 2007, 15 pharmacists were granted additional prescribing authority, and the numbers slowly grew up to 220 pharmacists by 2012. Early research found pharmacists who obtained additional prescribing authority identified the relative advantages, were in ambulatory care settings and had relationships with physicians (Hutchison et al., 2012; Makowsky et al., 2013). Still, many pharmacists found the application process for additional prescribing authorization onerous (Charrois et al., 2012; Hutchison et al., 2012). In 2012, a new compensation framework was released for pharmacy practice (Alberta Health, 2012). Pharmacists would be reimbursed for the assessment that accompanies prescribing as well as care plans (i.e., a medication review with a treatment plan) and their subsequent follow-ups. Of note, pharmacists who had obtained additional prescribing authority would be reimbursed at a rate 25% higher for all services. In 2013, the rate of pharmacists with additional prescribing authorization rose to 435, and by 2016 that number had reached 1658 (31%) of pharmacists in Alberta. The number of additional prescribing applications is still increasing each year (Alberta College of Pharmacists, 2017c). In hospitals, pharmacists reported using additional prescribing authorization for nearly half of patients with antibiotics and anticoagulants (Heck et al., 2015). Oncology pharmacists report applying using additional prescribing authorization to prescribe antiemetic medications in ambulatory clinics (Au et al., 2018). In Alberta, research studies have shown that pharmacist prescribing has resulted in a three-fold reduction in cholesterol (Tsuyuki et al., 2016) and two-fold reduction in hypertension (Tsuyuki et al., 2014) when compared with usual care without pharmacist prescribing.

Most pharmacists in Alberta prescribe to adapt new prescriptions or ensure continuity of care. A 2012 survey found 93.4% of the pharmacists had prescribed. The most common practices were renewing prescriptions for continuity of therapy (92.3%), altering doses (74.3%), and substituting a medication due to a shortage (80.6%) (Guirguis et al., 2017). Pharmacists in rural areas prescribed more frequently supporting the need for services in these areas (Guirguis et al., 2017). Community pharmacists are more likely to prescribe to continue therapy while pharmacists in hospitals or clinics were more likely to adapt prescriptions. Despite the ability to prescribe to extend a prescription for continuity, many pharmacists still contact the physician first to authorize the refills (Guirguis et al., 2014; Makowsky et al., 2013).

Pharmacists' themselves are not clear on what behaviors constitute prescribing. For example, a 2017 newsletter from the Alberta College of Pharmacists clarified examples of unauthorized pharmacist prescribing. These included prescribing to extend prescription for medications that were several years old, adjusting a renewal of a medication, or changing medications due to intolerance issues. All of these forms of prescribing require additional prescribing authorization, but appear similar to adapting a prescription (Alberta College of Pharmacists, 2017a). This may be further confused by the language pharmacists use to describe prescribing. Many pharmacists use the term extending a prescription to ensure patients have a supply of an existing therapy and resist the term prescribing to describe this activity (Hughes et al., 2014). The term prescribing is commonly reserved for the process of initiating a new medication.

Stakeholder Perceptions of Pharmacist Prescribing

In Canada, several studies have looked at stakeholder perceptions. The general public in Saskatchewan and Nova Scotia were supportive of an expanded role for pharmacists in tasks familiar to patients, such as continuing ongoing medication therapy and prescribing for minor ailments, but less supportive for initiating new medication therapy (Perepelkin, 2011; Bishop et al., 2015). Similarly, a review of lay literature found a lack of clarity and contradictory views around pharmacist prescribing (Schindel and Given, 2013). Healthcare stakeholders perceived that independent prescribing increased patient convenience and efficiency of health care (Henrich et al., 2011; Pojskic et al., 2014), Still, physicians with limited experience with pharmacist prescribing expressed concerns about patient safety and delegation of authority (Henrich et al., 2011).

Jebara et al. reviewed 65 international papers (i.e., United Kingdom, Canada, and Australia) on stakeholder opinions toward pharmacist prescribing (2018). Views were overwhelmingly positive, particularly in response to improved patient access, use of pharmacist skills, and reductions in physician workloads (2018). Negative perceptions were more prevalent before experience with pharmacist prescribing and centered on a lack of pharmacist diagnostic skills, access to medical records, and workplace organizational issues.

Prescribing Competencies

Standards of Practice are generally provided for pharmacist prescribing by regulatory bodies; however, they often do not include explicit competencies. A notable exception is the Royal Pharmaceutical Society in the United Kingdom that has produced "A Competency Framework for all Prescribers" (2016). This framework will be used as an example to explain the general competencies required for prescribing, as it relates to pharmacist prescribing and will be referred to as "The Framework" for the remainder of this section. The Framework is divided into ten competencies within two domains—"The Consultation" and "Prescribing Governance". Although not an explicit competency within The Framework, professionalism is expected of all prescribers in all activities, including being patient-centered, maintaining confidentiality, and being responsible for continuing professional development.

The Consultation consists of: (1) assessing the patient; (2) considering the options; (3) reaching a shared decision; (4) prescribing; (5) providing information; and (6) monitoring and reviewing. When assessing a patient, pharmacists should consult with patients directly and complete clinical assessments within their scope (e.g., measuring blood pressure), review all available patient information (medication records, lab test results, when available), and if it is within their scope, request additional tests (e.g. drug levels). Pharmacists should consider all non-pharmacological and pharmacological options for management of the condition, considering the potential risks (including cost) and benefits of the options available, as they relate to the individual patient and their concomitant conditions and medications. Pharmacists often have a greater understanding of pharmacological options than other prescribers, so may take into account additional factors, such as pharmacokinetics or formulations. Discussion with the patient or caregiver around the potential benefits and risks of the available options should lead to a shared decision and the prescribing of therapy with all required information included on the prescription. Counselling on the therapy, per usual pharmacy practice, and establishment of the monitoring plan, which should also be part of usual pharmacy practice, complete the Consultation.

Prescribing Governance consists of (1) prescribing safely, (2) prescribing professionally, (3) improving one's prescribing practice and (4) prescribing as part of a team. When prescribing, pharmacists stay within their scope of knowledge and skill in order to maintain patient safety. Prescribing errors and near misses should be reported and discussed. An example of a reporting system used is SafetyNetRx (http://www.safetynetrx.ca/) that is used in Nova Scotia, Canada. Pharmacists prescribe professionally by accepting personal responsibility for their decisions and staying within their legal scope of practice. Continually reflecting on one's prescribing practices and those of others, which may include reviewing error reports, can improve prescribing practices. Prescribing as part of a team is a common aspect of pharmacist prescribing and may be a requirement of some prescribing models. Fostering collaborative relationships and ensuring continuity of care through communication are important to ensure team functioning.

The Framework offers specific guidance and statements around prescribing and is an excellent resource. Most pharmacists will find that they are generally practicing within this framework on a daily basis, including when they are providing "over the counter" or "non-prescription" medication advice as well as assessing and educating patients with prescription medications. It is important to recognize that the competencies used in the long-standing parts of practice (such as "over the counter" recommendations) align with those used for a potentially newer aspect of practice, such as prescribing.

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Professionalism in Pharmacy Practice

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Introduction

In addressing the topic of professionalism in pharmacy practice, the chapter has been organized to address a series of questions. First, what is meant by the term professionalism as it pertains to pharmacy? What are the attributes of pharmacy that elevate it beyond a mere occupation to that of a profession? As a profession, what are the attributes that must be displayed by members to assure patients, other health professions, and the public in general that professionalism is a part of pharmacy practice? If professionalism is a part of pharmacy practice, are its attributes and behaviors displayed in a manner that assures us that it is practiced consistently and at an acceptable level across the profession? Is our understanding of the concept of professionalism evolving? Would professionalism as it is understood and applied today be recognizable to those who came before, and will professionalism as it is understood today still be relevant to those who come after us? How do we ensure the values and behaviors associated with professionalism are instilled into new entrants, and promoted and maintained in practitioners after graduation? Finally, does professionalism have value? Does it allow the profession of pharmacy to better serve the larger society in which it exists, or is it merely affectation and a sentimental adherence to old norms?

Occupation as Profession

Professionalism has been defined as demonstrating the traits of the profession (Agomo, 2012). Before addressing the topic of professionalism more fully; however, it is necessary to first establish what is meant by the concept of a profession, and what differentiates a profession from other occupations. Once the concept of profession is understood, the next question to be addressed is to what extent pharmacy can assume the title of profession rather than merely an occupation? Only then can the concept of professionalism, as it pertains to pharmacy, be addressed properly.

For many, an occupation is deemed a profession if it possesses a number of the traits ascribed to a profession. While there is no consensus on the traits of a profession (Waterfield, 2010), there are many that are generally agreed upon, while others reflect similar values. These traits are categorized as either structural or attitudinal (Hammer, 2000).

Some of the structural traits of a profession include the following: specialized knowledge and skills; performing a service important to society; prestige, autonomy for the service provider; self-regulation, formal organizations and codes of ethics; and a system for training others in the knowledge, skills and values of the profession (ASHP, 2008; Hammer, 2000; Waterfield, 2010). In addition to shared ethical values, practice based on theoretical knowledge, and a professional culture passed on to new entrants, Waterfield (2010) expands the concept of professional authority to include power and privilege sanctioned by community; similar to the prestige trait noted by Hammer (2000).

Attitudinal traits include having a belief in service to the public and a sense of a calling, or dedication to the profession (Hammer, 2000). Other attitudinal traits identified in the literature include commitment to self-improvement; service orientation to patients and to the profession, creativity and innovation, trustworthiness, accountability, integrity, duty, honor, and leadership (ASHP, 2008; Poirier and Gupchup, 2010).

Also identified as a professional, trait is the confidential nature of patient-client relationship (Waterfield, 2010). This trait, in particular, speaks to the covenantal or fiduciary relationship seen as essential between a member of a profession and the person being served. In this way, one may argue that professions differ most from nonprofessional occupations, in that the relationship between provider and recipient is not merely or primarily commercial (ACCP, 2009).

While a professional is expected to charge a fee (in some cases substantial) for the services provided, the primary goal of the exchange is to maximize the benefit received by the patient or client rather than the provider of the service. The relationship is built

upon the ability of the patient or client to trust that the professional will be working in the interests of the patient or client, and, as such, is not required to adopt the philosophy of *caveat emptor* (let the buyer beware).

Finally, In addition to traits associated with a profession, the literature also presents the concept of types or levels of professional designation that have been used to differentiate professions from occupations, and professions from one another. Historically, these have included established professions such as medicine and law, new professions such as engineers and academics, semi-professions such as pharmacy and nurse, and those occupations aspiring to obtain professional status (Agomo, 2012).

For the most part, the degree to which an occupation is designated a profession appears to draw primarily on the extent to which a group possesses special knowledge based on a theoretical framework and the ethical underpinnings that dictate the behavior of members, rather than merely the application of skills *per se*.

Pharmacy as a Profession

Is pharmacy a profession? In the past, pharmacy has been viewed as not a profession due to a lack of control over its work (i.e. medicines) (McCarthy et al., 2012); semi-professional based on an over-reliance on the mastery of technical skills (Agomo, 2012); or quasi-professional due to a lack of autonomy and equivalency of members (Hammer, 2000).

While not intending to provide a history of pharmacy's march toward greater professional status, the rise of medical hegemony in the nineteenth century, and the resulting subordination or elimination of most nonphysician health care provider groups (Starr, 1982), had a profound effect on the work and professional standing of pharmacy. While medical hegemony did not eliminate pharmacists from the health care environment, pharmacy's scope of control was greatly curtailed; as a result, it was confined mainly to the compounding and dispensing of medicines prescribed by physicians. Interactions with patients of a clinical or therapeutic nature were generally limited to only the most basic information regarding the administration of medicines and minor medical complaints, with the expectation, indeed the obligation, to defer all substantial concerns and issues regarding drug therapy to the prescribing physician for resolution or redress (Troy and Beringer, 2006).

The restricted and marginal health care provider role taken up by pharmacists was further eroded by the fact that, unlike other health care practitioners, most pharmacists worked outside the formal structures of the health care system; existing instead within an environment affected more overtly and to a greater extent by commercial realities and interests (Agomo, 2012; Dobson and Perepelkin, 2011; Perepelkin and Dobson, 2010). These commercial interests invariably conflicted with, and at times, dominated professional interests (Bradley et al., 2018a). As a result, the pharmacist was often labeled, and not necessarily unjustly, with the pejorative "shopkeeper" (Hughes and McCann, 2003). Pharmacy was viewed, and continues to be viewed by some, as primarily a commercial activity (Perepelkin, 2011), and by extension, the interactions that occurred between pharmacists and those receiving pharmacy services.

The nadir of pharmacy as well as its claim to professional status in North America is seen to have occurred in the mid-twentieth century with the erosion of demand for traditional pharmacy skills such as the compounding of medicine, and the virtual relinquishing of the patient care role as articulated in the 1952 American Pharmaceutical Association (APhA) Code of Ethics (Buerki and Vottero, 2002; Troy and Beringer, 2006).

> The pharmacist should never discuss the therapeutic effect of a physician's prescription with a patron nor disclose details of composition which the physician has withheld, suggesting to the patient that such details can be properly discussed with the prescriber only.
>
> APhA, 1952

The Code effectively banned the communicating of additional therapeutic information by the pharmacist to the patient. At this point, the relationship between patient and pharmacist can be seen a little more than a commercial transaction. Pharmacy and community pharmacy, in particular, appeared to function as little more than an esteemed occupation, and not as the profession it claimed to be.

Since the mid-twentieth century, however, pharmacy has made great strides toward claiming full standing as a health profession. Pharmacists have expanded their role beyond the dispensing of medicines to a range of health and drug related services and activities (Kelly et al., 2014; Owens and Gibbs, 2001; Perepelkin, 2011), and increasingly display collectively many of the attributes associated with a profession (Waterfield, 2010). Indeed, some are so optimistic as to conclude that pharmacy is a profession (Agomo, 2012). However, it can be argued that there are still many challenges and much in the way of attitudes and behaviors that must change before such an assertion goes wholly unchallenged (Davies and Tsuyuki, 2014).

As noted previously, pharmacy has faced many external challenges to its status as a profession (Beales and Austin, 2006), and these challenges continue as other professions and groups seek to advance their own status and authority (Agomo, 2012); in part, by claiming scopes of practice and roles that contest pharmacy's claim of professional exclusivity (Gregory and Austin, 2017). As well, technological changes are reducing the need for traditional pharmacy skills and claims to special, unattainable knowledge (Waterfield, 2010). Pharmacists have also done much to curtail their claim to professional status in the actions undertaken by some of its members within the pharmacy practice environment (Agomo, 2012; Davies and Tsuyuki, 2014). These "self-inflected wounds" often arise out of the commercial aspects of community pharmacy practice; but, nonetheless, suggest diminished professional expectations regarding appropriate values and behaviors within the profession of pharmacy.

To be seen as a profession; therefore, pharmacy must move away from the mere provision of a product (the prescription) toward patient-centered care that may or may not include the providing of a product (ACCP, 2009; Hammer, 2000). Further, more than merely shifting the focus of work, pharmacy must more consistently demonstrate the structural and behavior attributes of a health profession. Pharmacy must possess the clinical knowledge and skills, and the ability to control how these are used to provide patient care through self-regulation and professional autonomy. In addition, pharmacy must possess and convey the attitudes, values, and habits that are at the core of a profession (ACCP, 2009). Attributes such as altruism, accountability, excellence, duty, honor, integrity, and respect for others (Hammer, 2000).

In effect, to be a profession, pharmacy must place the well-being of the patient at the center of practice, and commit itself to the betterment of the profession and society (ASHP, 2008). Indeed, recent versions of codes of conduct for pharmacists seem to reiterate these principles. In the United Kingdom (UK), for example, pharmacists are called upon to make the care of the patient their first concern. In addition, the UK pharmacist should expect to " . . . exercise professional judgement in the interest of patients; show respect to others; encourage patients to participate in decisions about their care; develop . . . knowledge and competence; be honest and trustworthy; and be responsible for (their) actions" (Agomo, 2012)

Professionalism as a Construct

In reviewing the literature, various definitions of professionalism are provided (Elvey et al., 2011; Hammer, 2000; MacKenzie, 2007). In addition to possessing the structural and attitudinal traits of a profession, professionalism is also confirmed through behaviors that demonstrate various profession traits (Bumgarner et al., 2007; Thompson et al., 2008). To that end, a bicycle wheel metaphor is often used to explain the nature of professionalism and the relationship between various professional traits (ACCP, 2009; Bumgarner et al., 2007; Hammer et al., 2003).

Attributed mainly to the work of Hammer et al., the bicycle wheel conceptualization of professionalism includes the following: the hub representing professional values such as altruism, caring, and integrity; the spokes representing behaviors seen to arise from these values such as respect, accountability, and empathy; and the outer rim of the wheel representing the more superficial aspects of professionalism such as professional dress (Bumgarner et al., 2007).

While helpful in explaining, the relationship between various professional attributes associated with professionalism, Hammer's metaphor is somewhat limited in linking professionalism to actions or consequences. A more recent version of the bicycle wheel metaphor is offered by the American College of Clinical Pharmacy (ACCP, 2009) that identifies the hub as "the fiducial or covenantal relationship between pharmacist and patients." Similar to earlier versions, the spokes are seen as the behaviors expected to arise from a commitment to patients. Unlike the earlier version that viewed the tire or rim as the surface of the profession, the ACCP version perceives the rim as the interaction between professionalism and the various pharmacy activities that are affected by professional values and behaviors such as patient care, teaching, scientific discovery, application and scholarship, professional service, and leadership.

Patient-Centered Professionalism

The concept of professionalism in pharmacy practice has evolved over time, and will continue to evolve to reflect the values and beliefs of the profession, and the larger society in which the profession resides and seeks to serve. For some decades, the focus of the profession has been moving away from a product focus to a service focus, and from a medicines-focus toward a patient-focus; a patient-focus that has culminated with the adoption of a patient-centered model of care.

Just as there are a number of definitions for professionalism, a similar observation can be made for patient-centered care. This is partly due to an evolving understanding of a concept. Patient-centered care initially focused on providers working in the interests and preferences of the patient before moving toward a patient-driven paradigm of care. A paradigm based on the needs and values of patients functioning as engaged and informed participants in their care decisions (Hutchings et al., 2010).

The features of patient-centered professionalism build upon the core attributes of a profession and professionalism, but, in addition, seek to more fully articulate the primacy of the patient. The concept highlights the importance of a positive relationship between the patient and the provider, and the obligation of the provider to respect and support the right and ability of patients to make decisions about when and what care will be sought and accepted. The provider facilitates the process by communicating all relevant information and options. Information and options based on the preferences and values of the patient (Hutchings and Rapport, 2012).

Elvey et al. (2015) identify three constructs associated with patient-centered professionalism; including competence (knowledge and accountability); ethical values (trustworthy and patient-focussed); and communication. The third construct is most notable in building upon existing and past models of professionalism and includes attributes such as communicating clearly, listening, being approachable, and staying calm, and remaining polite and pleasant (Elvey et al., 2015). A key feature of communication in patient-centered professionalism is the ability of the provider not only to communicate effectively, but also to possess the skills, attitudes, and values that ensure patients receive the information they need to make choices that best reflect their interests and preferences (Hutchings and Rapport, 2012). By holding and demonstrating the values that align with these goals, the provider best displays patient-centered professionalism.

As health care providers move toward patient-centered professionalism, the concept of patient-centeredness approach continues to evolve. Presently, patient-centered care is viewed as a partnership between the patient and the health care provider(s); a process that encourages participatory decision-making, reflects patient preferences, and supports self-management that builds upon the benefits of the health services provided by the pharmacist. In addition, patients and those advocating on their behalf are increasingly seeking to influence health research and health policy (Laurance et al., 2014; Thomson et al., 2005). This can be seen in the growing level of participation by patients and their advocates through: research advisory groups (Hersh et al., 2016); drug regulatory authorities such as the Food and Drug Administration in the United States (Salcido, 2016); drug and technology assessment committees such as the Canadian Agency for Drugs and Technologies in Health (Berglas et al., 2016); and various disease advocacy groups.

As patient engagement in various aspects of the health care system continues to grow, the potential for conflict with the health professions can also be expected to increase. Despite the rhetoric around patient-centered care (Epstein et al., 2010), the health care domain is still dominated by the values and preferences of providers. While patients are beginning to find their voice and are encouraged to participate more in their own care, the fundamental nature of the relationship is dominated by the provider due to various power imbalances in knowledge, prestige, and social status.

If the patient/public voice should actually come to dominate the discourse around health care, policy and research, disruption of current power relationships will invariably lead to role conflict. As new power dynamics emerge, what constitutes a profession will also need to evolve, as those seeking to meet a societal need must respond to changing demands and expectations. Some of the traits currently associated with a profession, such as specialized knowledge and skills; performing a service important to society; prestige; autonomy; and self-regulation (Hammer, 2000), may be redefined or possibly curtailed to better fit the needs and goals of an increasing influential group existing outside the profession. At the same time, the fundamental concept of professionalism, in which the best interests of the patient have primacy, will remain at the core of the profession, and the patient-pharmacist relationship.

The Professionalization of Pharmacy Students and Practitioners

Professionalism is generally seen as possessing and/or demonstrating the structural and attitudinal traits of the profession (Bumgarner et al., 2007; Thompson et al., 2008). The acquisition of these traits is seen to occur through the ongoing professionalization of students and practitioners (Khanfar et al., 2012). While an individual, prior to joining a profession, may possess some of the traits of the profession (Hammer, 2000), it is through participation over time as a member of the profession, first as a new entrant/student and then as a licensed practitioner that the full range of traits may be developed to a level beyond the minimal standard acceptable to the profession, and the society it serves. In addition to developing these traits over time, practitioners must also adjust to changing expectations within society and the profession as to what constitutes professionalism; changes that oblige the individual practitioner to acquire and to modify the attitudes and skills needed to meet evolving professional standards.

Much of the pharmacy literature on professionalization (the acquiring of professional traits) focuses on pharmacy students (Hammer, 2000; Hammer et al., 2003; Hanna et al., 2017; Poirier and Gupchup 2010; Thompson et al., 2008). In addition to therapeutic knowledge and clinical skills, it is during undergraduate pharmacy training that students begin to acquire the values and behaviors of the profession through professional socialization (Thompson et al., 2008); a process by which acceptable group norms, values, and behaviors are communicated to, and it is being observed and adopted by the new entrant (Hammer, 2000).

For much of the recent history of the profession, the socialization of new pharmacy entrants was a relatively unstructured and informal process, in which students were expected to acquire the necessary values and attitudes through their participation in a pharmacy training program and the observation of role models, both within the pharmacy faculties and the wider profession. More recently, in part due to growing concerns over a perceived decline in professionalism (ASHP, 2008), pharmacy training programs have begun to introduce formal activities and explicit curricular content to support the adoption of professional attitudes and values by students.

An activity designed to instill professionalism in students that is familiar to many health care professions is the White Coat ceremony. Often this event is seen as celebratory with families and friends of the students attending to witness the assuming of the professional role.

Usually occurring in the first year of a professional program, students will collectively don white lab coats as a symbol of their acceptance of professional values, duties and responsibilities (Agomo, 2012). White coat ceremonies may include other activities such as professional oaths and pledges of professionalism (Poirier and Gupchup, 2010). To further support the communicating of professional values, students are often directed to create a specific professionalism pledge for their cohort to be recited at the White Coat ceremony (Hammer, 2000).

Students are also encouraged to actively participate in student and professional organizations (Poirier and Gupchup, 2010). Taking on leadership roles or contributing in other ways to advance the profession can illustrate and reenforce the values and behaviors that will be increasingly expected of them as they move through their program and on into pharmacy practice.

In addition to these extracurricular activities, explicit curricular content in many programs has expanded to address the various aspects and importance of professionalism. The literature also suggests that an integrated rather than a diffused approach is more effective in communicating the relevance of professionalism to students (Schafheutle et al., 2013). The importance of

professionalism as an explicit part of undergraduate training can be seen in the inclusion of professionalism within the educational standards of accrediting bodies such as the Accreditation Council of Pharmacy Education (United States) (Akiyode, 2016) and the educational outcomes identified by national associations such as the Association of Faculties of Pharmacy of Canada (AFPC, 2017).

In addition to the content of the pharmacy program, fellow students and those that deliver that program also play critical roles in ensuring the professionalization of pharmacy students. In addition to explicit curricular content designed to advance professionalism, students are also informed by the "hidden" curriculum (Akiyode, 2016; Schafheutle et al., 2013). The hidden curriculum often consists of the observation by students of the behaviors of other students, faculty, and preceptors within the program, and the consequences associated with these behaviors. The effects of the hidden curriculum often have a greater impact on student values, and behaviors as cause and effect are generally more easily observable, and therefore seen to be more credible than the theory-based content delivered within the formal curriculum.

The credibility of curricular content is also affected by the behaviors and attitudes adopted and demonstrated by program faculty. Faculty that fail to demonstrate professionalism can adversely affect student adoption of the professional values and behaviors put for by the faculty and the program (Do as I say, not as I do).

In an effort to communicate professional values and acceptable behaviors, many training programs also develop codes of conduct/ethics for both students and faculty (Hammer, 2000). However, as with the hidden curriculum, it is the extent to which these codes are "lived" or seen to be relevant, rather than what is espoused that determine their impact on professionalism over the long term.

Once students complete their formal training and enter pharmacy practice, the concept of professionalism as understood by the new pharmacy graduate will continue to develop. The importance and impact of professional mentors (ASHP, 2008; Schafheutle et al., 2013), especially in the early years of practice, cannot be overstated. Even with a solid foundation of professional values, new practitioners are not immune to the pressure to conform with, "how things are done" once they enter practice. Appropriate role models within pharmacy practice are therefore essential to reenforce and further develop professional values, attitudes, and behaviors gained during their undergraduate training.

The historical separation of practitioners and academic faculty ("town vs. gown") is often reflected in the holding of very different views of how a profession must function to be successful, an incongruence not confined to pharmacy. New graduates and even undergraduates in clinical placements will often be told by seasoned and not-so-seasoned practitioners, "That may be what they do in the ivory tower; but, things work differently here in the real world." While not understating the value and importance of hard won practical knowledge and the need for new pharmacists to gain the experience needed to become the drug experts they aspire to be, pragmatic practices and solutions must be tempered with adherence to principles, both professional and personal. Professionalism defined as adherence to the attributes of a profession (Agomo, 2012) ensures that new practitioners will successfully merge newly acquired values and behaviors with knowledge and experience, and so, in their turn, become professional role models to those that follow.

Why Professionalism Matters

Professionalism as a topic and as an issue in health care in general, and pharmacy in particular has grown in prevalence and importance over the past two decades (Elvey et al., 2011). A perception of a general decline in professional behavior and performance has been attributed to creating this increased interest, and a number factors have been ascribed to this perceived decline (ASHP, 2008).

Some of the factors seen to adverse affect professionalism, such as limited resources and rising levels of demand for health services, put a strain on the ability of health care providers to effectively care for patients in a manner deemed appropriate by both patients and providers.

At the same time, the fundamental nature of the relationship between patients and providers has been and continues to change as patients seek a greater voice in the decisions that affect their care (Benson et al., 2009), and, through new technologies, acquire the capacity to challenge the knowledge and associated authority previously ceded to providers.

As patients seek new relationships with various health care providers, providers such as pharmacists are also evolving in terms of their expertise and scopes of practice that, in and of themselves are changing the relationship between pharmacists and those they seek to serve. With expanded scopes of practice and increased capacity to materially affect patient care, pharmacists are being called upon to accept more responsibility and accountability for the manner in which care is provided, and the consequences that result from that care (Benson et al., 2009; Elvey et al., 2015).

In this environment of change and uncertainty, the need for a high level of professionalism cannot be understated. Professionalism in our dealings with patients will be essential as the roles and responsibilities of both patients and pharmacists are redefined. By maintaining a high level of professionalism, pharmacy can confirm its value to the people it seeks to serve. As asserted by Hammer nearly two decades earlier,

> . . . to maintain the trust and respect that has been historically afforded to the profession by the public, pharmacists need to keep professionalism as the basis of all professional activities
>
> Hammer, 2000

In addition to changing patient relationships, pharmacists are finding that their relationships with other health professions are also changing. Pharmacists are engaging more with other health professions in more collaborative approaches to care due to a wider recognition of the value and expertise of pharmacists, and an increasing willingness by other professions to access that expertise (Bradley et al., 2008b; Makowsky et al., 2009). How well pharmacists successfully engage with other health professions will be affected, in part, by their demonstrated competencies, attitudes, and behaviors. In this way, the professionalism displayed by the pharmacist will be critical to their ability to participate in and contribute to effective patient care.

The importance of professionalism in practice is also illustrated when the pharmacist is faced with situations where professional values may conflict with personal values (Benson et al., 2009). While not the intent of this chapter to extensively address the issue of professional ethics, when these conflicts do arise, how the pharmacist chooses to act is fundamentally a reflection of the professionalism of the pharmacist.

To express it another way, as moral beings, when we are faced with a moral or ethical decision we may ask, "What should I do and how should it be done?" (MacKenzie, 2007). In deciding how to respond, the individuals will seek to do so a way that is consistent with their values. Through the lens of professional ethics, which are based largely on collective values articulated in professional codes of ethics and role models of the "good pharmacist," the question the pharmacist must answer is, "What kind of person should I be to fulfill my professional obligations?" (MacKenzie, 2007). In this situation, the moral individual is subordinate to the societal role of the pharmacist, with the understanding that individuals who accept this role are expected to fulfill that role based on society's expectations.

Whether it is a patient seeking a legal, therapeutically justified therapy with which the pharmacist has personal moral concerns, or a colleague behaving in a manner that the pharmacist finds unprofessional, how the pharmacist chooses to respond will reflect the tension between these two competing approaches to decision-making. Ultimately, whether or not the conflict is resolved, whether the pharmacist elects to adopt a solution more consistent with their values as a moral individual or the values of the professional collective, professionalism will be critical to ensure that the pharmacist, within his/her capacity to do so, will act in a manner that ensures optimal care, that is, care that reflects the best interests and preferences of the patient. To do otherwise, is to demonstrate a lack of professionalism.

Summary

Professionalism has been defined as demonstrating the traits of the profession (Agomo, 2012). While there is no consensus on specific traits (Waterfield, 2010), professional traits are categorized as either structural or attitudinal (Hammer, 2000). Among the traits identified is the confidential nature of patient-client relationship (Waterfield, 2010). Professions differ most from nonprofessional occupations, in that the relationship between provider and recipient is built upon the ability of the patient or client to trust that the professional will be working in their interests.

The concept of professionalism in pharmacy practice has evolved over time, and has culminated with patient-centered professionalism. Patient-centered professionalism build upon the core attributes of a profession and professionalism; but, in addition, seek to more fully articulate the primacy of the patient.

The acquisition of professionalism is seen to occur through the ongoing professionalization of students and practitioners (Khanfar et al., 2012). In addition to developing these traits, practitioners must adjust to changing expectations within society and the profession as to what constitutes professionalism.

A perception of a general decline in professional behavior and performance has been attributed to a number factors (ASHP, 2008). With expanded scopes of practice and increased capacity to materially affect patient care, pharmacist are being called upon to accept more responsibility and accountability for the manner, in which care is provided, and the consequences that result from that care (Benson et al., 2009; Elvey et al., 2015).

In addition to patient relationships, pharmacists are finding that their relationships with other health professions are also changing. Pharmacists are engaging more with other health professions in more collaborative approaches to care due to a wider recognition of the value and expertise of pharmacists, and an increasing willingness by other professions to access that expertise the professionalism displayed by the pharmacist will be critical to their ability to participate in and contribute to effective patient care.

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Regulating Pharmacy Professionals

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Introduction and Scope

The governance and regulation of pharmacy professionals provides the framework through which individuals and families are enabled to experience the knowledge and skills of pharmacy professionals. It is also the structure through which pharmacy professionals' authority, responsibility, and accountability are demonstrated. Simply stated, the effective governance and regulation of pharmacy practices enable access to knowledge, skills, and services and balances this with the authorities, responsibilities, and accountabilities necessary to ensuring that they are provided in a manner that serves the publics' interest (Health Practitioner Regulation National Law Act, 2009; Health Professions Act, 2000; Pickett, 2017; The Pharmacy Order, 2010).

The governance of pharmacy professionals includes many tools and processes. The manner and extent in which each of these is applied differs between countries, and often between jurisdictions within countries. Jurisdiction is usually determined through national constitutions that determine whether the delivery and funding of health care is a national or provincial/state responsibility (Health Workforce Regulation, 2016).

This chapter explores the purpose, structure, and processes common to governing and regulating pharmacy professionals and briefly discusses some differences in the approach used in different countries and jurisdictions.

The Alberta College of Pharmacists (ACP), which governs and regulates pharmacists, pharmacy technicians, and the operation of licensed pharmacies in Alberta, Canada, will serve as a case study. It has been selected, as since April 2007, pharmacists practicing in Alberta have enjoyed one of the broadest scopes of practice of pharmacists in the world. The case study will share insights about the processes and policy considerations that enabled these privileges, the challenges of change, and structures and processes developed to effectively balance the authority with accountability.

The chapter concludes with a discussion about some of the new challenges facing the governance and regulation of pharmacists and pharmacy technicians, inviting thought about emerging considerations important to the future.

Why are Pharmacy Professionals Regulated?

Pharmacy professionals perform two fundamental functions important to society.

1. They are the stewards and the trusted source of drugs that individuals receive either pursuant to a prescription, through a pharmacist's recommendation, or through self-selected purchase in a pharmacy. In this stewardship role, pharmacy professionals are responsible for the procurement, storage, handling, packaging, labeling, and distribution of drugs in a manner that ensures the appropriate security and integrity of drugs. Pharmacy professionals hold responsibility to individuals and to society to ensure the quality and integrity of drugs received by an individual, their guardian, or any other individual who has responsibility for their care (Operation of Licensed Pharmacies, 2007; Standards for Pharmacy Professionals, 2017).
2. Pharmacists support individuals pursue their health goals by assessing, care planning, and supporting them in the selection and use of health interventions that meet their personal preference and needs. This includes providing advice about drug and nondrug alternatives and in a growing number of jurisdictions such as Alberta, which includes prescribing. The scope of this role differs substantively between jurisdictions. Regardless, pharmacists in their professional capacity are recognized throughout

society as having a "higher level of knowledge" about drugs and their proper use, and therefore, individuals and society entrust that knowledge to be used ethically and effectively to improve and/or maintain their health (Standards of Practice, 2011a; Standards for Registered Pharmacies, 2018a).

These responsibilities provide opportunities and benefit to individuals and society; however, if not exercised properly it invite risk. Governments use legislation as a tool to mitigate this risk. While the development and administration of legislation differs between jurisdictions, its primary purpose focuses on the interests of the public. The acts of developing public policy, creating legislation, and administering the authorities and processes that flow from it form the discipline of "regulation" (Standards of Practice, 2011b).

What Authority Supports the Governance and Regulation of Pharmacy Professionals?

While the practice of apothecaries and pharmacists has a long and varied history, the regulation of pharmacy practice has evolved from the guilds in Europe that recognized unique bodies of knowledge and skills that were restricted to individuals of the guild. In some jurisdictions, pharmacists were regulated with physicians as part of the medical community. In the western world, recognition of the unique attributes of pharmacists' knowledge and skills became more prevalent in the 1800s, leading to the autonomous regulation of their practices (Standards for Registered Pharmacies, 2018b).

The formal recognition and regulation of pharmacy technicians continues to evolve and has an increasing presence in the 21st century. Where regulated, pharmacy technicians are often regulated collectively under legislation that governs pharmacists. For example, pharmacy technicians became regulated under the Health Professions Act in Alberta, Canada, on July 1, 2011, the same day that the General Pharmaceutical Council was authorized to regulate technicians in England, Scotland, and Wales.

Today, pharmacy professionals are governed and regulated through two distinct models: the privilege of self-regulation or directly by the government.

Where self-regulation exists, it is a privilege that is granted by government through legislation. It is based on the belief that pharmacy professionals are the most knowledgeable about their profession(s) and the practice expectations of their registrants; and, that within the authorities and accountabilities granted through legislation, are the best positioned to regulate and adjudicate the practices of their own registrants. The concept of self-regulation is a privilege that can be granted and can be taken away (Standards of Practice, 2011b). While it is common in western societies, there is a high degree of variability in legislation, the autonomy that is granted by government, and how accountability is demonstrated (Health Workforce Regulation, 2016).

Regulatory Cultures Differ

The specific wording of legislation authorizing the regulation of pharmacy professionals is the foundation for the scope, interpretation, and application of the legislation. For example, " . . . protection of the public . . . " may be interpreted to provide narrower authority than " . . . in the public's interest . . . " Therefore, the authority granted in legislation will impact the culture and the approach a council/board responsible for administering the legislation will take.

The Health Professions Act in Alberta requires the council of the Alberta College of Pharmacists to "carry out its activities and govern its regulated members in a manner that protects and serves the public interest" (Health Practitioner Regulation National Law Act, 2009). The council has adopted the following vision statement: "Healthy Albertans through Excellence in Pharmacy Practice." Its mission is to "govern pharmacists, pharmacy technicians, and pharmacies in Alberta to support and protect the public's health and well-being. We take responsibility for pharmacy practice by setting and enforcing high standards of competence and ethical conduct" (Abpharmacy, 2018). The governing council has interpreted its responsibility to "act in the publics' interest" to be broader than simply "protecting the public." This invites the vision to pursue excellence in practice. It also means that the council focuses on quality, not simply safety, which is often defaulted to when behaviors are restricted to "protecting the public."

The college has adopted the Health Quality Matrix of the Health Quality Council of Alberta to define quality. The matrix includes six dimensions that collectively define quality: acceptability, accessibility, appropriateness, effectiveness, efficiency, and safety (Alberta Quality Matrix Users Guide, 2005).

As safety is only one of the six dimensions, this invites broader discussion and thinking by the college in its pursuit of quality pharmacy practices. It also requires the college to think more systemically and to be a recognized partner in the development of health policy where pharmacy professionals and drugs play a role.

These interpretations impact the culture and behaviors of pharmacy regulators in other ways too. Considerations that may be impacted are the relative balances that a regulator places on:

- risk tolerance versus risk aversity;
- quality improvement versus quality assurance; or
- encouraging a "just culture" versus a punitive approach to managing errors.

Pharmacy regulators and pharmacy professionals are also impacted by other systemic factors. Legislation governing pharmacy professionals does not exist in isolation and is part of a larger body of law that governs societies. For example, there are still

jurisdictions where dispensing errors may be addressed as a criminal offense (The Pharmacist, 2017). Societies that are highly litigious may be less compelled to adopt a "just culture," which impacts the culture of regulation, how decisions are made, and consequences arising from them. Arguably, this may impact the courage of pharmacy professionals to exercise critical thinking and professional judgment for the fear of consequences. It certainly impedes opportunities to learn from honest mistakes, a foundation to quality improvement processes.

How are Pharmacy Regulators Held Accountable?

Legislation is the tool through which pharmacy regulators are held accountable, and in turn is the foundation through which regulators hold pharmacy professionals accountable to society. Depending on the country, pharmacy professionals may be regulated nationally, or within state or provincial jurisdictions. For example, pharmacy professionals in Europe (The Pharmacy Order, 2010) and Australia (Health Practitioner Regulation National Law Act, 2009; Health Workforce Regulation, 2016) are most often regulated by a national body, whereas in North America (American Pharmacy Regulatory Authorities, 2019; Canadian Pharmacy Regulatory Authorities, 2009; Health Professions Act, 2000), the governance and regulation of pharmacy professions is a state or provincial responsibility, especially legislation governing the professions is national and state/provincial in scope. Where pharmacy professions are governed at the state or provincial level, there is still usually some linkage to federal policy, which is often determined by the national constitution.

The legislative structures and processes through which legislation is developed differ slightly between jurisdictions, but again have a high degree of commonality. At the highest level, members of the national or state/provincial government (as the case may be) approve legislation. The legislation defines governance and regulation, its scope, and who is responsible for its stewardship. It also defines processes for the development and approval of additional levels of control through regulations, codes of ethics, and standards. The legislation provides the highest level of definition for the authority and accountability granted to regulators (Health Practitioner Regulation National Law Act, 2009; Health Professions Act, 2000; The Pharmacy Order, 2010).

Legislation defines who has what authority, to make what rules, and how the development and approval of these must be carried out. Legislation is usually debated and approved at parliamentary or legislative assembly levels, including all parties of the legislative forum. Regulations often require approval of an element of government (i.e., the Minister or Cabinet), however, not the approval of an entire parliament or legislative assembly. Governing councils/boards of self-governing professions usually have authority and responsibility to develop and approve codes of ethics and standards, albeit the scope of each of these is usually defined and/or restricted in legislation.

Where the privilege of "self-governance" is enjoyed, legislation will establish the need for a governing council or board, its membership and how that is determined, the scope of its authority (including limitations), and requirements for reporting (including to who). Depending on the jurisdiction, the council/board may include elected pharmacy professionals and/or individuals appointed by government on behalf of the public. The legislation usually defines council/board membership; prescribing the number of council/board members and how many must be pharmacy professionals vs. individuals appointed by the government; and, the extent to which democracy is accommodated through elections. Government appointments are one means through which accountability to the public is exercised by governments.

A second means through which legislation accommodates accountability is by prescribing the processes that councils/boards must use in carrying out their business, and specifically the means through which regulatory instruments such as regulations, bylaws, standards, and codes of ethics are developed and approved. Transparency, objectivity, and fairness are common principles often required by legislation that are reflected in the processes of regulators. Examples of these are the need to consult with registrants, other professions, interested parties, and sometimes the public prior to approving regulations, standards, or a code of ethics (Health Practitioner Regulation National Law Act, 2009; Health Professions Act, 2000; The Pharmacy Order, 2010).

The process of consultation invites transparency and inclusiveness as a means of contributing to objective and fair decisions that effectively address the issue, problem, or risk that they are intended to mitigate. The most effective consultations include engagement and discussion, as compared to traditional processes of simply inviting feedback to a DRAFT proposal that may be limited by the insights and biases of a few individuals who have contributed to its development. Inclusiveness through broader engagement invites more possibility through a diversity of ideas and can identify alternatives that are not feasible or that are less likely to be accepted.

Legislation also prescribes rules and processes for investigating complaints and how they are resolved. This again includes a variety of tools and processes, these being highly influenced by the national constitution, the culture, and the traditional philosophies of the government. Where self-governance exists, processes often balance objectivity and fairness through rules of natural justice and balance this with accountabilities demonstrated through open and transparent processes. This includes but may not be limited to advising the public about when hearings are scheduled, allowing the public to observe proceedings, and transparent reporting of the proceedings and decisions arising from them. Legislation often requires that tribunals include a minimum number of individuals appointed by government as representatives of the public. Accountability is further accommodated by processes for review and appeal. In some jurisdictions, processes are open to review by an ombudsman appointed by government. In most jurisdictions, legislation accommodates the right to appeal decisions of the regulator to the judiciary (Health Practitioner Regulation National Law Act, 2009; Health Professions Act, 2000; The Pharmacy Order, 2010).

Finally, accountability is demonstrated through reporting. Legislation usually requires that pharmacy governing bodies publish an annual report to the public through government. This is the means through which the public learns about the annual business and affairs of the regulator. A, legislation usually accommodates or requires the publication of the decisions of any tribunals established by the regulator.

In conclusion, the act of self-governance is a privilege that has been delegated to pharmacy regulators by governments on behalf of the public. Governments have ultimate authority to establish how pharmacy professions are governed, how the work of governance and regulation is carried out, and how accountability of the publics' interest is exercised. Where regulators do not conduct themselves in a manner that is seen to be in the public's interest, governments may intervene, and in some cases, repeal the privilege of self-governance (Legislative Assembly of British Columbia, 2003).

Models of Regulation

While the responsibilities of pharmacy regulators are highly common, different legislative models exist.

Historical models reflect legislation that is specific to professions such as pharmacists and pharmacy technicians, unique from that for physicians, nurses, physical therapists, dentists, and other health professions (Health Workforce Regulation, 2016). These models often reflect exclusive scopes of practice, restricting acts such as dispensing, compounding, and the selling of drugs exclusively to pharmacists, and the prescribing of drugs exclusively to physicians, dentists, and other select professions. Where the legislative model is unique to each profession, there can also be differences in the authorities and processes between pieces of legislation, often determined by the era in which the legislation was developed and passed. This inconsistency can create conflict in how services are delivered, and by extension, inconsistencies in how professional responsibilities are monitored and held accountable.

More recent legislative models, such as the Health Professions Act in Alberta, are omnibus legislation, governing multiple professions under a single Act (Health Professions Act, 2000). This results in common authorities, scope, and processes for every council/board governing a profession under the legislation. The legislation accommodates overlapping scopes of practice, rather than exclusive scopes of practice, inviting optimization of professionals' roles. Whereas traditional models differentiate professions through activities that are exclusive to specific professions (i.e., dispensing by pharmacists and prescribing by physicians), this newer model differentiates professions through role definition and restricted titles (i.e., only individuals who qualify and register with the Alberta College of Pharmacists can hold themselves out as a pharmacist).

Roles and Responsibilities of Regulating Bodies

In 2016, the Professional Standards Authority in Great Britain, in its discussion document "Regulation Rethought – Proposal for Reform" proposed that "the set of core functions that should be carried out by regulators should be":

- to *maintain a shared, public register of appropriately qualified health and care practitioners*
- *to award and renew licenses to practice in specific occupations*
- *to set common standards that all registrants must meet*
- *to investigate allegations that registrants do not meet the standards and take action.*
- *implicit within these core functions are such roles as assuring that once registered, practitioners remain appropriately qualified and that they continue to meet professional standard* (Professional Standards Authority, 2016).

These core functions are recognized in some manner in most regulatory schemes governing pharmacy professionals.

Regardless of the legislative model, the roles and responsibilities of pharmacy regulators may be simplistically described as:

"balancing
- the authority granted to individuals who qualify to be registered as pharmacy professionals; with,
- the accountabilities required to ensure that such entitlement results in the delivery of services that are in the publics' interest."

The root of all pharmacy regulator responsibilities is to define the educational requirements that candidates must complete and the competencies that they must demonstrate prior to being admitted to the register administered by the regulatory body. These are dependent on the culture of the health system, the health and health-care needs of the population being served, and the role that pharmacy professionals play in meeting these needs. Role definition and the development of competencies and educational requirements are highly interdependent and constantly evolve (Pickett, 2017; Standards of Practice, 2011b).

Pharmacy regulators are responsible for defining the roles of pharmacy professionals, and by extension the education that is required, and the competencies that must be demonstrated at entry to practice. Eligibility to practice as a pharmacy professional requires completion of approved and/or accredited learning and training.

Most pharmacy educational curriculums include classroom learning and structured practical training (SPT)/experiential learning through which candidates hone competencies and build confidence in applying the knowledge and skills that they have learned. Good SPT programs are competency based, structured, and supervized and mentored by standardized pharmacy professionals. They include opportunities for candidates to observe, demonstrate, and be evaluated on their competencies in real practice settings. This is important to building both professional competence and confidence.

Pharmacy regulators are responsible for establishing requirements for evaluating and admitting candidates at entry to practice. Depending on jurisdiction, evaluation may include one or more proctored, psychometrically standardized examinations. These often include case-based knowledge evaluation, objective-structured clinical evaluations (OSCE) where candidates must demonstrate clinical skills in mock situations, and jurisprudence exams through which candidates demonstrate their competencies in applying law and ethics.

Beyond minimal educational requirements and demonstrating competency at entry to practice, other requirements may be required at entry to practice. Examples include but are not limited to demonstration of good character and a requirement to hold a minimal amount of professional malpractice/liability insurance.

In summary, one of the most critical responsibilities of pharmacy regulators is defining requirements for entry to practice and ensuring that rigorous and effective processes are used to evaluate candidates applying for admission to the register. Once a candidate is admitted to the register and authorized to practice as a pharmacy professional, their practice and behavior will have a direct impact on the public and by extension the profession.

Pharmacy regulators are responsible for establishing requirements, and in some cases, administering processes, to ensure the competence of registrants throughout their professional careers. The knowledge and technologies important to pharmacy practice are rapidly evolving; therefore, pharmacy professionals must constantly learn and evolve their skills to best meet the needs of individuals in their care and to be relevant within the health system within which they practice. They must be relevant to and be responsive to the needs of their community.

The concept of "competence" was introduced to professional legislation in the 1990s. The definition of competence has evolved, most recently including the knowledge, skills, judgment, and attitude required to fulfil a professional role. Processes to effectively evaluate knowledge and skills and to a lesser degree judgment are common at entry to pharmacy practice (Austin, 2017).

Pharmacy regulators continue to search for means to meaningfully and effectively measure attitude; albeit, it may be the competence indicator that most substantively differentiates pharmacy professionals. While pharmacy professionals have access to common learning experiences, the manner and extent to which they choose to use and apply learning in their practices is in part determined by their attitude. This impacts (positively or negatively) their relationships with other professionals they practice with and the experiences of individuals in their care.

There is no "gold standard" for measuring competence. 16 Therefore, the way regulators address the competence of pharmacy professionals throughout their careers differs. Some processes used by pharmacy regulators to monitor competence include:

- standardized "onsite" practice evaluations,
- routine knowledge-based evaluations/examinations,
- reflection and documentation of professional practice experiences (maintenance of professional practice portfolios)
- prescribed hours, and sometimes content, of professional development,
- 360° feedback from peers, other health professionals, and patients, and/or
- Prescribed minimum hours of practice.

Each of these alternatives has their own weaknesses. Therefore, the way pharmacy regulators address continuing competence programs and requirements differs substantively. Most common are requirements to annually participate in a minimum number of hours of professional development. In many jurisdictions, this is enhanced with secondary requirements, often including one or more of the examples listed above.

It has been argued that regulators need to revitalize the concept of "professionalism" within the professions they regulate. He argues that competent behaviors are intuitive when "professionalism" is demonstrated with every individual served. If we accept his argument, then a culture of professionalism is critical in all pharmacy education, both undergraduate and post-professional and within the practice culture of every pharmacy team (Austin, 2017).

The third core responsibility of pharmacy regulators is to establish codes of ethics and standards for the practice of pharmacy professionals. Codes of ethics include broad principles that guide the behaviors and decisions of pharmacy professionals. A Code of Ethics withstands changes in time and addresses the responsibilities of pharmacy professionals to the individuals they serve, society, and their profession. Decision making and behavior in accordance with the Code of Ethics demonstrate ethical conduct.

Standards of practice are more codified, usually less principally oriented, and often more prescriptive. Standards of practice do not withstand time to the extent that a well-written Code of Ethics does and require frequent review and enhancement as changes in knowledge, technology, and health systems occur.

Standards of practice are the root indicators that pharmacy regulators use for monitoring and adjudicating the acceptability and appropriateness of pharmacy practice. Standards prescribe "minimum requirements", and they are therefore not a good tool for measuring effectiveness or levels of performance. At best, monitoring adherence to standards of practice is an indicator of compliance and conformance. Therefore, standards of practice are not good tools for encouraging innovation, diversity, or excellence.

Where legislation authorizes regulators to license pharmacies, it usually provides authority to develop standards for operating pharmacies (Pharmacy and Drug Act, 2018). These often complement those for pharmacy professionals, however, establish minimum requirements for the pharmacy. They identify the minimum requirements of the pharmacy environment, which impacts the abilities and performance of pharmacy professionals.

These standards may address infrastructure and system requirements important to maintaining the integrity and security of the drug supply and information systems that provide secure solutions for recording and accessing patient specific information. They either address or complement other legislation in setting minimum requirements for cleanliness, hygiene, and workplace safety about hazardous products. They protect both the public and the health professionals practicing in the pharmacy (Standards for the Operation, 2011).

Standards for the practice of pharmacy professionals and standards for the operation of pharmacies are renowned for being highly prescriptive. This reflects the traditional roles of pharmacists for highly technical processes such as dispensing and compounding. As the responsibility of pharmacists evolves to increasingly focus on patient care rather than drug distribution, there is an urgency for pharmacy regulators to change how standards of practice are written.

Where pharmacist practice is based on person-centered care, success requires pharmacists to use critical thinking and exercise professional judgment. When standards of care are overly prescriptive, these expectations may be difficult to meet.

The final core responsibility of regulators is to receive, investigate, and resolve complaints. Processes for carrying out these responsibilities are defined in legislation to ensure "due process." In the developed world, these processes are usually based on the laws of natural justice, to ensure objectivity and fairness in both investigating and resolving complaints (Health Practitioner Regulation National Law Act, 2009; Health Professions Act, 2000; The Pharmacy Order, 2010).

Alternatives for resolving complaints are established in legislation and differ between jurisdictions. Most legislation provides for review by a panel of peers to determine the merits of the findings arising from an investigation; and where determined to be well-founded, authority to prescribe sanctions. The latitude for prescribing sanctions is established in legislation and differs between jurisdictions.

Most legislation provides opportunity to appeal the decision of a tribunal. Again, depending on legislation and jurisdiction, the procedures and avenue for appeal differs; but in the end, often includes the judiciary.

The Role of Regulators in Developing Public Policy

Regulators play an important role in developing public policy. As their authority either lies with government or is delegated from government on behalf of the public, they are an important resource to governments when developing policy about health systems.

Pharmacy regulators provide knowledge and experience important to health system design (particularly involving the role of pharmacy professionals), drug therapy, quality, and patient safety. It is important that they promote policies consistent with the mandate granted them through legislation, with a clear view to the public.

Regulators are often called upon to address expansion in the "scope of practice" for pharmacists and other pharmacy professionals. As establishing the roles of pharmacy professionals, their education, competency, code of ethics, and standards fall within the responsibilities of regulators, they are a source of expertise important to these discussions. However, as their legislative mandate focuses on the public, advocacy for such changes should reside with pharmacy professional/advocacy organizations, with the regulator providing secondary support consistent with their responsibilities.

Case Study—Pharmacy Practice in Alberta, Canada

Pharmacists in Alberta, Canada, enjoy one of the broadest scopes of pharmacist practice in the world. Since 2007, Alberta pharmacists have been able to prescribe drugs (except controlled substances) and administer injections (Pharmacists and Pharmacy Technicians Profession Regulation, 2011). While all pharmacists can "adapt" prescriptions written by other prescribers to modify or extend them to meet unique patient needs, a subset who have successfully completed a peer evaluation process, may be authorized by the Registrar to initiate and manage ongoing drug therapy. During the 2017/2018 influenza season, pharmacists administered over 50% of the publicly funded immunizations performed in Alberta (Abpharmacy, 2018). That's significant because government did not provide public funding for immunizations performed by pharmacists until December 2009, at the height of the H1N1 outbreak.

Pursuit of this scope of practice began in 1995, when Alberta's Premier appointed a committee on Health Workforce Rebalancing. Alberta was in an era of rapid economic and population growth, and it was observed that there would be a shortage of health professionals to meet public need. The committee observed that Alberta's existing health workforce could be optimized, if every health professional was able to fully use their knowledge and skills. This resulted in recommendations to rescind "exclusive" scopes

of practice and to create new legislation that accommodated overlapping scopes of practice and restricted titles. This provided opportunity for pharmacy to pursue broader roles and responsibilities for pharmacists in patient care. Beyond compounding, dispensing, and selling drugs, there was now possibility for pharmacists to prescribe and administer drugs by injection.

At that time, the Alberta Pharmaceutical Association (APhA) was the sole provincial organization for pharmacists. It held two mandates: one as regulator and the second as an advocate for the profession. Therefore, it had both authority and a responsibility to lead pharmacy's pursuit of an expanded scope of practice. Certainly, there was an expectation within the profession for it to champion this role.

The Alberta Government requested that all professions develop a role statement, describing what members of every health profession provided the public and the health system. The APhA's advisory committee delegated with this responsibility was intent on ensuring that pharmacy's role statement was futuristic, focusing on the role of pharmacists in patient care.

In 2000, government passed new omnibus legislation to govern and regulate 29 health professions, including pharmacists. The Health Professions Act includes two distinct sections. The first which is common to all regulated health professions addresses governance, registration, competence, and complaints resolution. The second section provides a unique schedule for each profession, providing a role statement and restricted titles (Health Professions Act, 2000).

The legislation requires that each profession be governed by "a college." Colleges are prohibited from negotiating fees or reimbursement for a profession. Therefore, in 2000, the Alberta Pharmaceutical Association was replaced by two new organizations; the Alberta College of Pharmacists (ACP) as the regulator and the Alberta Pharmacists Association (RxA) as the professional/advocacy organization for the profession. Leadership within ACP continued from the APhA; therefore, it took the lead in pursuing and bringing the current scope of practice to fruition.

Before being governed and regulated under the new legislation, regulations needed to be developed; both for governing pharmacists and the operation of licensed pharmacies. The new Act provided the foundation for evolving pharmacists' scope of practice to include prescribing and the administration of drugs by injection.

The governing council appointed a steering committee to conduct literature research and to develop a "whitepaper" to support the proposal (Literature Review and Whitepaper, 2003). It addressed public needs that pharmacists were well prepared to address because of their education and training. Complemented by their accessibility, this presented a new opportunity for Alberta's health system. The whitepaper was also supported by discussions evolving in Great Britain that proposed a new role for pharmacists in prescribing. This demonstrated that the vision of Alberta pharmacists was not isolated.

Additionally, research to demonstrate the ability of pharmacists to monitor drug treatment and to prescribe was initiated. A pharmacist lead and managed anticoagulation program was introduced at the University of Alberta Hospital in Edmonton, Alberta. A research team led by pharmacist Dr. Tammy Bungard, and including a Medical Internist, a Cardiologist, and a Hematologist, oversaw and evaluated the project. The results substantively supported an expansion of pharmacists' scope of practice to include prescribing. Bleeding times decreased, hospitalization related to anticoagulation decreased, health system costs decreased, and the satisfaction of patients, physicians, and pharmacists all increased. The project was so successful and that the demand for pharmacists in this role expanded across hospitals in Alberta and into the community (Bungard et al., 2006). This local research contributed to a perfect storm in Alberta, where policy makers were quickly seeing new opportunities through pharmacist practice. They began to recognize that the monitoring and prescribing roles performed by the anticoagulation pharmacy team were transferable to other chronic disease conditions.

The whitepaper and the results of the anticoagulation project were the foundation for engagement with patients, health advocacy organization leaders, regional health authorities, other professionals, and government. A joint working group was formed with the College of Physicians and Surgeons of Alberta (CPSA) to study ACP's proposal. It included two physicians, a community and hospital pharmacist, two members of the public, and the registrars of the CPSA and ACP. This provided better understanding of pharmacy's proposal by organized medicine.

The College and Association of Registered Nurses of Alberta were pursuing enhancements to the educational requirements of registered nurses at the same time. They agreed to support the pharmacy's proposal for pharmacists to prescribe and administer drugs by injection, if ACP would support their proposal for broadened educational requirements at entry to practice.

This engagement and these partnerships were instrumental to the support ACP required when presenting its proposal that pharmacists be entitled to prescribe and administer drugs by injection to government's Health Professions Advisory Committee in November 2003. This committee was responsible for advising the Minister about whether an expansion to the scope of practice for pharmacists should be made in the regulations under the Health Professions Act.

In 2005, the Pharmacists Profession Regulation was passed, followed by the Pharmacy and Drug Regulation in 2006, both coming into effect on April 1, 2007. This was a significant milestone in the history of pharmacist practice as pharmacists were finally recognized as having the competencies to make drug use decisions, rather than having to receive the authorization of other prescribers when drug-related problems were identified. This success was largely due to the following critical success factors:

- Government Policy—the goal of the provincial government was to optimize the role of all regulated health professionals under the new Health Professions Act.
- Timing—organized pharmacy engaged and was ready to respond to this opportunity.
- Local Research—the anticoagulation project provided local context and demonstrated value.
- Engagement—the whitepaper and local research provided a solid foundation for discussions with the public, policy makers, and other professions, providing them evidence to be advocates for the proposal.

- External Champions—the anticoagulation project created physician champions that supported pharmacists in prescribing
- Partnerships—the partnerships with CPSA and CARNA, both mitigated risk and created opportunity to support the proposal.

Emerging Considerations in Regulation

The governance and regulation of pharmacy professionals is increasingly complex, and the concept of "self-regulation" is scrutinized.

The public and some governments are increasingly sceptical about whether self-governing professions truly act in their interest, or whether they are too "internally preoccupied." Governments have responded in many ways. In some jurisdictions, they have required that a greater percentage of governing councils be members of the public appointed by government. In others, legislation has been amended allowing the Minister of Health to intervene on decisions of regulatory colleges, if they felt that the college was not acting in the public's interest. In extreme cases, governments have rescinded the privilege of some professions to govern themselves. Therefore, pharmacy regulators must always be seen to be acting and making decisions that are in the public's interest (Legislative Assembly of British Columbia, 2003; Professional Standards Authority, 2016).

The advent of new technologies facilitates new possibilities in how health services are delivered. The distant delivery of pharmacy services is growing. This extends beyond drug distribution, and now includes patient care services. New transportation and communication alternatives facilitate the delivery of these services over jurisdictional boundaries. This presents both opportunity and risk. It clearly invites new discussions about the governance of services that span jurisdictions and that could become international in scope.

Dispensing and patient care records developed by pharmacists are no longer simply relevant to the pharmacist/patient relationship. These records are now used and relied upon by other members of each patient's team. Where services are delivered between jurisdictions, information systems are seldom integrated, resulting in gaps in the local patient record. This fragmentation perils decisions by other health professionals who rely upon this information to make informed patient care decisions.

An increased value is being placed on "team-based" care; yet, governance and regulation are usually profession specific. This makes collaboration and partnerships between health regulators critical. Some argue that profession-specific regulation should be replaced by team-based regulation as this may facilitate a more integrated approach to the quality and safety that is in the public's interest.

Summary

The regulation of pharmacy professionals is increasingly complex, yet an important privilege that contributes to the identity and definition of pharmacy professions. The roles and responsibilities of pharmacy regulators are clearly entrenched in legislation. Sentinel is the responsibility of pharmacy regulators to observe the public as their primary customer. Their "means" is to provide stewardship over the practice of pharmacy professionals, while their "end" is to ensure that the public's interest is served and safety ensured.

Regulations governing pharmacy professionals differ substantively between jurisdictions; however, include core common responsibilities. While authorities and processes differ, legislation supporting the regulation of pharmacy professionals usually addresses governance, registration, competence, standard setting, and complaints resolution responsibilities.

Pharmacy regulators have an important complementary role in defining the scope of practice of pharmacy professionals. Their expertise in establishing roles, competencies, education, standards, and codes of ethics is important to supporting proposals lead by pharmacy professional/advocacy organizations. Policy support provided by regulators should always address the publics' interest.

Internationally, there is interest in expanding the scope of practice of pharmacists. In Canada alone, there is diversity in the scope of practice of pharmacists between provinces. Success in expanding the scope of practice depends on the alignment of multiple critical success factors.

The regulation of pharmacy professionals is increasingly complex and scrutinized. New technologies and globalization have invited new ways of delivering services. This invites new governance considerations when services cross jurisdictional boundaries. Further, new technologies invite new ways of doing things; and therefore, the need for new standards, and sometimes threats to some pharmacy professionals. In responding to these threats, pharmacy regulators must constantly be conscious of their responsibility to make decisions in the publics' interest, to ensure the confidence of their morale owner.

Glossary

- *Drugs*—infer scheduled substances that are licensed through legislated processes for the prevention, maintenance, and treatment of health conditions.
- *Governance*—is how society or groups within it, organize to make decisions. In pharmacy, the group authorized to govern may be delegated by government, or it may be government itself, depending on the jurisdiction.
- *Jurisdiction*—infers a country, province, state, or other regional form of government that holds responsibility for legislation that governs the practice of pharmacy professionals.

- *Pharmacy professionals*—infers pharmacists and pharmacy technicians and any other associated class of individuals who are regulated to support the practice of pharmacy.
- *Premier*—means the leader of the provincial government in Alberta, Canada
- *Regulates*—infers both governs and regulates.
- *Rules of natural justice*—In English law, natural justice is technical terminology for the **rule** against bias (nemo iudex in causa sua) and the right to a fair hearing (audi alteram partem). While the term natural justice is often retained as a general concept, it has largely been replaced and extended by the general "duty to act fairly."

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Public Health and Health Promotion in Pharmacy Practice

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What is Health?

There are numerous concepts and definitions of health and they can be narrowly technical to moral and philosophical. People's views on what health is vary considerably and an individual health professional's views might be very different from those of their patients. The Western scientific model of health dominates while being challenged by holistic and social models of heath. The common meaning of health is the absence of disease. In 1948 the WHO defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

This model has been criticized for being very hard to attain and also for medicalizing society.

By 1984 the WHO definition was more of a wellness model health as defined as "The extent to which an individual or group is able to realize aspirations and satisfy needs, and to change or cope with the environment. Health is a resource for everyday life, not the objective of living; it is a positive concept, emphasizing social and personal resources, as well as physical capacities." The Jakarta Declaration for health promotion, 1997 defined health as a basic human right and essential for economic and social development.

Health should not be thought of as simply as the absence of disease or the basis of physical fitness.

Health is holistic and comprises physical, mental, emotional, social, spiritual, and sexual dimensions.

It is also influenced by societal, environmental, and global issues. To be a healthy society, a society needs a basic infrastructure such as shelter, peace, food, and income. Well-being is about feeling good and functioning well and is used widely to encompass physical and mental health.

Defining Public Health

Like health itself there are numerous definitions of public health. A commonly used definition is "the science and art of preventing disease, prolonging life and promoting health through he organized efforts and informed choices of society."

There are three domains of public health: the first is health improvement; this includes people's lifestyles, inequalities in health, and the wider social influences on health. Second is the health protection including infectious diseases, environmental hazards, and emergency preparedness. Third is the health service delivery and quality (healthcare public health) including service planning, efficiency, audit, and evaluation. Pharmacy can play a role across all three domains.

Activities to strengthen public health aim to provide conditions under which people can stay healthy and maintain their health, improve their health and well-being, or prevent the deterioration of their health. Public health focuses on the entire spectrum of health and well-being, not only the eradication of particular diseases. Many activities are targeted at populations such as health campaigns. Public health services also include the provision of services to individuals, such as vaccinations, behavioral counseling, or health advice.

Five Waves of Public Health

Public health has been characterized into five waves. The first wave focuses on overcrowding, poor sanitation, contaminated water, poor nutrition, and a poor built environment. The second wave was when medicine emerged as science and during this time paternalistic approaches to healthcare gained precedence. This was institutionalized in the third wave through the redesign of social institutions in the early 20th century and the birth of the welfare state in the UK. The fourth wave in the 1960s moved to the risk theory of disease and the role played by individuals' lifestyle factors, including smoking, diet and physical activity, alongside concerns with social inequalities in health. The more recent fifth wave is defined by a "culture of health and well-being," in which the value of health and well-being and incentives for healthy behavior are maximized, healthy choices are promoted by default so that they are easier choices, and factors that create a culture and environment which promote unhealthy behavior are minimized.

The health improvements that have been seen in high-income countries are due to the impact of cleaner air, good housing, improved education, as well as changes to legislation and fiscal policies for example, immunization, family planning, antenatal care, screening programs, universal healthcare, and advances in diagnosis and medical interventions. Despite improvements in health, major inequalities in health outcomes, reflecting social and economic inequalities, remain. For example, in England, average life expectancy in the poorest communities remains seven years lower than in the wealthiest areas. Disability-free life expectancy is 17 years lower in the poorest communities. Health inequalities persist, despite policies aimed at reducing them.

The UN Sustainable Development Goals

The UN developed the sustainable development goals (SDGs) to be completed by 2030, (https://sustainabledevelopment.un.org/sdgs) following on from the previous millennium development goals. The goals cover a broad spectrum of global development. Goals 1–6 in particular address key issues in global public health: no poverty, zero hunger, good health, and well-being, quality education gender inequality, and clean water and sanitation.

The UN Secretary-General at the time of their launch, Ban Ki-Moon, said that "The 17 SDGs are our shared vision of humanity and a social contract between the world's leaders and the people. They are a to-do list for people and planet, and a blueprint for success."

See http://www.undp.org/content/undp/en/home/sustainable-development-goals.html

SDG 3—Ensure Healthy Lives and Promote Well-Being for All at All Ages

Each SDG has a number of associated targets. The associated targets for SDG3 are wide ranging and aim at the reduction of global maternal mortality, the end of preventable deaths of newborns, the end of the epidemics of AIDS, tuberculosis and malaria as well as the reduction by one third of premature mortality from noncommunicable diseases, tobacco control, prevention of substance and alcohol misuse, providing access to medicines for all, access to family planning as well as substantially increase health financing and the recruitment, development, training, and retention of the health workforce in developing countries. Pharmacy and pharmaceutical science can have an influence on most of these targets.

Eradicating Malaria as an Example

If eradicating malaria is taken as an example, it can be clearly seen that many of the SDGs apply to it.

SDG	*Implications for malaria*
SDg1 no poverty	Malaria disproportionately affects poor and vulnerable people.
SDG3 good health and well-being	By reducing the prevalence of waterborne diseases, vector control will contribute to defeating malaria and reducing mortality.
SDG4 quality education	Malaria can cause a significant level of school absenteeism seriously impacting on children's educational opportunities and futures.
SDG5 gender equality	Pregnant women are more vulnerable to malaria, and occupational exposure may make men more vulnerable.
SDG 6 clean water and sanitation	Cleaner water and sanitation water play a crucial part in the malarial parasite's lifecycle. Cooperation with the water and sanitation sectors is essential for control of malaria.
SDG 7 affordable and clean energy	The construction of hydroelectric dams has been associated with changes to malaria epidemiology
SDG8 decent work and economic growth	Time off work due to malaria causes lost productivity in the workplace
SDG9 industry, innovation, and infrastructure	Towns and cities need to be designed to reduce mosquito habitats
SDG11 sustainable cities and communities	Successfully implemented malaria control will lead to cleaner, safer, and more sustainable cities and communities without the breeding ground for mosquitoes
SDG13 climate action	It is expected that global warming will lead to an increase in malaria, leading to a higher disease burden across more countries
SDG17 partnerships for the goals	Successful control of malaria will require concerted efforts by numerous global partners

TB as a Global Public Health Issue

Another example of a global public health issues is TB, which is a leading killer worldwide, alongside HIV/AIDS. TB disproportionally affects world's most poor and vulnerable, aggravating existing inequalities. Because of TB, people face costs or suffer income loss equivalent on average to more than 50% of their income. In 2014 9.6 million people fell ill with TB and 1.5 people died from it, 1.2 million people living with HIV developed TB, and 480,000 people developed MDR-TB (multidrug-resistant TB), with 190,000 associated deaths. The WHO wish to eradicate TB by 2035 and have developed the end TB strategy (http://www.who.int/tb/post2015_strategy/en/); the WHO's aim of ending the global TB epidemic is feasible with the dramatic decline in TB deaths and cases, and elimination of economic and social burden of TB. Failure to do so will carry serious individual and global public health consequences. Achievement of this goal by 2035 requires: expanding the scope and reach of interventions for TB care and prevention, with a focus on high-impact, integrated and patient-centered approaches. Collaborative HIV and TB activities; bold policies and supportive systems through engaging a much wider set of collaborators across government, communities, and the private sector, intensified research and innovation that can dramatically change TB prevention and care.

At a more local level public health England have developed a TB strategy that aims to achieve a year-on-year decrease in incidence of TB, a reduction in health inequalities, and ultimately the elimination of TB as a public health problem in England. The strategy has 10 key areas for action:

1. Improving access to services and ensuring early diagnosis.
2. Providing universal access to high quality diagnostics.
3. Improving treatment and care services.
4. Ensuring comprehensive contact tracing.
5. Improving BCG vaccination uptake.
6. Reducing drug-resistant TB.
7. Increasing awareness.
8. Providing context-specific information for professionals and patients on the prevention and management of TB.
9. Tackling TB in under-served populations, systematically implementing new entrant latent TB screening.
10. Ensuring an appropriate workforce to deliver TB control.

Pharmacists can be involved in this strategy at every level from increasing awareness, screening, and pharmaceutical care of people with TB and developing new and effective antimicrobial treatments.

Alongside global measures such as the UN SDGs which focus on health, health inequalities, and many of the wider drivers of health, a number of new ideas and concepts are emerging in public health, including "fifth wave of public health," "ecological public health" and "planetary health."

Ecological Public Health

Ecological public health focuses on the array of environments through which health is influenced and the complex interactions between them. Ecological public health proposes that ill health is the result of a "mismatch of bodies and environment," which can be improved by addressing the factors across four environmental dimensions: material, biological, cultural, and social.

Planetary Health

Planetary health recognizes "the health of human civilization and the state of the natural systems on which it depends." The global increase in life expectancy and decrease in poverty and child mortality rates over the past 50 years have coincided with a depletion of the Earth's natural resources and increasing environmental impact. Planetary health acknowledges that as population size and demands on the planet increase, maintaining the health of the planet is vital to protecting future human health. It calls for "promoting sustainable and equitable patterns of consumption, reducing population growth, and harnessing the power of technology for change."

What is Health Promotion?

Health promotion is a range of activities and interventions, which aim to help people maintain and enhance good health and prevent ill-health by taking greater control over their health. Downie argued that, "the overall goal of health promotion may be summed up as the balanced enhancement of physical, mental and social facets of positive health, coupled with the prevention of physical, mental, and social ill-health."

The term encompasses a range of activities including those which support healthy lifestyles, encourage access to services, and involvement in healthy decisions, and seek to promote an environment in which healthy choices become easy choices and educate people about the body and keeping healthy. These may include both individual and societal aspects, overlapping with public health. At one end of this range are government policy and legislation affecting health. These include actions with a direct influence on health (e.g., legislation to ban tobacco smoking in public places) as well as those which affect the determinants of health (e.g., social welfare and benefits policies). Until the 1980s these activities were referred to as health education and it is only more recently that the term health promotion became used. The WHO moved the definition of health promotion away from disease prevention and screening toward the health and well-being of whole populations.

Heath Education

Health education is part of health promotion and involves activities to facilitate learning about health. WHO define it as "any combination of learning experiences designed to help individuals and communities improve their health, by increasing their knowledge or influencing their attitudes."

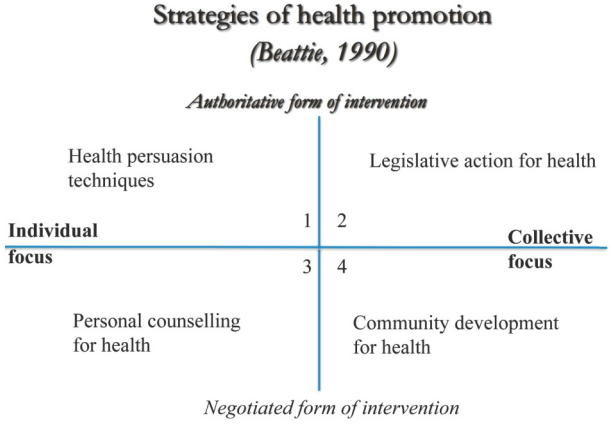
Tones and Tilford said that health promotion should be an umbrella term that includes all interventions to promote health and they proposed a smile formula health promotion = health education X healthy public policy.

Pharmacy and Health Promotion

Pharmacists and their teams provide information to promote and maintain good health, to support people's actions and behaviors related to health, and to contribute to improving quality of life. However, pharmacists often feel more comfortable linking such advice giving to the use of medicines and other health-related goods, as the provision of medicines and services focused around medicines remains their major role.

Health professionals engage in "people-centered health promotion," working over time with individuals and communities as well as policy makers and the overall political system empowering them to have the positive stares of and conditions for physical mental social and spiritual health.

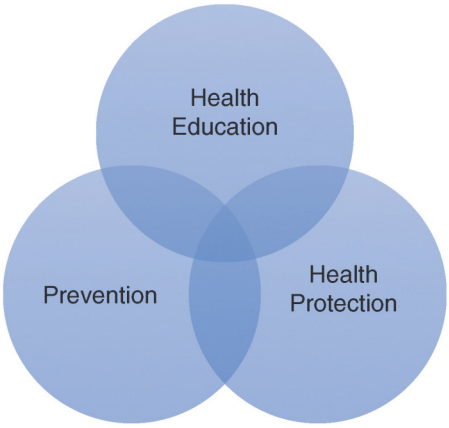
Beattie's strategies of health promotion are a useful way to explore the pharmacy team's contribution to health promotion. The grid provides a way of comparing the different philosophies of various health promoters through an analysis of the quadrant within which their work originates.



In Beattie's framework, pharmacists' involvement in health promotion has primarily fallen within quadrant 1, providing expert information to individuals. Health professionals may be tempted to act in a "telling" rather than a "discussing" mode. However, the evidence shows that people tend not to respond so positively to such approaches. Current thinking is that the pharmacist's most effective contribution would be through adopting an approach consistent with quadrant 3, working with individuals to negotiate change. Individual pharmacy teams may also be involved in community development for health, for example, providing interventions that seek to empower a group in the community, for example, running weight management or stop smoking clinics.

Health promotion embraces the concepts of both community and individual development. Tannahill's model for health promotion includes health education, prevention, and health protection.

Tannahill's model



The pharmacist has an important role as an advocate for their community, in lobbying at local and national levels, and supporting local community groups working for health improvement. However, to effectively engage with the health promotion agenda, pharmacists also need to understand its relationship with the social and economic context.

Pharmacists who want to develop health promoting activities need to adopt a style of consulting, which involves listening and negotiating rather than merely telling, taking into account the individual's social circumstances. This may involve the role of family members, carers, or friends in the management of medicines, while taking into consideration living conditions, health status and socioeconomic resources. Any pharmacist may participate in health promotion and those working in community and hospital practice are well placed to do so. Their level of input has been classified as:

Level 1: displaying leaflets on health topics and responding to requests for advice and information about health.
Level 2: in addition to level 1, offering information and advice opportunistically and proactively, working in a coordinated way with community-based healthcare workers.

The difference in these two levels is essentially that in the first, the pharmacist is passive and working at an individual level and in the second active and using community networks effectively.

The health promotion input from pharmacists is summarized below, and pharmacists should adopt a holistic approach and think creatively about the opportunities to promote health. A holistic approach means addressing issues not traditionally associated with pharmacy, but which may still be linked to the sale or supply of medicines or health-related goods. Pharmacists may be uncomfortable when providing dietary advice or recommending physical activity programs. This initial discomfort may be alleviated by targeting advice to particular groups of people, for instance:

- Target information about effective physical activity to those receiving prescriptions for medicines to prevent or treat osteoporosis. This might be the availability and timing of local sessions to promote strength and balance as part of a "falls reduction program."
- Asking patients presenting prescriptions for medicines for coronary heart disease whether they would like further information about diet and physical exercise.

Health Promotion in the National Health Service Contract in England

The National Health Service (NHS) contract in England includes health promotion as an essential service and states that this includes "the provision of opportunistic healthy lifestyle advice and public health advice to patients receiving prescriptions who appear to: have diabetes; or be at risk of coronary heart disease, especially those with high pressure; or who smoke; or are overweight, and pro-active participation in national/local campaigns, to promote public health messages to general pharmacy visitors during specific targeted campaign periods."

Prescription-Linked Interventions

Pharmacists and their staff will give opportunistic advice, as appropriate, on specified healthy living/public health topics to people presenting prescriptions with diabetes, those at risk of coronary heart disease, especially patients with high blood pressure,

those who smoke, and those who are overweight. The advice will be given verbally, but may be backed up by the provision of written information, for example, leaflets and a referral to another source of advice or assistance. A record of the advice given will be made on the patient's pharmacy record. This record will facilitate service audit and also future follow-up with the patient. Pharmacy contractors should have systems in place to ensure that appropriate advice is given to patients.

Campaign-Based Services

Pharmacists and their staff will proactively take part in and contribute to national/local campaigns for patients and general pharmacy visitors during the campaign period, including giving advice to people on the campaign issues. This advice may be supplemented by provision of written information and in-store displays. The pharmacy will provide this service for up to six campaigns per year. The pharmacy will record the number of people who receive advice if requested to do so by their primary care organization. The primary care organization will determine the topics of the campaigns and will provide any appropriate support, for example, briefing packs and patient literature to support campaign messages.

The Components of Pharmacists' Health Promotion Activities

- Using the pharmacy premises effectively to promote health through the display of posters and leaflets on health topics.
- Providing an advice or counseling area.
- Using written information opportunistically to supplement verbal advice (e.g., using a leaflet on healthy eating as well as selling a bulk laxative, as part of the response to a customer asking for advice on constipation).
- Offering one to one advice about individual behaviors (e.g., smoking cessation), this might often be linked with the sale of nicotine replacement therapy.
- Offering clinics (perhaps in conjunction with local medical practices) on specific topics such as the menopause.
- Targeting individuals known to be at risk (e.g., those receiving prescription medicines for angina, osteoporosis) and discussing management options, involving family, friends, and carers in management if appropriate and considering with the individual the effect of the treatment on their quality of life and offering further information if required.
- Networking with other health professionals and health agencies to participate in activities and campaigns that address the local community's health needs.

There is evidence that even the shortest of interventions can be effective providing they are delivered in a way that has been shown in research to work.

Types of Pharmacy Intervention Adapted From Nice

Very Brief Intervention

A very brief intervention can take from 30 s to a couple of minutes. It is mainly about giving people information or directing them where to go for further help. It may also include other activities such as raising awareness of risks or providing encouragement and support for change. It follows an "ask, advise, assist" structure. For example, very brief advice on smoking would involve recording the person's smoking status and advising them that stop smoking services offer effective help to quit. Then, depending on the person's response, they may be directed to these services for additional support.

Brief Intervention

A brief intervention involves oral discussion, negotiation, or encouragement, with or without written or other support or follow-up. It may also involve a referral for further interventions, directing people to other options, or more intensive support. Brief interventions can be delivered by anyone who is trained in the necessary skills and knowledge. These interventions are often carried out when the opportunity arises, typically taking no more than a few minutes for basic advice.

Extended Brief Intervention

An extended brief intervention is similar in content to a brief intervention but usually lasts more than 30 min and consists of an individually focused discussion. It can involve a single session or multiple brief sessions.

Local authorities in England have responsibility for commissioning a wide range of services, including most public health services and social care services. The following public health services provided by community pharmacies have been commissioned by local authorities:

- Supervised consumption
- Needle and syringe program
- NHS health check
- EHC and contraceptive services
- Sexual health screening services
- Stop smoking
- Chlamydia testing and treatment
- Weight management
- Alcohol screening and brief interventions

The Evidence Base for Pharmacists' Role in Improving the Health of the Public

A 2013 public health England commissioned review of pharmacy's role in improving the health of the public identified twenty relevant review papers on the contribution of community pharmacy to public health. The review found that a considerable body of evidence exists for the role of community pharmacy for a range of services, not only aimed at improving general health, but also at maintaining the health of those with existing disease. The evidence for positive outcomes is strongest in services including smoking cessation, supply of emergency hormonal contraception, cardiovascular disease prevention, blood pressure management, diabetes and possibly asthma, and heart failure. There was strong evidence of improvements in lipid levels that were sustained for at least 1 year in both primary and secondary prevention of coronary heart disease. Community pharmacists can also make an important contribution to the management of people with diabetes for screening, improved adherence with medicines, and reduced blood glucose levels or HbA1c.

Although published evidence is currently less strong in other areas such as COPD, infection control, substance abuse, weight management, and minor ailments schemes, there are some reports of successes in the community pharmacy provision of these services. The authors concluded that further research is necessary to justify the role of community pharmacy in these areas.

Greater efforts to prevent ill health and promote well-being are recognized globally as being crucial for the future. Various interventions are being made to encourage individuals to improve their diet and become more physically active, lose weight if they are overweight or obese, stop smoking, reduce their alcohol intake, and practice safe sex to prevent unwanted pregnancies and a range of infectious diseases such as HIV and chlamydia. Community pharmacists and their teams are ideally placed to act as health promoters.

Smoking Cessation

There is strong evidence for community pharmacy-based smoking cessation services and smoking cessation is the most common public health activity in UK community pharmacies. The evidence suggests that community pharmacy-based stop smoking services run by trained pharmacy staff are effective and cost-effective in helping smokers quit. The studies included are RCTs and therefore of high levels of evidence. A Cochrane review found some evidence to suggest that properly trained community pharmacy staff may have a positive effect on smoking cessation rates. A later publication that community pharmacists trained in behavior-change methods are effective in helping people to stop smoking based on high quality RCTs and that the service is cost-effective. The authors found that training was fundamental to the success of stop smoking services provided by community pharmacists.

Community pharmacy interventions are effective for smoking cessation. Twenty-four relevant studies of pharmacy-delivered interventions were identified; most of the evidence was focused on smoking cessation interventions. Pharmacy-based smoking cessation interventions, including behavioral support and/or NRT, are effective and cost-effective in helping adults to stop smoking, particularly compared with usual care.

A recent realist review and analysis of smoking cessation support from community pharmacists and their staff that although there is evidence that smoking cessation interventions in pharmacy are effective and cost effective, there is very limited empirical evidence on organizational and system influences on this role. Key findings from the realist analysis were that for the community pharmacy to become the site of smoking cessation, they must view themselves as a public health professional rather than (merely) a dispenser of medicines, and the authors stated that this was something that is far more likely to happen if undergraduate training, professional bodies, and national policy depict them in this way and endorse the role positively. Training needs to be accessible and include a broad curriculum that goes beyond "tasks and facts." Pharmacists are more likely to be motivated (from a professional, business, and personal perspective) if other pharmacists locally and nationally are also delivering smoking cessation services; if the work is received positively at appraisal and performance review; if structural and logistical issues including avoiding excessive paperwork and adequate remuneration are addressed; and if the work is adequately remunerated. Finally, pharmacists must have the confidence of other health professionals and the trust of the wider public, professional bodies, and the media.

Emergency Hormonal Contraception Supply

A review of the international literature on emergency hormonal contraception supply through community pharmacies found that pharmacies provided timely access to treatment and the service was well received by women. The one randomized controlled trial included in the review showed that provision of EHC through community pharmacies did not reduce the use of other contraceptives, leads to an increase in risky sexual behavior or increases the incidence of STIs. An observational study showed that the average time to access EHC was 16 h through community pharmacies compared to 41 h through family planning clinics. It is clear that the service is unlikely to provide unwanted effects, is well received, and reduces access times which is known to improve treatment effectiveness but evidence for cost-effectiveness of EHC supply services provided through community pharmacy is not available.

Chlamydia Screening and Treatment Services

Chlamydia screening is designed to identify and treat Chlamydia infections early and before they may progress to pelvic inflammatory disease and ultimate infertility. A national screening program was introduced in England in 2010 and included community

pharmacies where treatment was also offered for those screening positive. A systematic review of the literature regarding community pharmacy provided chlamydia screening, and treatment services found that Chlamydia screening from community pharmacies is feasible and can provide an accessible, convenient venue to get a test.

Case Finding Type II Diabetes Screening

It has been shown that community pharmacists can effectively screen for type II diabetes enabling early diagnoses. Research in the UK suggests that while screening with intervention for diabetes and impaired glucose tolerance for those between 45 and 75 is likely to be cost-effective, the cost-effectiveness of diabetes screening alone is uncertain. Strategies to improve cost-effectiveness of diabetes screening services include focusing screening on those at greater risk, for example, those with known high-risk ethnic groups with an increased body mass index and using more specific and sensitive screening methods specificity. The UK government recommends that diabetes screening should be focused on patients from known high-risk ethnic groups with increased body mass index and those prescribed lipid lowering and hypertensive treatments. The community pharmacist has access to sufficient information to enable them to use such criteria to identify people with those risk factors and provide a diabetes case finding and intervention service. In Australian pharmacies, a diabetes risk assessment followed by a blood test resulted in fewer referrals and greater uptake by patients than when using risk assessment only.

Harm Reduction Services

Community pharmacists contribute to the health of opioid-dependent patients through supervised consumption of opioid substitution medicines like methadone and buprenorphine to ensure that the individual prescribed the medicine actually takes it and prevent diversion or sale to other users which can result in accidental overdosage. A review of pharmacist supervision's effect on methadone-related deaths between 1993 and 2008 found that the number of deaths in Scotland reduced from 20 per 1 million defined daily doses of methadone to 2 and in England from 25 to 6. The reduction has been sustained and with the main change in practice being the introduction of supervised consumption, this can largely be attributable to the contribution made by community pharmacy. The cost-effectiveness of the service is currently unknown and therefore the question is whether the cost is justified by the significant reduction in deaths resulting from methadone seen.

Needle and syringe programs, which may or may not include the provision of other related materials to minimize harm to users, are commissioned throughout England by local authorities. Needle exchange services are a cost-effective use of resources

Weight Management

A recent systematic review reported that community-based weight management services were as effective as other primary care strategies. The actual cost of service delivery, however, seemed to be greater than private providers and consequently the cost-effectiveness of commissioning services via this route was stated to be unclear.

Brief Alcohol Interventions

A number of interventions for brief alcohol interventions for problem drinkers have been implemented within community pharmacies in the UK. Two RCTs showed no long-term benefits. A recent systematic review identified the need for more research and evidence for brief alcohol interventions in community pharmacies before they can be adopted. A large RCT is currently being set up.

Case Finding in Pharmacy

The Community Pharmacy Future group, a collaboration between community pharmacy chains and independent pharmacies in the UK, introduced a person-centered service for patients with multiple long-term conditions in 50 pharmacies in Northern England.

After 3 months, 683 patients had baseline clinical data recorded, of which around 87% were overweight or obese, 54% had hypertension, and 81% had high cardiovascular risk. 77% patients set themselves at least one goal during the first consultation and 22% set multiple goals. The majority of goals were identified as improvement in condition, activity, or quality of life. Pharmacists acknowledged the patient benefit and the service provided.

Pharmacy and Health Inequalities

A recent review of pharmacy smoking cessation, weight management, and multicomponent interventions that included pharmacotherapy and lifestyle changes in participants with diabetes mellitus, dyslipidemia, or hypertension concluded that the effect of community pharmacy interventions on health inequalities remains unclear. The authors stated that future research in this area is warranted, and trials should include the assessment of age, sex, ethnicity, socioeconomic status, and contextual factors, and present analysis of how these factors moderate effectiveness.

Professional Standards for Pharmacy and Public Health

The Royal Pharmaceutical Society has developed a set of professional standards for public Health (https://www.rpharms.com/resources/professional-standards/professional-standards-for-public-health).

The nine standards provide a framework to help pharmacy teams, commissioners, and those contracting services to design, implement, deliver, and monitor high-quality public health practice through pharmacy, regardless of the pharmacy settings from which services are delivered.

1. Surveillance and assessment of the population's health and well-being
2. Public health intelligence
3. Assessing the evidence of effectiveness of health and healthcare interventions, programs, and services
4. Health improvement
5. Health protection
6. Health and social service quality (also known as healthcare public health)
7. Policy and strategy development and implementation
8. Strategic leadership and collaborative working for health
9. Academic public health

So to take, for example, standard 4, the standard states that: pharmacists and their teams improve the health and well-being of the population and help to reduce health inequalities by proactively promoting health and well-being messages and supporting and enabling people to adopt healthier lifestyles and take responsibility for their own and their family's health and support self-care. Pharmacy teams use every interaction as an opportunity to provide health-promoting messages, contributing to improving population health and reducing health inequalities, making every contact count.

Advice and Information

Pharmacists and their teams are confident and knowledgeable and provide healthy lifestyle advice and information that is clear and consistent with national and/or local public health messages; seek opportunities to provide patients and the public with advice and information to enable people to look after their own and their family's health and support self-care; work in partnership with other practitioners and agencies to provide evidence-based advice and information to improve the health and well-being of their local communities and improve health literacy.

Communication

Pharmacists and their teams are aware of the wider factors influencing health (including health literacy, socioeconomic, ethnic, and genetic factors) and the health needs of their local population or community; communicate and signpost public health advice and information in a clear, non-judgmental and consistent way; are appropriately trained in evidence-based communication techniques, for example, motivational interviewing techniques and brief intervention skills; provide nonjudgmental support to improve health literacy and access to health-related information to enable people to set their own health goals to achieve better population health outcomes.

Service Delivery

Pharmacists and their teams are competent in the effective delivery of public health services and interventions designed to improve people's health; are aware of, and signpost to relevant local and national public health services to support people to live healthier lives (when appropriate and when they are not themselves able to provide support) deliver services which support self-care and enable people to take responsibility for their own and their family's health; are aware of the groups and communities within their local population at most risk of experiencing health inequalities and take steps to assist them in accessing and delivering public health services to meet their needs; seek opportunities to deliver public health services, based on local public health need. Pharmacy leads promote personal, team and organizational development to ensure a skilled pharmacy public health workforce that is integrated with the wider public health workforce and fit for purpose to deliver high-quality public health services and outcomes.

Ethical Health Promotion

Ethical health promotion practice is based on a commitment to health as a human right, which is central to human development. It demonstrates respect for the rights, dignity, confidentiality and worth of individuals, groups and communities; and for diversity of gender, sexual orientation, age, religion, disability, and cultural beliefs. Ethical health promotion practice addresses health inequities and social injustice, and prioritizes the needs of those experiencing poverty and social marginalization. It acts on the political, economic, social, cultural, environmental, behavioral, and biological determinants of health

and well-being. A health promotion practitioner ensures that health promotion action is beneficial and causes no harm; and is honest about what health promotion is, and what it can and cannot achieve. In all areas of health promotion practice, he/she acts professionally and ethically by:

Enabling change by providing individuals, groups, communities, and organizations to build capacity for health promoting action to improve health and reduce health inequities.
Advocating for health advocate with, and on behalf of individuals, communities, and organizations to improve health and well-being and build capacity for health promotion action.
Mediating through partnership work collaboratively across disciplines, sectors, and partners to enhance the impact and sustainability of health promotion action.
Communicating health promotion actions effectively using appropriate techniques and technologies for diverse audiences.
Leadership contributes to the development of a shared vision and strategic direction for health promotion action.

Assessment

Conduct assessment of needs and assets, in partnership with stakeholders, in the context of the political, economic, social, cultural, environmental, behavioral, and biological determinants that promote or comprise health.

Planning

Develop measurable health promotion goals and objectives based on assessment of needs and assets in partnership with stakeholders.

Implementation

Implement effective and efficient, culturally sensitive, and ethical health promotion action in partnership with stakeholders.

Evaluation and Research

Use appropriate evaluation and research methods, in partnership with stakeholders, to determine the reach, impact, and effectiveness of health promotion action.

Ethical Values Underpinning the IUHPE Core Competencies and Professional Standards for Health Promotion

Ethical values and principles for health promotion include a belief in equity and social justice, respect for the autonomy and choice of both individuals and groups, and collaborative and consultative ways of working.

Ethical Health Promotion practice is based on a commitment to:

- Health as a human right, which is central to human development, respect for the rights, dignity, confidentiality and worth of individuals and groups; and respect for all aspects of diversity including gender, sexual orientation, age, religion, disability, ethnicity, race, and cultural beliefs.
- Addressing health inequities, social injustice, and prioritizing the needs of those experiencing poverty and social marginalization.
- Addressing the political, economic, social, cultural, environmental, behavioral, and biological determinants of health and well-being.
- Ensuring that health promotion action is beneficial and causes no harm.
- Being honest about what health promotion is, and what it can and cannot achieve.
- Seeking the best available information and evidence needed to implement effective policies and programs that influence health.
- Collaboration and partnership as the basis for health promotion action.
- The empowerment of individuals and groups to build autonomy and self-respect as the basis for health promotion action.
- Sustainable development and sustainable health promotion action.
- Being accountable for the quality of one's own practice and taking responsibility for maintaining and improving knowledge and skills.

Core Competencies for Health Promotion

The IUHPE http://www.iuhpe.org/images/JC-Accreditation/Core_Competencies_Standards_linkE.pdf

Core competencies and professional standards for health promotion are underpinned by an understanding that health promotion has been shown to be an ethical, principled, effective and evidence-based discipline and that there are well-developed theories, strategies, evidence, and values that determine good practice in Health Promotion (Fig. 1).

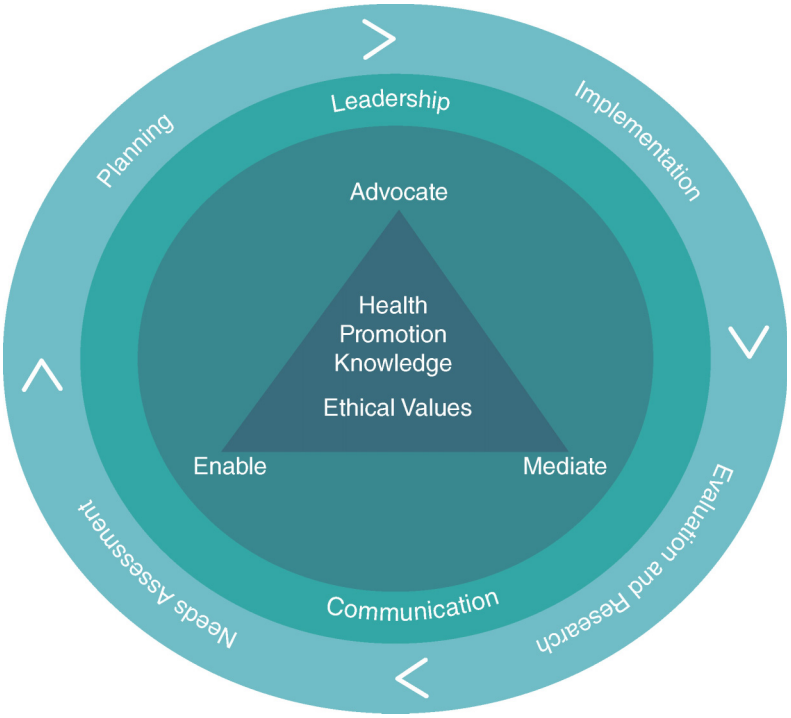


Figure 1 IUHPE core competencies for health promotion.

Healthy Living Pharmacy

The UK continues to be at the leading edge of health promoting pharmacy practice in community pharmacy with the healthy living pharmacy movement providing a focus for development. The concept of healthy living pharmacies (HLP) was developed alongside national policy and a direction of travel published in the 2008 White Paper, Pharmacy in England: building on strengths, delivering the future. The healthy living pharmacy (HLP) is a tiered framework (levels 1–3) aimed at achieving consistent delivery of a broad range of health improvement interventions through community pharmacies to meet local needs, improve the health and well-being of the local population, and help to reduce health inequalities.

The HLP framework is underpinned by workforce development; a skilled pharmacy support team to proactively support and promote behavior change, improving health, and well-being; premises that are fit for purpose; engagement with the local community, other health professionals (especially general practitioners), social care and public health professionals and local authorities (who commission public health services in England).

A HLP builds on existing pharmacy services with provision of NHS locally commissioned enhanced services at three different levels of engagement.

Level 1

The pharmacy has a consultation room

- In the past year, the pharmacy has participated in the provision of both medicines use reviews (MURs) and the new medicine service (NMS), and has proactively engaged in health promoting conversations.
- In the past year, the pharmacy has participated in the provision of the NHS Community Pharmacy Seasonal Influenza Vaccination Advanced Service or has actively referred patients to other NHS providers of vaccinations.
- The pharmacy complies with the General Pharmaceutical Council's Standards for Registered Premises and Standards of Conduct, Ethics and Performance.
- The pharmacy complies with the NHS community pharmacy contractual framework (CPCF) requirements.

Achieving HLP level 1 (self-assessment) is now a quality payment criterion for the quality payments scheme part of the English community pharmacy contract.

An example of the stepwise approach that HLP takes would be for smoking cessation. A HLP level 1 service provides brief interventions, assessing willingness of patients and signposts over services as appropriate. Level 2 may provide an NHS smoking cessation service, health checks, or cancer awareness service. Level 3 may provide COPD and cancer risk assessment with referral and be a prescriber for the stop smoking service.

Participating pharmacies are expected to deliver a range of commissioned services in line with local needs rather than selectively provide enhanced services of their own choice. The principle categories of service delivery are based around promotion, prevention, and protection.

An Example of a Health Promoting Pharmacy

Mrs P's pharmacy is much more patient and health-orientated than it used to be. She has refitted her pharmacy, making a number of special consultation areas. She put a pharmacist computer workstation next to the over-the-counter medicines. She has also installed wireless Internet. Her pharmacy counter assistants all roam the floor with ipads to enable them to answer queries in a timely manner. She has a window display about dental health that she has developed with the local dental practice as part of her towns' contribution to national dental health week. She is auditing customers' responses to it.

While Mr. G is waiting for the technician to dispense his prescription, he picks up a booklet about healthy eating from a display rack and starts to read it. He looks around at the posters about the pharmacy's smoking cessation services. While the technician gets his prescription ready, he sees Mrs. Ps second pharmacist talking to a patient seemingly explaining her medicines in detail and another about using insect repellents containing DEET, as well as taking antimalarials during her visit to Kenya. Mrs P then takes a phone call from a pharmacist colleague to discuss a patient's medicines he has noted a problem during a medicines use review in the local care home. They agreed that he should contact the patient's doctor and suggest he cancels the prescription.

As well as providing the locally commissioned public health services chlamydia Screening, supply of emergency hormonal contraception, stop smoking support, supervised consumption of methadone, needle exchange service, and supply of medicines during emergency situations, for example, supply of antivirals during an influenza epidemic.

Mrs. P considered the key health needs for her local area and decided that she should also concentrate on developing those areas rather than trying to do everything. These included diabetes care and reducing hypertension. After a meeting with her local GPs, with whom she already had a close relationship, she decided she would use her patient medication records for identifying people with diabetes and people with hypertension invite them in for a review and that they would refer them to her. She was one of the first community pharmacists in her area to become an independent prescriber and is now prescribing for many of these diabetic they have been diagnosed by the GP. She often contacts the other community, primary care, and hospital pharmacists whom she met on the prescribing course. She works closely with them and has developed a discharge medicines review service. She works closely with the pharmacist in the local GP surgery too improving the transfer of care. She also did a critical appraisal course and regularly uses computer-based systems to evaluate the evidence and to check guidelines.

At 8.30pm one evening Mr G returns to the pharmacy and asks for a quiet word. Mrs P greets him warmly and takes him to a private consultation area. He is worried about the effects that his "water tablets" might have on his bladder as he often has to attend long board meetings and does not want to always be excusing himself. Mrs P tells him that it should not cause too many problems and that he should take his tablets on rising in the morning. He also tells her that his cholesterol level was raised and the GP has told him to change his diet. The pharmacist reinforces this advice and asks him if he is taking any exercise. He plays golf once a month, but that is all he can manage now, owing to pressure of work and so on. She discusses with him some simple things he can change, like walking instead of always going short distances by car, and using the stairs instead of lifts, and she encourages him to think about taking up another sport, or playing golf once a week.

He returns a month later with a repeat prescription. He tells her that his tablets do not seem to be causing him any problems and that he has lost half a stone; he has been cutting down on business lunches and he is walking a bit more. His blood pressure has come down too. He notices a poster and asks Mrs. P if she can come along to his business and talk about heart health and smoking cessation.

Mrs P had been concerned that other pharmacies needed to change like she had and approached her local commissioning group to see if they could arrange a mentoring system whereby other pharmacists could visit her pharmacy and see what she was doing.

Mrs P has had to invest in her premises and in IT. She has also had to employ a second pharmacist and two checking technicians so that she can continue to advise people opportunistically as well as provide appointments for medicines review. She employs a nurse on Saturdays to run a travel clinic and to help her with flu vaccinations in season. She has more than recouped her investment.

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Collaborative and Interprofessional Pharmacy Practice

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Introduction

This chapter will briefly review collaborative and interprofessional pharmacy practice (CPP/IPP). This chapter has been set out in four sections to give you an overview of the topic. The first section will introduce the topic and definitions, the second is a review of the general evidence for collaboration and CPP/IPP, the third uses primary care as an example for CPP/IPP and describes how three jurisdictions have instituted CPP/IPP. The last section reviews available instruments to measure collaboration. By the end of this chapter, pharmacists should recognize the aspects and evidence for CPP/IPP and use this to apply to their own CPP/IPP.

Collaboration is common. Collaborative teams have been the foundation of practice in many settings (e.g. inpatient units in hospital, rehabilitation settings) but are becoming more prevalent in other settings. This spreading of collaborative teams is due the significant healthcare reforms across many jurisdictions. One of the largest areas for new collaborative teams is primary care. The reason to increase collaborative practice is that it has demonstrated improved outcomes for the patient, the team-member, and the health-care system.

All professionals should be prepared to work together successfully. This is a common competency for pharmacists and other healthcare professionals (e.g. physicians and nurses). As such, many universities and professional programs are dedicating time and resources to teaching this competency using various strategies captured under interprofessional education. Interprofessional education is a new pedagogy which has happened in parallel and supporting the new emphasis on collaboration in healthcare. Interprofessional education is out of the scope of this section but it is an important facilitator to success.

Pharmacists and other pharmacy professionals must be prepared to work with others. Many pharmacist will have participated in collaborative practice for their entire career. However, CPP/IPP is an opportunity for all pharmacists to improve patient and healthcare outcomes. With the recent spread of collaboration into primary care, pharmacists have the opportunity to collaborate more than ever before. Pharmacists practicing in community settings have historically worked with physicians but this relationship may have been perceived as one-way or reactive. CPP/IPP is deliberate integration with all members working towards patient-centered care and common goals.

Collaboration

Collaboration is becoming the foundation for health care delivery across all sectors, and a focus of curricular, research, and policy activity. This can be attributed to various policymakers calling for the use of collaboration as a key approach to the quality and safety of patient care (World Health Organization 2010; Centre for Advancement of Interprofessional Education (CAIPE) 2007; Health Canada 2007; Institute of Medicine (US) Committee on Quality of Health Care in America 2000). The reason for this transformation in health care delivery is that collaborative practice improves efficiency and care by maximizing the professionals' scope. Collaboration is expected to be more cost-effective by: substituting non-physician labor inputs for physicians (increased access); coordinating health services for multiple treatments and assessments to deal with co-morbidities; generating scales of efficiency; and performing better through sharing of knowledge and skills (Howard et al., 2011; Jesmin et al., 2012). CPP/IPPs are a subgroup of collaborative practice which includes a pharmacist or other pharmacy professionals.

To discuss collaboration, one area that must be addressed is the lack of clarity in the language to describe these endeavors. There have been overlapping definitions and poor conceptualization around collaboration. Recent reviews investigating the language used in research and description of collaboration have discussed the following terms potential used for collaboration: collaboration, coordinated, interdisciplinary, integrated, interprofessional, multidisciplinary, network, and teamwork (Reeves et al., 2011; Boon

Table 1 Definitions of health care collaboration (Canadian Interprofessional Healthcare Collaborative (CIHC)., 2010; Health Canada, 2012; Mitchell et al., 2012; World Health Organization, 2010)

World Health Organization (WHO): Collaborative practice in health-care occurs when multiple health workers from different professional backgrounds provide comprehensive services by working with patients, their families, carers and communities to deliver the highest quality of care across settings. The practice includes both clinical and nonclinical health-related work, such as diagnosis, treatment, surveillance, health communications, management and sanitation engineering.
Canadian Interprofessional Health care Collaborative (CIHC): Interprofessional Collaboration is a partnership between a team of health providers and a client in a participatory, collaborative and coordinated approach to shared decision-making around health and social issues. The six competency domains are: (1) interprofessional communication; (2) patient/client/family/community-centered care; (3) role clarification; (4) team functioning; (5) collaborative leadership; (6) interprofessional conflict resolution.
Health Canada: Interprofessional Collaboration (IPC) involves "working together with one or more members of the health care team who each make a unique contribution to achieving a common goal, enhancing the benefit for patients. It is a process for communication and decision-making that enables the separate and shared knowledge and skills of different care providers to synergistically influence the care provided through changed attitudes and behaviors, all the while emphasizing patient-centered goals and values."
Institute of Medicine (IOM): Team-based health care is the provision of health services to individuals, families, and/or their communities by at least two health providers who work collaboratively with patients and their caregivers—to the extent preferred by each patient— to accomplish shared goals within and across settings to achieve coordinated, high-quality care.

et al., 2009; Reeves et al., 2018). To break down some of the terms that have been used: Discipline is linked to academic domains; Profession is linked to occupations; Multi- refers to different professions or disciplines working autonomously; Inter- refers to them working closer together on a common goal and sharing a team identity (Reeves et al., 2011). Although these definitions vary they do share commonalities and can be viewed as along a continuum of health care professionals working in tandem. In clinical practice, collaboration can refer to the process in which different professional groups work to positively impact patient and health care (Dey et al., 2011). To further highlight the use of different definitions of collaboration and how specific organizations have defined it are listed in **Table 1**. This list is not exhaustive but are commonly used for policymakers and allow a comparison of common elements of collaboration.

Despite the lack of conceptual clarity, pharmacists must understand collaboration and its various meanings adequately to ensure their full participation in CPP/IPP. Since each team is unique, comprised of different members and with its own purpose and setting, a common set of elements for collaboration should be identified. These elements can be competencies for the professional, are integrated knowledge, skills, or attitude that is required, or elements regarding the team which enable the CPP/IPP. These elements that can be delineated for collaboration are: accountability, coordination, interdependence, respect/ trust, responsibility, and role clarity (Reeves et al., 2018; Canadian Interprofessional Healthcare Collaborative (CIHC) 2010; Bradley et al., 2012; Van et al., 2012, 2013; Zillich et al., 2005, 2004; Mitchell et al., 2012; Agency for Healthcare Research and Quality, 2016). Several authors have looked at collaboration involving pharmacists, in most cases with physicians, and described collaborations using these elements (Zillich et al., 2005; Mcdonough and Doucette, 2003; Bradley et al., 2012; Van et al., 2012, 2013). These frameworks are available for clinicians or researchers to use when describing or evaluating their own local CPP/IPP context.

1. Accountability
2. Coordination
3. Interdependence
4. Respect/ Trust
5. Responsibility
6. Role clarity

In addition to the elements of team based care described above, there are enabling factors which are often cited as essential components of collaboration or components which improve collaboration. These are not specific to CPP/IPP but can help a pharmacist to implement or integrate with a collaboration.

1. Leadership
2. Patient centeredness
3. Proximity or co-location

Even within the review of the core elements of collaboration, it is easy to identify potential areas of conflict, multidisciplinary participants, shared authority and resources, and high levels of interaction and interdependence. These endeavors can be well-meaning but can devolve if professions feel their own values and culture are being supplanted. These may be role/boundary disputes, status issues, or clinical orientation to patient/client. Management of conflict is essential for effective collaboration.

Evidence for collaboration

The new focus on collaboration is based on the theory that collaboration between multiple professionals provides effective and comprehensive care, and produce the best outcome for the patients (Xyrichis and Lowton, 2008). Research has been complicated by

the previously discussed clarity issues with terminology. Despite the variation among collaboration which can make it difficult to collate and assess the evidence in its entirety, overall it appears to lead to positive results (O'leary et al., 2012; Lemieux-Charles and Mcguire, 2006; Xyrichis and Ream, 2008).

The Canadian Health Services Research Foundation (2007) demonstrated benefits in patient outcomes such as increased access, timeliness of referrals, improved screening for chronic diseases, and increased patient/client satisfaction (Barrett et al., 2007). Other notable system outcomes summarized in the Canadian Health Services Research Foundation demonstrated changes in scopes for many health care providers (e.g. pharmacists and midwives), increased after-hours access, and improved utilization (e.g. reduced emergency room visits). Initial improvements were shown in providers' understanding of roles, provider satisfaction, provider confidence, and increased information sharing (Barrett et al., 2007). In an updated systematic review in 2017, Reeves and colleagues evaluated the impact of collaborative activities on specific outcomes (Reeves et al., 2017). The studies identified were very low/low-GRADE evidence indicating concerns with the certainty of conclusions. However the systematic review did demonstrate that interprofessional activities and meetings may improve prescribing and other practices, and may slightly improve resource use, length of stay and cost (Reeves et al., 2017).

Although most studies do report positive outcomes there are common concerns including training and workload, changing professional roles, and impact on patient–professional relationships. An important area of benefit for collaboration is to the providers themselves. This is an area of great interest due to the high level of known burnout and turnover in health care. Evidence is available for increased job satisfaction (Körner 2010), improved team climate (Deneckere et al., 2013), and decreased burnout (Deneckere et al., 2013) and job turnover (Xyrichis and Ream, 2008; Grumbach and Bodenheimer, 2004).

Evidence for CPP/IPP

The evidence for general collaborative relationships shows benefit, it is important to review the evidence specifically for those collaborations which include pharmacists (CPP/IPP). The rationale for including pharmacists in collaborations has a significant theoretical basis. With the changing health care needs of patients and populations, there is a high reliance on medications. Medications represent the single biggest intervention for most health care jurisdictions. Pharmacists may provide contributions towards efficacy, safety, and costs of care related to medications. In a meta-analysis by Chisholm-Burns and colleagues (2010), adding pharmacists as team members improved clinical outcomes (e.g. lipid lowering, reducing glycated hemoglobin (HbA1C) and blood pressure (BP)) but as well improved medication adherence and improved quality of life (QoL) and general health (Chisholm-Burns et al., 2010). Although the medication adherence result is not as robust due to the heterogeneity in the studies included, it is similar and supported by another large meta-analysis about medication adherence by Conn and Ruppar (2017) which showed improved adherence with face-to-face pharmacist interventions (Chisholm-Burns et al., 2010; Conn and Ruppar, 2017). Another more recent meta-analysis by Tan et al., 2014 demonstrated that pharmacists who are co-located with general practitioners (GP) delivered similar beneficial effects in clinical outcomes specifically in diabetes and cardiovascular diseases (Tan et al., 2014). These authors concluded that positive effects were seen for pharmacists and teams using combinations of medication review and interprofessional verbal communication. If there were additional incorporation of adherence assessment, health advice, medication adjustment, and monitoring along with medication review, patients were more likely to show improved clinical outcomes (Tan et al., 2014). This finding that a more holistic involvement or multi-prong approach is supported by previous research by Zillich et al. (2004). Overall, CPP/IPP has shown improvement in clinical outcomes and adherence. Along with clinical outcomes, it is important to recognize that medications may contribute to important negative outcomes. In the United States, medications contribute to ~100,000 premature deaths annually and medication related problems cost $200 billion of which half is related to non-adherence (Lewis et al., 2014). The World Health Organization has stated adherence among patients with chronic diseases averages only 50% (World Health Organization, 2003). Both adverse reactions and non-adherence are important issues in healthcare, and pharmacists have been shown to benefit patients for both of these issues. In Chisholm-Burns and colleagues' meta-analysis (2010), the authors reported that when a pharmacist is added to a team medication errors are reduced in 80% of studies and improved reporting of adverse drug reactions in 60% of studies (Chisholm-Burns et al., 2010). Pharmacists practicing in team is well supported by evidence, and by their specialized education and clinical expertise. The addition of a pharmacist to a team has been shown to improve clinical outcomes in chronic diseases, reduce adverse reactions, and potentially contribute to reduced costs related to health care.

Although pharmacists can be included on many different types of teams and settings for collaborations. This chapter will use the primary care setting as an example. Primary care an area of health care with significant recent reformation and has focused on new ways to integrate and include pharmacists. One of the largest changes in primary care is the formation of teams which place pharmacists with providers such as physicians, nurses, nurse practitioners, social workers, dietitians, and others. While professional practice is guided by each provider's regulated scope of practice, it is recognized that the working relationships between members of the team will also be impacted by individuals' expertise, preferences and skill set, team dynamics, and systemic factors. No two teams will function exactly alike (Dolovich et al., 2008). However, as previously discussed there are common elements throughout examples of collaboration. Three jurisdictions (Canada, United Kingdom, United States of America) will be reviewed to highlight similarities and differences between their institution of CPP/IPP in primary care. It is essential to recognize that there is no structure or format of CPP/IPP that has been shown to deliver more effective or higher quality care. As such, each jurisdiction is implementing CPP/IPP with differences. Although each shares the qualities of CPP/IPP, there are important distinctions which may impact pharmacy practice, provision of patient care, and health care outcomes.

Table 2 CPP/IPP Organizations in Canada

Province	*CPP/IPP Organization Name*
British Columbia	Primary Health Care organizations
	Integrated Primary Care Centre
Alberta	Primary Care Networks
Saskatchewan	Primary Health Care Teams
Manitoba	My Health Team
Ontario	Aboriginal Health Access Centre
	Community Health Centre
	Family Health Team
	Nurse-led Practitioner Clinics
Quebec	Family Medicin Groups
Nova Scotia	Family Health Team
Prince Edward Island	Primary Health Care Networks
	Family Health Centre

Canada

The initial work for CPP/IPP in Canada was based on a demonstration project in Ontario called Integrating Family Medicine and Pharmacy to Advance Primary Care Therapeutics (IMPACT) (Dolovich et al., 2008). IMPACT evaluated pharmacists placed in primary care teams on a part-time basis. The project had components which were simultaneously employed to support integration and optimal medication management. The four components were: individual patient assessments, health care provider education, system practice enhancements (e.g. clinical pathways and transition care), and integration activities. The results of IMPACT were presented in several papers and they demonstrated several different aspects of pharmacists within primary care teams. The elements that were facilitative: trust and pharmacists demonstrating value; and barriers: role clarity and underutilization. Physicians appreciated drug information, confidence in prescribing, and new medication related protocols. Pharmacists appreciated a mentor to assist with integration and their complementary skill set to physicians. A common finding across all the different research questions was that time in practice tended to mitigate any concerns the physicians had prior to the integration of the pharmacist. The outcomes seen were 94% of patients had at least one drug therapy problem with 27% of patients having an adverse drug reaction (Dolovich et al., 2008; Farrell et al., 2008a, 2008b; Pottie et al., 2008, 2009).

After IMPACT there was a proliferation of pharmacists placed in primary care teams in Ontario and across Canada. Within Canada there are several types of primary care CPP/IPP (**Table 2**) which can be described as embedded (e.g. Community Health Centre, Family Health Teams), affiliated (e.g. academic faculty in British Colombia, Manitoba), and regionally affiliated (e.g. hired by government and centralized). Overall, each CPP/IPP organization has a similar vision: By employing a variety of health care professionals who work together to improve access to primary care, and provide patient care and improve clinical outcomes to a community of patients. As these pharmacists are hired by the organizations with which they are providing care, this allows the pharmacist to build relationships within the team. However, because the leadership and accounting structures for each of these teams are different, there may be specific differences between each CPP/IPP.

Ontario is Canada's largest and most populous province, the CPP/IPP organization that constitutes more than 50% of all its teams is the Family Health Team (FHT). There are 184 FHTs in Ontario, each FHT is its own corporation with a board of directors. Most boards are comprised of a physician majority (51–100%), as the physicians have created the corporation and maintain leadership over the activities of FHT (Ministry of Health and Long-term Care 2016). FHTs bring together a variety of health care professionals including pharmacists, minimally there must be a physician, a nurse, and one other health care professional. The choice of health care professionals beyond the physicians and nurses is meant to be selected based on the patient population that is being served. Currently, there are ~150 pharmacists working in 120 FHTs (Gillespie et al., 2014). In all cases, pharmacists are salaried employees of the FHT, their salary being provided annually to the FHT via a transfer from the Ministry of Health but they have no specific reporting centrally to the Ministry. In some cases, the pharmacists' salary is supplemented by additional funds from either a hospital or university. There is no official job description or role description for the pharmacist, as it is expected that the pharmacist will contribute by "Optimizing drug therapy through patient assessment, medication management, education, advocacy, and collaboration with physicians and other health care providers" (Gillespie et al., 2014). A recent review by Gocan et al. (2014) of the published literature for Ontario's Family Health Team (FHTs) concluded:

> "Patient and provider perceptions around the outcomes of collaborative care in a FHT setting indicate that interprofessional teams were able to provide enhanced access to care and extended health care services compared to what had previously been offered in a uniprofessional model of care. Both patients and providers experienced more time for care and enhanced quality of health services. Interprofessional collaboration also assisted providers with shifting their approach to health care, addressing mental health or chronic disease concerns they previously avoided given their lack of professional resources or expertise. Providers described changes to health management approaches that were directly related to having access to skilled interprofessional healthcare providers (IHPs) who could assist patients to effectively cope with diverse aspects of their health condition(s)."

One of the strategies that FHTs use to improve access or quality of care for patients is to create workgroups ("teams within teams") for specific patient populations. These programs usually serve complex patients by having multiple providers working together, or by caring for less complex patients instead of using an outside referral to subspecialty physicians. They are often staffed by a combination of providers (e.g. nurse (RN) and pharmacist providing hypertension management), or by hiring specialists (e.g. addictions counselors, diabetes educators). Examples of these types of programs in Ontario's Family Health Teams are: hypertension (Tobe et al., 2013), diabetes (Gucciardi et al., 2015), mental health (Kates et al., 2011), pain management (Angeles et al., 2013), dementia (Lee et al., 2014), and elderly or complex multi-morbidity patients (Tracy et al., 2013). All of these workgroups had a pharmacist involved either directly or as an opportunity for referrals. These services require coordination of multiple providers, and may need to be adapted to local contexts depending on the provider complement at CPP/IPP. The benefits seen in these types of programs are improved function of the interprofessional team, increased convenience and access to care, enhanced patient experience, patient empowerment and self-management, and improved quality of life and health care utilization (Tobe et al., 2013; Gucciardi et al., 2015; Kates et al., 2011; Angeles et al., 2013; Lee et al., 2014; Tracy et al., 2013). However, research into Ontario's FHTs has not always borne all of these benefits in each team. Recent research has shown that interprofessional teams have not consistently improved access to primary care for vulnerable populations (e.g. multimorbidity, or mental health illness) (Glazier et al., 2012; Jaakkimainen et al., 2011; Steele et al., 2013; Hutchison and Glazier, 2013; Rudoler et al., 2015). Additionally, economic evaluations do not show overall benefits to the FHT model and no specific cost-effectiveness analyses are available for CPP/IPP.

United Kingdom model

In the UK, general practitioner (GP) practices provided ~400 million consults and almost 1 billion prescriptions (Primary Care Pharmacy Association, unknown). In the General Practice Forward report, National Health Service (NHS) CEO Simon Stevens talks about the importance of primary care and why changes are needed.

> "The strength of British general practice is its personal response to a dedicated patient list; its weakness is its failure to develop consistent systems that free up time and resources to devote to improving care for patients. The current shift toward groups of practices working together offers a major opportunity to tackle the frustrations that so many people feel in accessing care in general practice." Simon Stevens NHS CEO (National Health Service (NHS) England, 2017)

One of the ways for the NHS to improve primary care was the call to have greater involvement of a pharmacist in medical practices (Stone and Williams, 2015). This pilot project started in 2015 and was for 450 pharmacists to be contracted to ~650 GP. This number will increase to 1500 pharmacists in 2020 (~1 pharmacist for every 30,000 population) (National Health Service (NHS) England, 2017). An important feature of the redesign for pharmacists in GP practices is that pharmacists will work together in a given geographical area (British Medical Association (BMA) 2017). This will allow for mentoring and sharing across the pharmacists' network, however the pharmacist will not be available onsite to every GP clinic. The key outcomes for adding a pharmacist to a GP service were: (1) To support the GP by working with patients and wider primary care workforce; and (2) To utilize their knowledge and skills to support primary care transformation (Snow-Miller 2016; British Medical Association (BMA) 2017). The addition of clinical pharmacists was given a significant financial investment (~ £30 million) which will triple with the expansion over the next stage (National Health Service (NHS) England, 2017). The funding is being provided for three years in a tapering manner, with 100% being covered in the first year only. In subsequent years, GP practices will be required to find larger percentages of funding resources for the pharmacists' salary. This funding requirement will ensure that the GP practice is recouping enough money from the addition of the pharmacist and their practice to make the CPP/IPP tenable. Practice-based pharmacists work as part of the general practice team to resolve day-to-day medication issues, and consult with and treat patients directly. The pharmacist may provide additional expertise in managing long-term conditions, medication optimization, advising patients at risk of polypharmacy, and increasing access to health care screening (Royal Pharmaceutical Society (RPS) 2016; British Medical Association (BMA) 2017). Along with the direct patient care that a pharmacist may provide, there will be population level activities, such as leadership about medications and quality improvement, including contributing to the general practice by the Quality & Outcomes Framework (QOF) (Primary Care Pharmacy Association, unknown, Royal Pharmaceutical Society (RPS) 2016). QOF is a voluntary incentive in United Kingdom's GP contract but can be a major source of potential income. The funding is based on a GP practice meeting certain quality indicators thereby incentivizing care that meets specific standards. By redesigning primary care, it is hoped to open up opportunities in pathway design, case management and shared care with specialists, increased use of technology, and sharing best practices. In different parts of England general practices have started to include clinical pharmacists in their multi-disciplinary teams. In many cases experience suggests that there have been significant benefits for patients and for the practice teams. Bush et al., 2017 looked at one clinical commissioning group (CCG) in England where ~5.5 pharmacists were integrated. Over 9 months, pharmacists' interventions completed were estimated to save in excess of 1 million pounds and save >600 h of GP time and >600 additional GP appointments. This early research demonstrates return on investment for the UK model for CPP/IPP (Bush et al., 2017).

United States of America

In mid-2000s, the emergence of the patient-centered medical home (PCMH) came about to improve care, costs, and patient satisfaction with primary care in the United States (Nigro et al., 2014). The concept of PCMH does not reflect a building or house but is the approach to providing comprehensive and coordinated care. PCMHs are the centerpiece of primary care

Table 3 Comparison of CPP/IPP in Primary Care

Parameter	*Canada (FHT)*	*United Kingdom*	*United States (PCMH)*
Accountability	Local (Family Health Team)	Clinical Commissioning Group	Varied
Role Clarity Provided	No	Yes	No
Leadership	Local	Clinical Commissioning Group	Local (PCMH)
Proximity	Co-located	Not co-located but geographically close	Co-located
Payment	Ministry via FHT (100%)	Ministry 1st year only then reducing % until GP Clinic (100%) after 3 years of pilot	PCMH or parent institution
Governance	Local FHT board of directors (MD led with community members)	CCG (Majority MD with other clinicians)	PCMH or parent institution board of directors (MD led)
# of clinics	1 but can be multiple sites	Multiple clinics	Varied

transformation in the US. They are intended to improve care coordination and communication, enhance health care quality and patient experiences, and lower health care costs by linking patients to a physician-led interdisciplinary health care team. The Agency for Healthcare Research and Quality (AHRQ) defines five main attributes for PCMH are: (1) Comprehensive care is provided by a team; (2) Patient-centered care; (3) Coordinated care across the spectrum of settings; (4) Increased access; and (5) It should also provide improved quality and safety using system-based approaches while incorporating evidence-based therapeutics and tools that make decisions easier and more transparent to patients across the health care system (Lewis et al., 2014; Nigro et al., 2014).

Pharmacists integrated with PCMH can improve many aspects of care including multiple medication issues (e.g. quality and safety) and drug safety issues (e.g. transitions in care). The PCMH model is meant to encourage pharmacists to work at the top of their scope by expanding patient-centered pharmaceutical care (Smith and Nigro, 2011; Nigro et al., 2014). Pharmacists in PCMHs are similar to those in the family health team model in Canada and can be embedded (e.g. employee, faculty member) or have an external role (e.g. contract, consultant) to the team (Smith and Nigro, 2011). Reasons for these differences may be due to the size of the PCMH, available partnerships with an academic faculties, and the geographic area serviced by the PCMH or parent institution. Context for the pharmacist's employment is important, as accountability structures and responsibilities may be different. General roles such as medication therapy management (MTM) and improving continuity of care, can be done by all pharmacists within any PCMHs. Another important aspect of a pharmacist role is those population initiatives which can be embedded into a quality and safety initiatives. These types of initiatives rely on information technology to help identify undertreated patients (e.g. patients with missing medications as per guidelines), those at risk of adverse effects (e.g. declining renal function), and opportunities to decrease costs (Nigro et al., 2014). Pharmacists can create registries to improve standardization and ensure that patients are optimally managed. An early study of roles in PCMH by the American College of Clinical Pharmacists surveyed their members and found an equal distribution (1/3) described their role as: no formal role, key team member, and leading medication-specific initiatives (Nigro et al., 2014). A more recent study by Kennedy et al. (2015) done in a single PCMH in Vermont evaluated the impact of pharmacists. This PCMH had pharmacists were partnered into five primary care practices 1 day per week to provide direct patient care, population-based medication management, and prescriber education. Pharmacists' recommendations to correct drug therapy problems were accepted by prescribers 86% of the time and in a cost avoidance model suggests $2.11 in cost was avoided for every $1.00 spent on a pharmacist ($373,092/$176,690) (Kennedy et al., 2015). This study shows a return on investment for pharmacists in the PCMH model.

Across the three jurisdictions, there was clear value in integrating pharmacists into primary care teams. Their inclusion improved clinical outcomes, processes within CPP/IPP, prevented adverse drug events, and improved health care costs. Although CPP/IPP has been reviewed here as formal team-based organizations, much primary care is delivered by community pharmacists who are not embedded. This can be visualized as "weak-tie" collaborations with primary care providers (e.g. physicians or nurse practitioners), or themselves as independent prescribers to offload health care delivery. These partnerships are essential collaborations as it likely is how the majority of pharmacists interact with physicians in primary care. The elements of CPP/IPP can be applied similarly to community practice.

The reason to highlight the three variations on CPP/IPP in primary care is that implementation differences may contribute to the reason for the varied outcomes have been shown in the literature. If there is no "optimal" CPP/IPP structure or form this leaves each jurisdiction or team to plan a best possible strategy. However, throughout the descriptions the elements can be reviewed in **Table 3**. One of the most important issues for CPP/IPP will be rigorous and pharmacy-led research to demonstrate and evaluate the role of the pharmacist.

Instruments to measure collaboration

After reviewing the evidence for collaborations including CPP/IPP, it may be helpful for clinicians and researchers to have instruments to measure collaboration. To assist the reader, a comparison of available instruments is presented in **Table 4**. To assess each

Table 4 Comparison of Instruments on Performance and Psychometric Properties

	AITCS	*ATCI-GP*	*CATME*	*ICAR*	*MIIC*	*PPCI*
DOMAINS (Number of items testing domains)						
Leadership	3	2	19	3	2	1
Interdependence	5	2	27	4	11	5
Coordination	8	1	11	4	10	2
Respect/ Trust	3	3	0	5	1	2
Accountability/ Responsibility	2	4	20	4	4	1
Role Clarity	2	1	6	3	6	1
Patient Centeredness	3	N/A	N/A	2	3	N/A
PERFORMANCE						
Response Options	5 point Likert-type	5 point Likert-type	7 point Likert-type	4 point rubric	5 point Likert-type	7 point Likert-type
Respondent burden	10–15 min	13 item (short)	87 item 33 (short item)	31 items	42 items	14 item
Method of Administration	Self	Self	Self	Evaluator	Self	Self
PSYCHOMETRIC PROPERTIES						
Internal consistency (Cronbach)	0.98 (Overall) 0.80 (Coordination) 0.94 (Cooperation) 0.97 (partnership)	0.94 (Factor 1) 0.66 (Factor 2)	0.77–0.93	No	0.935 (Overall) >0.77 for subscales	0.91–0.97
Reliability (ICC, Kappa, Pearson r)	Pearson correlation >0.8	No	From Ohland 0.3–0.9	No	No	0.86–0.96
Content	24 IPE experts	8 GP, 8 RPh, 2 HSR	7 scholars	Delphi panel	Done for IIC	Pilot test 127 MD
Construct	No	No	Yes, in same study	No	No	Yes, in same study.

instruments' performance, the COSMIN guidelines were used (COSMIN 2015). Each instrument will be compared for performance and psychometric properties. The characteristics are (Bryan et al., 2013; COSMIN 2015):

1. Performance properties
    a. Domains covered – refers to the elements previously discussed, and the number of items which fall into each domain category;
    b. Response options – refers to the type of questions and scoring on the particular instrument. Common types of response are: Binary (yes or no), Likert scale, Free-text, or Ratings;
    c. Respondent burden – refers to the number of items, or the time required to complete when available;
    d. Reported method of administration – refers to how the survey is provided to the respondent, and common methods are self-administered, and interviewer.
2. Psychometric properties
    a. Internal consistency – provides an estimate of relatedness between different questions. A positive rating will be given to instruments with Cronbach's $\alpha > 0.7$, and when subscales are available they are unidimensional.
    b. Reliability – usually assessed by examining correlation between score at two time points. This may be measured using intraclass correlation coefficients (ICC), Kappas, or Pearson's *r*.
    c. Content validity – an assessment of comprehensiveness and relevance of an instrument for the population being used.
    d. Construct validity – an assessment to the degree that an instrument's items measures the aspects it is hypothesized to measure.
    e. Criterion validity and responsiveness – will not be used, as there is no gold standard to compare other instruments.

The six instruments which will be compared are:

1. Assessment of Interprofessional Team Collaboration Scale (AITCS) (Orchard et al., 2012)
2. Attitudes Towards Collaboration Instrument for GPs (ATCI-GP) (Van et al., 2013)
3. Comprehensive Assessment of Team Member Effectiveness (CATME) (Loughry et al., 2007)
4. Interprofessional Collaboration Assessment Rubric (ICAR) (Curran et al., 2011)

5. Modified Index for Interdisciplinary Collaboration (MIIC) (Oliver et al., 2007) and
6. Physician-Pharmacist Collaboration Index (PPCI).(Zillich et al., 2005)

This section provides an analysis of six instruments which can be used to measure collaboration in many health care settings. These six instruments were selected from an original 58 instruments (unpublished information, Jennifer Lake). Each of these six instruments have appropriate performance and psychometric testing. As well, each covers the majority of domains that are important to collaboration and interprofessional practice. Using a reliable and valid instrument will support research involving collaboration and interprofessional practices.

Conclusion

CPP/IPP is a clinical and research area which is increasing and moving into many different settings. This is leading to pharmacists being integrated into well-developed teams, or creating new types of teams that include a pharmacist. Although there is a lack of clarity around the concept of collaboration, there are some essential elements defined which include accountability, responsibility, trust, respect, and role clarity. Strong leadership, proximity and a common mission such as patient-centered (or client-centered) care will help to enable CPP/IPP.

There is evidence in both general collaborations and CPP/IPP which can help guide the pharmacist. Overall, the evidence for collaboration is positive, however the lack of standardized definitions and structure lead to a lack of consistent outcomes. Pharmacists can use previous work to help assist them in new CPP/IPP work. Additionally, there are instruments to measure collaboration which can help teams assess their current collaboration or their progress with new initiatives.

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Interpersonal Communication in Pharmacy Practice

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Introduction

Methods used by people to communicate information, ideas, and opinions(interpersonal communication) have evolved over many millennium, and we continue today to strive, develop, and implement the best strategies to communicate. Communicating health information is perhaps one of the most challenging tasks that health-care providers have, and we use this process to engage patients in taking care of their own health. The definition of communication by Merriam-Webster is "a process by which information is exchanged between individuals through a common system of symbols, signs, or behavior" (Merriam-Webster, 2018). The art of interpersonal communication is a "work in progress," one that requires ongoing iterative processes that allow for continuous improvement and increased confidence in our communication strategies with patients and others involved in their care.

This paper aims to discuss (1) what comprises effective interpersonal communication and (2) the impact of a pharmacist's relationship with patients, caregivers, and other health-care professionals on communicating effectively.

Depending on where you are in the world, the messages you are trying to communicate and with whom you are communicating influence the type of methods and techniques a pharmacist may choose to use. Today, pharmacists are not only counseling patients on how to properly take their medications, but also how to use nonprescription medications, dietary supplements, and implement appropriate lifestyle behaviors. Oftentimes, there is a lot of information to convey; many times it may be more than a patient can process in one encounter. In addition, pharmacists as members of health-care teams are communicating with family members, caregivers, and other health-care professionals about information that directly impacts a patient's treatment plan (Chisholm-Burns et al., 2010).

Pharmacists are the respected and trusted health-care providers. They often are the first-line and most accessible health-care provider to patients. Today, it is much easier to gain access to a pharmacist than perhaps a general primary care physician. Pharmacists are public health servants and are available to reinforce healthy practices that can reduce the risk of disease as well as prevent disease. The incidence of chronic diseases is rising and is the leading cause of death worldwide (Gerteis et al., 2014; World Health Organization, 2018). The use and number of medications to treat chronic diseases has grown making medication adherence vital to achieving desired patient outcomes (Brown and Bussell, 2011).

Factors Influencing Interpersonal Communication

Technology plays an important role in today's transmission of information. No matter where you are in the world, one can gain access to information through a variety of technology platforms. Written words in digital form are at our fingertips, and many patients will access information as a way to educate themselves on their medical conditions as well as the medications they take to treat their conditions and symptoms. The ongoing challenge is determining the accuracy of the information patients find through

their searches, and this provides an opportunity for the pharmacist and the patient to partner to evaluate the quality of the information (Hesse et al., 2005; Hou and Shim, 2010).

The growing use of technical devices designed to help patients monitor their medications, clinical outcomes, diet, and exercise routines will provide important information that should be included in the conversations related to assessing the patient's progress. Pharmacists then collaborate with patients to develop plans to manage their conditions. It is important for the pharmacist to take this into account and make it part of the discussions with patients.

Telemedicine is another option that has changed the way we can communicate with patients. It can be an important method for providing counseling and education. For patients who are not able to come to the clinic or to the community pharmacy, the use of this technology has increased the convenience for those patients. The use of telephones or videoconferencing has shifted the traditional norms of working with patients in person, and will continue to force the pharmacist as well as other health-care professionals to maintain skills that can be used in face-to-face encounters and those over the Internet (Hesse et al., 2005). Technology is here to stay and will be more advanced over time. The challenge will be how to find the balance of using technology to enhance our communications and strategies to deliver information to patients as well as to assist patients in their Internet searches for health information (Hargie et al., 2000; Hou and Shim, 2010).

There is an incredible amount of information that is available in a variety of forms to patients. Information is being discovered and published on a daily basis at a rapid pace. Traditional means of reading books, magazines, direct-to-consumer advertising, Internet sources, and well-meaning family and friends are all available sources of information for patients.

Individuals, including pharmacists and other health professionals, may feel overwhelmed with the amount of information. As medication experts, the pharmacist will be sought after for their expertise to sort out the relevant and accurate information. Patients, nurses, and physicians, as examples, may come to pharmacists with information that requires discussion and explanation to ensure that the correct information is available to help inform the decision-making process about their medication regimens. The relationship and rapport developed with the various parties involved will enhance pharmacist interpersonal communication with increased trust and collaboration.

Pharmacist–Patient Relationship and Communication

The patient–pharmacist relationship is the critical component of an effective communication. As the role of the pharmacists has evolved, the ways in which pharmacists interact with patients have changed. With the increasing use of medications and management of chronic diseases, worldwide the relationship between the pharmacist and the patient has evolved to one where both the pharmacist and patient have responsibilities to maintain the professional relationship. Pharmacists are providing more services, education, and counseling, and patients, to the extent possible, are taking on more responsibility for managing their conditions and carrying out the agreed-upon plan to pursue the desired goal of improved health outcomes.

Developing a rapport with a patient takes time, and the community pharmacy or clinic is an ideal setting for this to concur. However, even in the shortest of encounters that can occur in a hospital setting, how the patients feel when they walk away from the experience will influence how the patients will behave in the future, and whether or not the patients will return for services provided by the pharmacist (Antunes et al., 2015).

Due to the complexities of patient counseling, taking a holistic approach to communicating involves much more than just the transmission of information. All factors, internal and external to the patient, are considered in developing strategies for interpersonal communication with patients. Patient specific factors include age, level of education, literacy levels, what patients expect from pharmacists, culture, health beliefs, social support mechanisms, socioeconomic status, and past experiences with the health-care system. All of these shape the perspectives of patients and their level of trust with the health-care system.

Research has shown that the characteristics that they look for in their pharmacist include trustworthiness, ability to listen, and approachability (Donald et al., 2017). These same qualities help to engage others that the pharmacist has to communicate with in order to ensure smooth transitions of care.

Verbal and written communication skills are the hallmark of how we provide care for patients. As medication experts, pharmacists have many techniques and resources to call upon when counseling and educating patients. As individuals use a variety of communication styles and techniques (Chong et al., 2014; Maguire and Pitceathly, 2002), our body language that includes facial expressions, the way we sit, and the use of our hands collectively send messages to our patients. The tone and inflexion of our voice, as well as the choice of the words we use, influence how our messages are received and interpreted by the patient.

Communication is a collaborative bi-directional process that includes the flow of information, viewpoints and perspectives of patients. Patients may or may not be the experts on specific medications, but they are experts on who they are as individuals, their bodies, their opinions, and their feelings.

Other Pharmacist Relationships and Communication

Caregivers

Whether the caregiver is a hired professional or an immediate family member (spouse, significant other, parent, grandparent, or friend) establishing a relationship that includes clear lines of communication can be very helpful to the caregiver. As an example,

communicating with parents, who oftentimes become immediate at-home medical care providers, has added pressures to continually doing the right thing for their child even when they have no formal training to do so. The discussions not only include what the purpose of the medication is and how it works, but also in some cases when and how the medication is to be administered to the patient.

A pharmacist, serving as a resource for caregivers, provides level of assurance that the caregiver can reach out to ask questions and clarify information previously provided. Awareness, acknowledgment, and discussion of the challenges that caregivers experience and the associated stressors contribute to healthlines of communication with the pharmacist. The pharmacist plays an important supportive role to caregivers in addition to being an educator and counselor (Noureldin et al., 2016).

Pharmacist–Other Health-Care Professionals Relationship

Although the pharmacist–patient relationship is paramount, effective communication with the health-care team has a tremendous impact on patient outcomes making sure that the health-care team goals (including the patient as a team member) are aligned when it comes to the details of the treatment plan and how all of the other nonmedication recommendations integrate and support the patient's entire plan. Research has shown that medication errors have stemmed from poor communication or miscommunications among health-care professionals.

The increased attention given to interprofessional team-based care all the more supports the need for effective communication that cuts across our specific disciplines and roles in taking care of patients. The Interprofessional Education Collaborative (IPEC) competencies that have been endorsed say that interprofessional communication and effective, open communication lead to better integrated care for our patients (Interprofessional Education Collaborative, 2016).

A major challenge that pharmacists face in their attempts to provide health care is the lack of a universal health care record that includes accurate medication lists, recorded medication adverse reactions, and hospital and clinic visits. The various health systems include hospitals, clinics, pharmacies, and even insurance companies that for the most part are not connected in a way to provide complete and up-to-date information about the patients' encounters with the system units. The patient is the one individual who knows what has transpired, but the records are not necessarily written down in an organized fashion. This is a disadvantage for pharmacists because they may not have all of the information needed in order to piece together the rationale for certain medication decisions or to even have access to an accurate patient medication list. This is an ongoing struggle particularly with community-based pharmacists.

Pharmacist–Public Society Relationship at Large

Historically, the practice of pharmacy has focused on the individual; however, it has become increasingly important for the attention be turned to the public at large. Pharmacists communicating health information to the public at large is key to informing the public of the role and responsibilities of the pharmacist as a member of the health-care team. The pharmacist is viewed as a health-care professional in the community, and the message to the public at large is that the pharmacist is available to help the community address its health-care concerns.

The "public" voice of the pharmacist is an extension of public health that addresses issues concerning the health of the individual and the community. The presence of a pharmacy in the community is more than a building where one goes to get medications; it supports the health of individuals and the community at large.

Theoretical Foundation for Interpersonal Communication

An in-depth description and discussion on communication and health behavior theories and models and their role in effective interpersonal communication are beyond the scope of this paper. It is important to note that there is a theoretical basis for why and how individuals act related to health behaviors, and that theoretical underpinnings can guide and shape the communication strategies used to convey information. Particularly in understanding that patients may not necessarily act upon just receiving instructions, but that the communication should go deeper into how the patient is supported in carrying out the instructions and recommendations.

A "theory" is defined as a set of concepts, definitions, and constructs that are used to explain or predict an activity or behavior (Kerlinger, 1986). A "model" can include a number of theories to help understand a specific problem (Earp and Ennett, 1991). Effective interpersonal communication is about changing behavior. Examples of classic models and theories of health behaviors include the Health Belief Model, The Transtheoretical Model and Stages of Change, and Theory of Planned Behavior and Theory of Reasoned Action. These provide the concepts of the theories and models and real-world health-related examples of each concept for consideration.

These models and theories are part of the curriculum in public health but not so much in pharmacy degree programs. A brief description of these with real-world examples can shed light on how one can strategize their communications with their patients. Depending on the task at hand, the pharmacists can use multiple strategies when communicating health information. The choice of

strategy can also be influenced by theories and models of health behavior in understanding what motivates individuals to carry out recommendations and instructions.

Components of Effective Communication

Decades of research has described the elements of effective communication and overtime the descriptions have evolved and expanded. As health providers, communication of information is the mainstay of our role and these concepts should be revisited from time to time.

When thinking about your communication style you can refer to the seven Cs of clear communication (Mind Tools, 2018) and apply them in any encounter of communicating information to anyone.

Seven Cs of clear communication are as follows:

- Clear
- Concise
- Concrete
- Correct
- Coherent
- Complete
- Courteous

Communication Techniques

There are many communication techniques available in the literature. The two most popular used in health care and in pharmacy curriculum include motivational interviewing (Berger and Villaume, 2013) and the teach-back method (Tamura-Lis, 2013). Books, classes, and workshops are available for health-care professionals, and once these techniques are learned these can be added to your communication toolbox.

Factors Associated With Ineffective Communication

Being equipped with effective communication skills and techniques, being aware of the barriers to effective communication is just as important. These barriers exist at the level of the patient, the pharmacist, and the health system. The following are factors that have been studied and are associated with ineffective communication, and should be taken into account when communicating any messages to patients and their caregivers (Schillinger et al., 2003).

Patient-Level Barriers to Effective Patient–Pharmacist Communication

- Age $>$ 65 years or age $<$18
- Cognitive and physical impairments
- Culture
- Education level
- Health beliefs
- Language (e.g., English as a second language)
- Low health literacy
- Low socio/economic status
- Mental health issues
- Minority racial/ethnic background
- Substance abuse issues
- Underserved communities (e.g., rural, LGBTQI)

Pharmacist-Level Barriers to Effective Patient–Pharmacist Communication

There are barriers that pharmacists must overcome at the professional level for effective communication with patients, family members, and caregivers (Collum et al., 2013).

- Level of cultural sensitivity (e.g., taking into account a patient's health beliefs about the medical condition and the role of medications to treat their condition)
- Patient care setting (e.g., providing adequate space to have a private conversation)

- Privacy (e.g., providing a place away from other patients or customers and even pharmacy staff)
- Time restraints (e.g., very busy pharmacy with additional responsibilities and not enough time to adequately counsel a patient)
- Use of open-ended questions (e.g., instead of asking "Do you have any questions," you ask, "What questions do you have for me today?")
- Use of lay language instead of medical jargon (e.g., instead of saying "hyperglycemia," you say instead, "High blood sugar")

Patient Scenarios With Suggested Communication Strategies

The following scenarios try to depict the various encounters where pharmacists have to strategically use their communications skills and techniques in order to address the concerns of patients and/or their caregivers. These examples are by no means a complete list of possible scenarios. As you read the scenarios you can draw on their professional experiences and recall similar situations. The purpose of the scenarios is to provide a starting point that can be tailored to an individual's communication style and use of communication strategies and techniques.

Negotiating with patients

Patient TA is a 56-year-old who has been experiencing increased difficulty with breathing, but he says that he is not ready to quit smoking. He has tried to quit smoking several times in the past, but has not been successful. He is stressed most of the time and says smoking helps "calm my nerves." As a pharmacist what strategy would you use to help Patient TA make a decision about his smoking status? What factors would you consider? What challenges exist for this encounter?

A conversation to achieve the goals of getting patients to agree to carry out the recommendations to change their behavior is challenging. As health-care professionals, the intent is to encourage and support patients to make a decision and then to sustain the behaviors required to make the change. Quitting smoking can be difficult, even if the patient believes it is what's best for their overall health.

There are resources available to assist pharmacists in counseling patients who want to quit and to approach patients with the idea of attempting to quit, to inquire from the patients where they are in their thinking about quitting. A curriculum that provides the steps on how to initially approach a patient about quitting smoking to recommendations for a variety of nicotine replacement therapies—"Rx for Change"—is developed and is available online, hot lines for counseling, and prescription medication options (Rx for Change: Clinician-Assisted Tobacco Cessation, http://rxforchange.ucsf.edu/.).

Negotiating a timeline for patients is to make decisions about quit dates and nicotine replacements plans, all taking into consideration the preferences of the patients and their sense of self-efficacy in following through on the agreed-upon steps in the action plan. As with all negotiations, it is important to try and understand what the patient factors are that cause the resistance to change and what does it take to get the patient's buy-in that will have a positive impact on the patient's overall health. In the process of developing a communication strategy, one may want to consider the following: How as a pharmacist can I collaborate with the patient to achieve their goals? How do I encourage the patient to voice their ideas and concerns? How would I go about creating a "safe space" for patients to express their concerns about not being able to quit smoking? With all negotiations, knowing how to compromise and continue the process if the first encounter is not successful in having the patient agree on concrete steps to quit smoking or any other behavior that needs to change is essential.

Patient counseling

Patient SK is at the pharmacy counter with a product to help relieve symptoms she has been experiencing this past week. She complains of feeling a burning sensation in her chest and she is belching more than normal for her. What strategies would you as a pharmacist use to counsel the patient on how to provide self-care to relieve her symptoms? What factors would you take into consideration in providing the counseling she needs?

What are the main objectives for providing counseling to patients? Deciding the purpose may be driven by the encounter, if it is the very first time that the patient is taking the medication or if a review is needed for how the patient is experiencing after the medication. Counseling a patient to take a seven-day course of antibiotics is different from counseling on taking a new medication for high blood pressure and is different from taking a self-care medication for heart burn symptoms due to the seriousness and complexity of the condition.

In the above scenario, the pharmacist is imparting information and teaching the patient about the medication, but, in addition, information is provided for how the patient will carry out the instructions of how to use the medication, how it will personally impact their health, and to consider the impact of other medications or lifestyle behaviors may have on the medication(s).

In this self-care scenario, the objective is to determine if self-care treatment is appropriate or if a referral is required, or perhaps both. Examples of strategies that can be used may include:

- Use of open-ended questions to get the patient to describe the experience is important to make the right recommendations for the patient.
  - Describe for me what you are feeling?
  - How long have you been feeling the burning sensation?

  - How often do you feel the symptoms?
  - What foods are associated with when you feel the symptoms?
- Taking a complete medication history would be important to identify a possible drug-induced problem.
  - What nonprescription medications do you take?
  - What dietary supplements and/or vitamins do you take?
- What have you used before to treat these symptoms?

The answers to these questions will help in guiding the pharmacist to determine the severity of the symptoms and engage the patient as a partner to determine the best approach to remedy the problem.

Patient education

Patient JK is interested in learning about vaccines. He has heard that vaccines are important, but as an adult he has no idea what vaccines, if any, he should get. He has also heard that perhaps vaccines may not be safe, especially for children. What would be your strategy or approach to educate Patient JK about vaccines?

This scenario provides the opportunity to consider both counseling and education. For some individuals, this is a controversial topic, and the goal is to provide objective information to the patient for consideration. Keeping personal opinions to oneself is important, unless asked. Just present the evidence and facts and answer the questions as completely as possible. Providing resources that the patients can access in the future is part of the education session. Listening to what the patient is really asking, and asking that patient to voice their concerns and describe the information they have read or heard can assist in building a sense that you want to help the patient and not necessarily convince the patient to your way of thinking. In this situation, referring the seven Cs for clear communication can help frame our approach to sharing information with this patient.

In this education scenario, the objective is to provide the patient with factual information about immunizations, to hear the patient's perspective, and to have the patient share where they have gotten the information that informs their opinions. Examples of strategies that can be used that are not all inclusive:

- Tell me about your concerns regarding vaccines?
- Where do you go to get information about vaccines?
- What questions do you have about vaccines in general or any specific vaccine?
- May I have your permission to share with you information I have about vaccines?

Assessing medication adherence

Patient RM has experienced many challenges in the management of his heart failure, hypertension, and diabetes. He has frequent hospitalizations with medication regimen changes upon discharge. He currently takes seven medications to manage his heart disease and diabetes. Patient RM's primary care physician has asked that you assess RM's adherence to the medication prescribed. What would be your strategies to begin this conversation?

Assessing medication adherence is a difficult task as there is no one gold standard for measuring adherence (Lehmann et al., 2014). For patients taking medications, poor adherence is increasing with the increase in number of medications being used to treat the growing number of chronic diseases across the world. A WHO report states that nonadherence rates are as much as 50% in developing countries (World Health Organization, 2003). Medications taken improperly or not at all result in increased hospitalizations, increased use of health-care resources, and overall poor health outcomes for patients (Iuga and McGuire, 2014). Many factors are associated with patients being nonadherent to medication regimens, and the goal is to identify those factors and suggest interventions tailored to the patient.

Questions pharmacists can ask to assess medication adherence (each medication):

- Can you tell me what this medication is for?
- Tell me how you take this medication?
- What specific times of the day do you take this medication?
- How does this medication make you feel?
- What were you told to expect from this medication in terms of side-effects?
- How many doses of this medication have you missed in the past week?
- If you are not able to take your medications, what are some of the reasons and why you missed the medication dose?

Overall approach to medication adherence:

- If you could change anything about your medication regimen, what would it be?
- What tools or devices do you currently use to assist you in remembering to take your medications?

In addition to asking the patients to describe how they take their medications, there are risk factors that can be a signal that the patient may not be adherent with their medications.

Risk factors for poor medication adherence include but are not limited to (Jimmy and Jose, 2011):

- Medication side effects—For example, patient may unknowingly take more medication than is prescribed, and therefore may experience adverse effects of the medication.
- Complex medication regimens—For example, the more medications a patient is prescribed, the more confusing it is for patients to keep track of medications.
- Confusion—For example, patient may be confused with sound alike (clonidine and colchicine) and look alike (all round white pills).
- Cognitive/physical impairment—For example, patients with visual impairments unable to read labels.
- Low health literacy—For example, patient's inability to not only read words but also not understand how to carry out instructions (take one tablet twice a day, is that 8 a.m. and 8 p.m. or is it 9 a.m. and 10 a.m.).
- Cost—Medications that are not affordable are not bought. Multiple co-pays not affordable. Medication is not covered by prescription insurance.
- Substance use—Under the influence of substances that interview with the cognitive ability to follow through on medication instructions as intended.
- Poor patient-provider communication—Communication that is not clear or direct or if the patient is not trusting of the pharmacist.

Communicating with caregivers

PJ is taking care of his father who is diagnosed with Alzheimer's disease. PJ is concerned that the medication is not working and wants to know if there is an alternative that can be prescribed for his father. PJ is feeling helpless and you, the pharmacist, see the strain on his face and can hear the frustration in his voice. What is your communication strategy to address PJ's concerns?

As the population ages and more children are taking care of their parents, the caregiver has become an increasingly important member of the team taking care of the patient. As a partner, the pharmacist must have a relationship with all who are close to the patient, especially those administering medications, whether it is a child or an adult. Being a sounding board for the caregiver can give insight into the realities of providing care and what strategies are and are not working to ensure that the patient is adherent with the medication regimens. Using the same principles of communication and keeping the lines of communication open and clear will strengthen the partnership that has the end goal of providing the best care for the patient.

The pharmacist may not be able to do anything but refer the caregiver to other resources specially trained to support caregivers. As it is important to simplify regimens for patients, a simple, easy-to-follow regimen can also be helpful to the caregiver or the person responsible for administering the medications to the patient. The following are examples of strategies that can be used that are not all inclusive:

- Tell me how are you doing caring for your father?
- Tell me what you are most concerned about with your father's medications?
- Tell me about your expectations about how the medicines are to work for your father?
- How can I best support you with your job of administering medications to father?
- What do you think would be helpful to support you with administering the medications to your father?

Communicating with children

Patient JT is being discharged from the hospital with several medications to manage the side-effects of her chemotherapy treatment. JT is eight years old and understands her condition and the medications prescribed by her doctor. Her parents will administer the medications at home. What would be your approach to counseling JT and her parents on the prescribed medication regimen?

It is incumbent upon the pharmacist to determine in their discussions with parents if it is appropriate for their child (pediatric patient) to be included in the medication counseling sessions. Children can be well aware of what is happening, and depending on the age, can have some understanding of their medications.

Interactive and educational technologies may enhance this interaction. Pharmacists can reach out to include age appropriate pediatric patients as often as possible (Abraham et al., 2017).

Examples of strategies that can be used that are not all inclusive:

- What questions do you have about JT's medications?
  - Purpose of medications?
  - Duration to continue taking the medications?
  - Special measuring devices to administer the medications?

- What questions do you have about administering JT's medications?
- What concerns you most about JT's medication regimen?

Disclosing medication errors

Patient MEW has picked up a new prescription at the pharmacy. After the patient has left the pharmacy and returns home, it is discovered that the wrong strength of the medication has dispensed. Patient MEW has taken one dose of the new medication. You asked that he return to the pharmacy as soon as he can to get the correct medication. How do you go about discussing this issue with MEW?

Patient safety is the ultimate objective as patients interface with the health-care system at many junctures. When dispensing medications, the objective is to get the right medication, to the right patient, in a timely fashion. Wherever a pharmacist is working to provide medications to patients, safety is paramount. Not only is the medication the correct one for patient but also the dose, frequency, and dosage form are appropriate. Due to the fact that pharmacists are human, errors do occur, and it is our responsibility to disclose these errors to patients and caregivers (Kim et al., 2017).

There are a wide variety of reasons why medication errors do occur and one source is poor or miscommunication between health providers or between the health-care provider and the patient. There are a variety of reasons even for the miscommunications stemming from the characteristics of the patient (culture, language, and literacy), factors in our health-care systems (complex processes to access medications, insurance issues), and characteristics of the health-care provider (communication skills and techniques, use of medical jargon). As health-care providers, our responsibility is to use the most effective techniques available that are appropriate for our individual patients. There is no "one size fits all" approach or one "golden standard."

Pharmacist can disclose with patients when there are errors in prescribing and the delay that will occur until the problem is resolved. The timelines and professional handling of the situation keep the patient informed with the goal being to resolve the issue as soon as possible.

Pharmacists disclosing errors made in dispensing is disheartening and serious. Given that humans make errors, one should be honest and disclose the error as soon as possible and communicate the plan to correct the error. All appreciate a sincere apology that is empathetic and sympathetic. Take into account the emotional state of the patient. Answer all questions as clearly as possible. Pharmacists closely involved with the error are the one to talk with the patient. Explanation of how the error occurred and what will be done to prevent it from happening again. Identify any adverse effects of the error and what the patient should look out for

Communicating through conflict

Chief Pharmacist HP has received multiple complaints from a patient because of the way the pharmacy staff treats him. Today he is in the pharmacy and is not only visibly upset, but he is yelling and threatening to never come back to the pharmacy and he will tell all of his friends to avoid using this pharmacy. At this point Pharmacist HP does not have all the facts of what has transpired. What strategies can Pharmacist HP implement to resolve this conflict?

Providing high-quality customer service and patient care is what we all strive for. However, there are occasions when issues that upset the patient arise. Reasons may range from patients being unwell and was thus short with their patience with everyone, to miscommunications between the patient and staff, to other personal issues experienced by both the patient and staff that are unknown.

The first step in managing a conflict is how we speak with the individual who is upset and wants the results immediately. What communication strategies can be used to de-escalate the situation in order to come to a reasonable solution?

An important component of a strong interpersonal communication is being an active listener and giving individuals the opportunity to state their case in a compassionate and empathetic way. It is not, all the time, about who is right or who is wrong; it's just making space for the person who is upset, and in this case, the customer to be heard in an authentic way. Asking lots of questions and for elaboration on the circumstances can allow for relief of frustration. For example, asking questions like tell me about your experiences? Tell me how the issues we dealt with up to this date? What solutions would you suggest to resolve the issue? How do you suggest that we try to resolve this issue together? In every case, there is no guarantee that the situations will be resolved. There is often a reasonable compromise for both sides that could be agreed to. In your role as the pharmacist, it is not the goal to be right, but to do what is right to come to some understanding together and then to move forward.

Conclusion

Effective interpersonal communication is essential to providing high-quality patient care. Over time individual styles develop but the core components to effective communication are basic and should be part of every pharmacist's communication toolbox. Pharmacists can seek a variety of trainings, books, and articles on the art of communication. Nothing takes the place of real-life situations experienced in daily work routines. Constant practice and refining of the art of communication is a lifelong journey. More research is needed to understand how to best engage patients and those who care for them into the conversation as a total team effort

to achieve positive health outcomes. It's all about changing behavior, which is not accomplished in one visit or one encounter. It's a constant effort, and both the pharmacist and the patient have a role and responsibilities in communicating effectively.

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Evidence-Based Medicine: An Overview for Pharmacists

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What is Drug Information (DI)?

Definition

One of the pharmacist's main responsibilities is to educate patients on the safe and proper use of medications. In addition to educating patients, it is the pharmacist's role to create and provide advice to other health care practitioners on medication management decisions. In order to be experts in medication management, pharmacists must master the ability to effectively retrieve drug information (DI) from credible resources. "DI" is a broad concept, but the practice of DI has been defined as "the efficient retrieval, evaluation, and communication of medication information in order to assist in care decisions, develop evidence-based recommendations, and improve patient outcomes" (Gabay and McKeever, 2016, p. 2). Pharmacists regularly retrieve, evaluate, and communicate answers to DI questions about adverse effects, cost, compounding, dosing, drug interactions, natural health products, pharmacokinetics, drug composition, toxicology, and much more.

Primary, Secondary, Tertiary Literature

Pharmacists answer DI requests using a variety of literature. These sources of information can be classified as either primary, secondary, or tertiary. Primary literature is considered "original," as the author(s) have carried out their own research and reported on the results of their experiment or discovery (Yale University Library, 2017). Some examples of primary literature include

randomized controlled trials (RCTs), cohort studies, case-control studies, and case reports. Primary literature is often sought and consulted when very little secondary or tertiary information exists on a topic, as it may be the only option for learning more about a new drug, rare disease, or emerging evidence. A limitation of primary literature is that the reader must spend time critically appraising the study design and results, as the study may have been improperly conducted (Gooch Wright et al., 1998, p.155). There may be errors in how the results have been analyzed, which means the reader must also have some knowledge of interpreting statistical tests. In addition, a significant amount of primary literature is published everyday, which poses difficulties for the pharmacist in terms of staying abreast of the latest information.

Secondary literature describes, analyzes, evaluates, or interprets information reported by the authors of primary literature (University of Toronto Libraries, 2015). Some examples of secondary literature include review articles, such as narrative, scoping, or systematic reviews, and clinical practice guidelines (CPGs). Secondary literature aims to collect many, if not all, primary research studies on a given topic via a thorough literature search. After the literature search is complete, the included primary research studies are read and the appropriate data is extracted. In systematic reviews, the included studies are critically appraised to assess validity and the data which is extracted may be combined to form overarching conclusions of greater power and precision (Cook et al., 1997, p. 378). If a pharmacist can find secondary literature related to their DI request, this will save a considerable amount of time, as they will not be needed to read several primary studies, appraise each one individually, and then form their own conclusions. However, secondary literature does have some limitations. For example, the literature search for finding primary studies may be very weak, or the authors may have only included primary studies which support their research objectives (Crowther and Cook, 2007, pp. 494–496).

Tertiary literature summarizes information from the primary and secondary literature (Yale University Library, 2017). Some examples of tertiary literature include online and print textbooks, handbooks, encyclopedias, and online DI databases like Lexicomp. This type of literature is excellent for acquiring background information on a topic, such as an overview of a drug's clinical use, interactions, mechanism of action, and much more. Tertiary literature is easy to use and navigate, but it too has some limitations. These limitations include the lack of an exhaustive overview of a subject due to chapter length restrictions or for print tertiary literature—the likelihood that it does not incorporate the most current research, as the publication process can take a long time (Kee and Duba, 2016, p. 32). In addition, the reader cannot determine whether all of the appropriate information was consulted to write the content or whether it was appraised by the authors (Gooch Wright et al., 1998, p. 151).

One can find both primary and secondary literature in databases, such as PubMed (MEDLINE), Embase, International Pharmaceutical Abstracts, as well as many others. As mentioned earlier, tertiary literature can be found in textbooks, such as *Goodman's and Gilman's Pharmacological Basis of Therapeutics*, or handbooks such as the *Handbook on Injectable Drugs*. In addition to Lexicomp, other online DI databases, such as MicroMedex, or Natural Medicines, provide access to tertiary information.

The typical order of consulting literature is tertiary-secondary-primary (Shields and Blythe, 2014). The pharmacist should acquire the appropriate "background" knowledge about a disease or drug before attempting to search for and interpret the secondary or primary literature. The tertiary literature may also prompt the pharmacist to ask further questions about the DI request before trying to navigate the secondary and primary literature. In situations where the DI request involves a new and emerging topic, rare situation, or there is no agreement among experts, the pharmacist should consult the secondary and primary literature, as there would not be enough evidence in the tertiary literature to formulate a response (Conrad, 2016, p. 84).

Responding to a DI Request

The role of the pharmacist is not simply to provide an answer to a DI request. It involves clarifying the question, finding an answer through use of multiple resources, synthesizing the DI in order to provide guidance to the requestor, and effectively communicating the response based on the requestor's level of health literacy.

Brown and Choy (2016, p. 12) outline a "4 Rs" approach—receive, research, respond, and record—for handling DI requests. The first step of this process is "receive," which focuses on identifying the requestor-specific question, acquiring background information, and collecting requestor demographics, which will aid in formulating an answer to the request. What may seem like one simple question may morph into multiple questions or a more complex question. It is not uncommon for requestors to be vague or omit pertinent details, as requestors are not always aware of what information is needed by the pharmacist in order to answer the question. Gathering background information, such as patient specifics, may lead to the actual question being asked. Patient specifics, like previous medical history or known allergies, are two of many factors to consider when formulating an answer to a DI request. Identifying a requestor's demographics (e.g., nurse, physician, Department of Critical Care) is also helpful, as it will help the pharmacist determine what level of information to include in the response. Asking the requestor whether they have conducted any of their own previous research on the request and how quickly they expect an answer will help the pharmacist to prioritize which resources to search. Once the pharmacist has obtained all of the required information, they can categorize the request (e.g., drug interaction, alternative medicine, pregnancy), which may also dictate resource selection (Brown and Choy, 2016, pp. 13, 15, 16). Asking the right questions of the requestor will significantly reduce the chance of misinterpretation and the potential risk of negatively impacting patient care.

After identifying and categorizing the requestor's question, the second step is to "research" an answer (Brown and Choy, 2016, p. 18). The order of consulting resources is tertiary, followed by secondary and primary, as many DI requests can be answered using tertiary resources (Shields and Blythe, 2014). However, for complex or rare DI requests, the pharmacist will need to consult the secondary or primary literature, as requests of such specific nature would not be addressed by the tertiary literature.

There are many databases, which pharmacists can use to locate primary and secondary literature, such as PubMed (MEDLINE) or International Pharmaceutical Abstracts. Pharmacists should look for an answer in more than one resource, in order to compare answers, as each resource may provide different rationale for their recommendations, or contain differences in information itself (Brown and Choy, 2016, p. 19). The caliber of evidence should be considered when looking for an answer, as answers should be based on the best available evidence, such as meta-analyses, systematic reviews, or RCTs, if available (Brown and Choy, 2016, p. 20).

The information from multiple resources, as well as the patient's background information, should be assessed for validity and synthesized into a response for the requestor, which leads to the third step, that is, "respond" (Brown and Choy, 2016, p. 20). The pharmacist should consider all information found, whether it is negative or positive, when formulating a response to the requestor, as objectivity is important. Responses should be accurate and concise and include the requestor's original question, an overview of the available evidence, as well as a summary of recommendations based on the evidence and the pharmacist's expertise (Brown and Choy, 2016, p. 20). In anticipation of follow-up questions, the pharmacist should be thorough and provide additional information of potential relevance, like the side effects of the treatment recommendation and what to monitor (Brown and Choy, 2016, p. 21). Recommendations should be supported by references from unbiased, high-quality literature. Pharmacists should only consider weaker evidence, such as case series, case reports, or expert opinion, if evidence of higher quality does not exist. The inclusion of weaker evidence should be clearly communicated to the requestor. Prepared responses can be formatted and delivered depending on the requestor's preferences—either via telephone, email, or in-person.

Once the answer has been communicated, the pharmacist completes the "4 Rs" approach by documenting the process used to address the request, otherwise known as "record" (Brown and Choy, 2016, p. 22). A file containing the specifics of the request, classification, the search process, recommendations, and supporting evidence should be kept for legal reasons and in case a similar request is posed again by another requestor. If a similar request surfaces, the pharmacist should complete another search, as new evidence may have emerged since the original request was submitted. Pharmacists should document any new evidence and also provide this to previous requestors, as this will have implications for patient care (Brown and Choy, 2016, p. 23). Finally, follow-up with the requestor should occur, in order to assess if their needs have been met, if the information impacted patient care, and if further assistance is required. This will strengthen the pharmacist's relationship with the requestor.

What is Evidence-Based Medicine (EBM)?

Origins and Definition

In 1981, David Sackett, a physician and professor at McMaster University, wrote several articles for the Canadian Medical Association Journal about the "critical appraisal," or evaluation of scientific research, which laid the foundation for the rise of the evidence-based medicine (EBM) movement (Smith and Rennie, 2014, p. 366). EBM is defined as the "conscientious, explicit, and judicious use of current, best evidence in making decisions about the care of individual patients" while "integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett et al., 1996, p. 71). This definition has since been modified to also include patient "values and preferences," as the patient's circumstances or feelings toward risk or cost may ultimately influence whether therapy is pursued (Guyatt et al., 2015b, p. 8). A primary aim of EBM is to demonstrate that patient care decisions should be influenced by scientific fact and that relying solely on clinical expertise, or the expertise of more experienced coworkers, is no longer sufficient (Evidence-Based Medicine Working Group, 1992, p. 2421).

Practicing EBM is not an innate skill; pharmacists must make a conscious effort in order to become proficient at integrating EBM into their patient care decision-making. Straus, Glasziou, Richardson and Haynes (2011, p. 3) outline the process of EBM in five steps, which include: (1) based on the information request, construct an answerable question; (2) search the literature for the best evidence; (3) critically appraise the search results for validity and applicability; (4) integrate the appraised evidence with your clinical expertise, and patient values and preferences; and (5) evaluate your performance and assess whether the integration of EBM had an effect on patient care. This 5-step approach to EBM will be outlined in further detail later in the chapter.

How do Pharmacists Practice EBM?

Pharmacists are well-positioned to exercise the components of EBM. As pharmacists are usually the patient's first point of contact to the health care system (Ontario Pharmacists Association, 2016), they are faced with a multitude of unique questions—some based on what the patient has read on the Internet or from family and friends. This presents the pharmacist with an opportunity to educate the patient about evidence-based information and the importance of using credible sources. In addition to counseling patients, pharmacists may be called upon by physicians or nurses in order to provide guidance on how to properly administer medications, titrate doses, switch therapies, or how to monitor and avoid adverse effects. Hospital pharmacists are often a part of pharmacy and therapeutics committees, which provide information and guidance to all healthcare practitioners on drug safety, evaluation, and complying with drug use guidelines (Bernknopf et al., 2009, pp. 339–340). During student work placements, internships, or co-op terms, supervising pharmacists can provide education around the importance of finding and using evidence to inform patient care decisions. Pharmacists contribute to the body of evidence-based literature as well, by publishing and presenting research findings in journals and conference proceedings.

Levels of Evidence and Study Designs

Levels of Evidence

There is an insurmountable amount of research available online and in print. The challenge for pharmacists is wading through this sea of information and determining what should be considered the "best evidence" when answering a DI request, as not all evidence is equal. Fortunately, there are researchers who have developed useful tools, like evidence pyramids, which can be used to categorize the quality of research studies, based on the strength and precision of the research methods.

Fig. 1, "hierarchy of evidence," is an example of one of these EBM pyramids. This pyramid ranks the highest quality research at the top of the pyramid, with a reduction in the strength and quality of the evidence as you work your way to the bottom.

At the top of the pyramid is the meta-analysis and systematic review. Systematic reviews focus on a specific research question and defined eligibility criteria for the inclusion of studies. A thorough search of the literature is conducted and all results are screened based on the eligibility criteria. The included studies are critically appraised and the data is extracted and summarized from the remaining studies. If the data is similar enough across studies, it can be combined to form an overall conclusion of greater statistical power, otherwise known as a meta-analysis (Green et al., 2008, p. 6). Systematic reviews are ranked one level below the meta-analysis on the evidence pyramid, as not all systematic reviews contain meta-analyses, due to the heterogeneity of some systematic review results.

Beneath the meta-analysis and systematic review, you will find an experimental study design known as the RCT. In a RCT, an intervention (e.g., medication) is introduced to the study participants in order to change the course of a disease. Patients are randomly assigned to either an intervention group or a control group (placebo or standard treatment) and then followed forward to an outcome (Guyatt et al., 2015a, p. 670). RCTs are considered high-quality evidence because the study participants have an equal chance of being placed into either the intervention or control group; the researchers and participants usually do not know which treatment is administered to each group and causation can be proven, due to randomization of the patients and reduced risk of bias.

After RCTs, you will find two types of observational study designs: cohort and case-control studies. The cohort study follows a group of patients with an exposure over time and compares them for outcomes with a group of patients without the exposure (Guyatt et al., 2015a, p. 649). They are useful for answering questions related to etiology, incidence, prognosis, and harm. The case-control study is the opposite; patients with and without a specific condition are compared by the researchers in an attempt to identify which exposures may have contributed to the condition (Guyatt et al., 2015a, p. 647). Case-control studies are useful for acquiring information related to rare outcomes, which may otherwise take a long time to appear in other types of study designs.

Case series and case reports describe the characteristics, diagnosis, and treatment of a few patients or one patient, and they do not utilize a control group (Guyatt et al., 2015a, p. 647). They highlight rare or new and emerging issues, such as the side effects of a new drug, and their statistical significance is low, due to small sample size.

At the bottom of the pyramid, you will find editorials, expert opinion, and animal research, which are considered to be weaker evidence. Editorials and expert opinion pieces are published commentary, based on a clinician's experience in a particular area, with greater risk of bias or selective reporting (Mayer, 2010, p. 27). Animal research is self-explanatory—it can provide useful background information, but the findings cannot always be applied to humans.

Another type of evidence pyramid is the "6S hierarchy of preappraised evidence" (Fig. 2), first developed by R. Brian Haynes and revised by Alba DiCenso and Liz Bayley, all from McMaster University. The sources near the top of this pyramid contain high-quality preappraised evidence, meaning the user does not need to spend time conducting their own appraisal of the evidence. These sources are easy to use while with a patient, or at the immediate point-of-care. "Systems," also known as decision support tools, are at the top of the pyramid and they link relevant preappraised evidence to the patient's electronic health record, based on the patient's profile and circumstances (Dicenso et al., 2009, p. 100).

"Summaries" are also considered high-level evidence. Clinical practice guidelines (CPGs) are considered summaries, as many base their care recommendations on high-quality evidence. You can find CPGs in resources like the National Institute for Health and Care Excellence and the Turning Research Into Practice (TRIP) database. Another example of a summary is the electronic

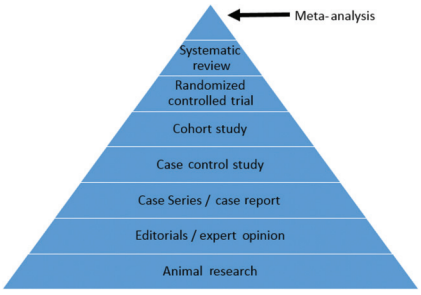


Figure 1 Hierarchy of evidence. Adapted from Mulimani, P.S., 2017. Evidence-based practice and the evidence pyramid: a 21st century orthodontic odyssey. Am. J. Orthod. Dentofacial. Orthop. 152 (1), 1–8.

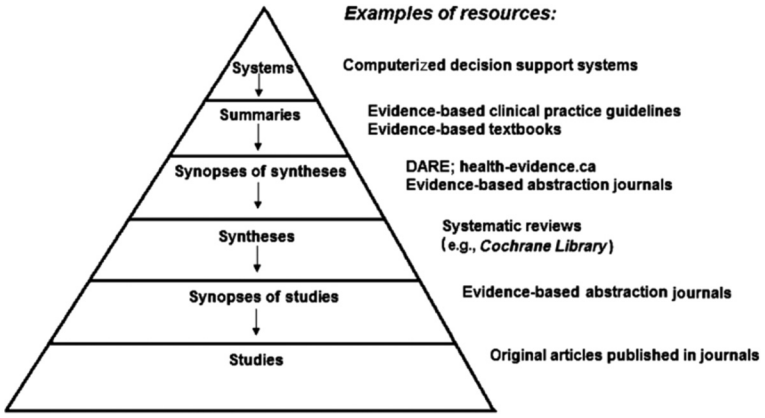


Figure 2 6S hierarchy of preappraised evidence. From Dicenso, A., Bayley L., Haynes, R.B., 2009. Accessing pre-appraised evidence: fine-tuning the 5S model into a 6S model. Evid. Based Nurs. 12 (4), 99–101.

evidence-based textbook or handbook, such as BMJ's Clinical Evidence, DynaMed, or UpToDate. These resources summarize evidence from the literature about specific clinical problems and the content is updated as new evidence becomes available (Dicenso et al., 2009, p. 100).

"Synopses of syntheses" are next on the pyramid. These synopses summarize the results from systematic reviews and often include commentary, which can help inform patient care decisions (Dicenso et al., 2009, p. 100). Systematic reviews may be very long—sometimes up to 100 pages in length. It is simply not realistic to read through this much content while with a patient, making "synopses of syntheses" a useful alternative. "Synopses of syntheses" can be found in journals like the ACP Journal Club, Evidence-Based Medicine, and the Database of Abstracts of Reviews of Effects (DARE) (Dicenso et al., 2009, p. 100).

Unfortunately, "synopses of syntheses" are not available for every systematic review. When this occurs, the original systematic review will need to be consulted. Systematic reviews are referred to as "syntheses" on the 6S pyramid. "Syntheses" take time to read through and digest, requiring more time investment from the user. They are lower on the pyramid, meaning the user will need to appraise the systematic review for validity and reliability on their own. "Syntheses" can be found in most databases, but perhaps the most well-known database for finding "syntheses" is the Cochrane Library's Database of Systematic Reviews (CDSR) (Dicenso et al., 2009, p. 101).

The bottom two levels of the 6S pyramid include "synopses of single studies" and "studies." The former refers to a concise overview of an appraised single study, which may include commentary that can guide clinical practice (Dicenso et al., 2009, p. 101). The latter refers to a single study, which is the last stop on the 6S pyramid, if none of the other types of appraised evidence can be found. You can find "synopses of single studies" in the same journals as "synopses of syntheses" and individual "studies" can be found in resources like PubMed (Medline) and the EBSCO and Ovid databases (Dicenso et al., 2009, p. 101).

These pyramids are meant to serve as guides and do not suggest that you must find a meta-analysis or always use a "system" in order to answer your DI requests. High-quality and pre-appraised evidence does not exist for every patient care scenario. This means there will be situations when evidence of lesser value will need to be reviewed and assessed, as it may be the only evidence available. Understanding the levels of evidence and various study designs will help you determine which type of study can best answer your DI request.

EBM Step 1: Constructing an Answerable Question

Background/Foreground Questions and PICO

The most important step of the EBM process is the formulation of an answerable question, as poorly structured questions will lead to disorganized and unproductive searches of the literature. Before constructing an answerable question, the pharmacist may need to answer some general background questions, in order to construct a focused, overall answerable question. Background questions are usually related to topics studied in pharmacy school, such as pharmacology or pharmacokinetics. Fig. 3 contains a case scenario, as well as associated background questions of potential relevance.

Once the pharmacist has gathered the appropriate background information, the more complex foreground question can be constructed, as asking a very broad question like "should I change the patient's osteoporosis therapy?" will not lend itself well to the literature-searching component of the EBM process. Foreground questions can be constructed using the PICO model. The PICO mnemonic stands for: patient or problem (P), intervention (I), comparison (C), and outcome(s) (O) (Richardson et al., 1995, p. A12). The "patient" or "problem" may include the patient's characteristics, such as gender, age, disease, condition, or comorbidities. The "intervention" focuses on what will be introduced to modify the course of the disease, like a new drug therapy. "Comparison" includes any alternative to the intervention, which may be the standard therapy or placebo. It is important to note that in some scenarios, there may be no comparison, which is acceptable. The "outcome(s)" include what you wish to do, or would

A pharmacist has been asked by a physician to find evidence supporting the use of denosumab over bisphosphonates for the treatment of osteoporosis in a 65 year old female patient. Over the course of several years, the patient has experienced many bothersome side effects, suspected to be caused by the use of different bisphosphonates, and the physician would like to know if denosumab will be better tolerated, with less risk of fracture. The pharmacist learns that the patient is also taking melatonin for sleep disturbances, as well as rosuvastatin for high cholesterol and levothyroxine for hypothyroidism. Before constructing an answerable question, the pharmacist may want to research and answer some background questions, such as:

- What is the pathophysiology of osteoporosis?
- What is denosumab?
- What is denosumab's mechanism of action?
- Are there known interactions between denosumab, melatonin, rosuvastatin, or levothyroxine?

Figure 3 Case scenario.

Table 1 PICO

P-patient or problem	65-year-old female with osteoporosis
I-intervention	Denosumab
C-comparison	Bisphosphonates (remember, "comparison" is optional, but in this situation, there is a comparator)
O-outcome(s)	Better tolerance, less side effects, and risk of fracture

like to improve for the patient, such as reduce side effects, mortality, or pain (Richardson et al., 1995, p. A12). Based on the scenario in Fig. 3, the PICO in Table 1 would be as follows:

Once the PICO has been identified, the foreground or answerable question can be constructed. For the aforementioned PICO, a possible foreground question could be:

In a 65-year-old female patient with osteoporosis, is denosumab better tolerated than bisphosphonates and more effective for reducing side effects and risk of fracture?

Schardt, Adams, Owens, et al. (2007, p. 2) add that the PICO formula can be expanded from PICO to PICOTT, which takes into account the type (T) of question (therapy, harm, prognosis, etc.) being asked and the type (T) of study (meta-analysis, RCT, etc.) that may best answer the question. The PICOTT approach can help the pharmacist further narrow their foreground question. Furthermore, Straus, et al. (2011, p. 21) identify that "clinicians who are taught this structured approach ask more specific questions, undertake more searches for evidence, use more detailed search methods, and find more precise answers."

Creating the right answerable question does take practice and can be quite difficult—especially in scenarios with greater complexity. In these situations, it is best to create more than one answerable question, rather than try to combine all elements into one overarching question. This will also make the question(s) easier to articulate to other health care practitioners. The precise wording of the question guides the search of the literature and helps to reduce the amount of irrelevant results.

EBM Step 2: Choosing Your Sources and Performing the Literature Search

Identifying Search Terms and Using AND/OR/NOT

Once an answerable question has been decided upon, the next step is to isolate the most important concepts from your PICO, which can be used to build a search strategy. Once you have isolated these main concepts, you should think of synonyms or alternative ways of referring to these terms. For example, in the scenario from the previous section, "female" was identified as a part of the "P—patient" component. Other ways of referring to "female" would be women or woman. Additionally, you may wish to further break down "bisphosphonates" into specific drugs from this class, such as alendronate, or risedronate.

After coming up with a list of search terms and synonyms, the next step is to combine the terms using Boolean operators, such as OR/AND. The "OR" operator connects similar concepts and the "AND" operator connects different concepts. Figs. 4 and 5 illustrate these operators in action.

Another operator that is sometimes used is "NOT." The "NOT" operator can be used to exclude specific search terms from your results. An example of this operator is depicted in Fig. 6. This operator should be used with caution, as it can exclude results, which are actually of relevance.

Once you have thought about how to combine your concepts, you can begin to draft some search strategies. Your first search strategy will not likely be your last, as searching is a very iterative process and several strategies are usually tested before finding a

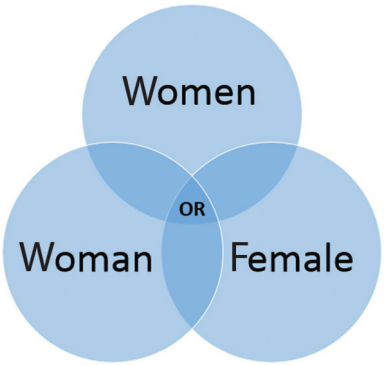


Figure 4 OR operator.

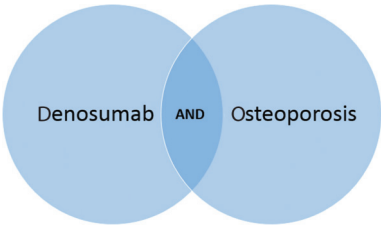


Figure 5 AND operator.

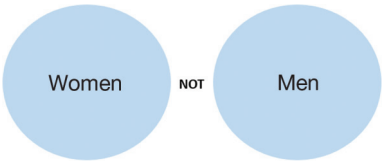


Figure 6 NOT operator.

strategy which yields the best results. If possible, it is a good idea to consult a medical librarian, as these librarians can provide guidance on building and running effective search strategies.

PubMed (MEDLINE)

The next step is to think about the databases or resources to be searched for high-quality evidence. PubMed (MEDLINE), run by the National Library of Medicine, is one of the world's most commonly searched databases. PubMed contains the entire MEDLINE collection, which is why it is often referred to as PubMed (MEDLINE). As of this writing, PubMed (MEDLINE) contains over 28 million references to research articles published in the health and life sciences disciplines. Due to its extensive coverage, it is often the first stop for health care practitioners. In addition, it is free to search; although, access to certain full-text articles may be behind a paywall.

A simple PubMed (MEDLINE) keyword search, based off of the PICO in Table 1, would look as follows:

(female* OR woman OR women) AND osteoporosis AND denosumab AND (diphosphonate* OR bisphosphonate*)

The *asterisk*, also known as "truncation," can be used to search for word ending variations, such as the singular or plural variations of a word. Synonymous terms, connected with "OR," like (diphosphonate* OR bisphosphonate*) must be enclosed with parentheses, as these terms are searched as one unit. Boolean operators must be capitalized in PubMed, or PubMed may change all "OR" operators to "AND" operators.

Upon entering your search strategy into PubMed's main search box, PubMed will try to match or "map" the keywords in your search strategy to the appropriate MeSH terms or medical subject headings. What is MeSH? When an article is added to PubMed, it is read by a content expert, who selects the MeSH terms from the MeSH thesaurus, which best describe the main subjects or topics of the article. MeSH terms can be compared to modern-day hashtags. In Fig. 7, PubMed has attempted to automatically

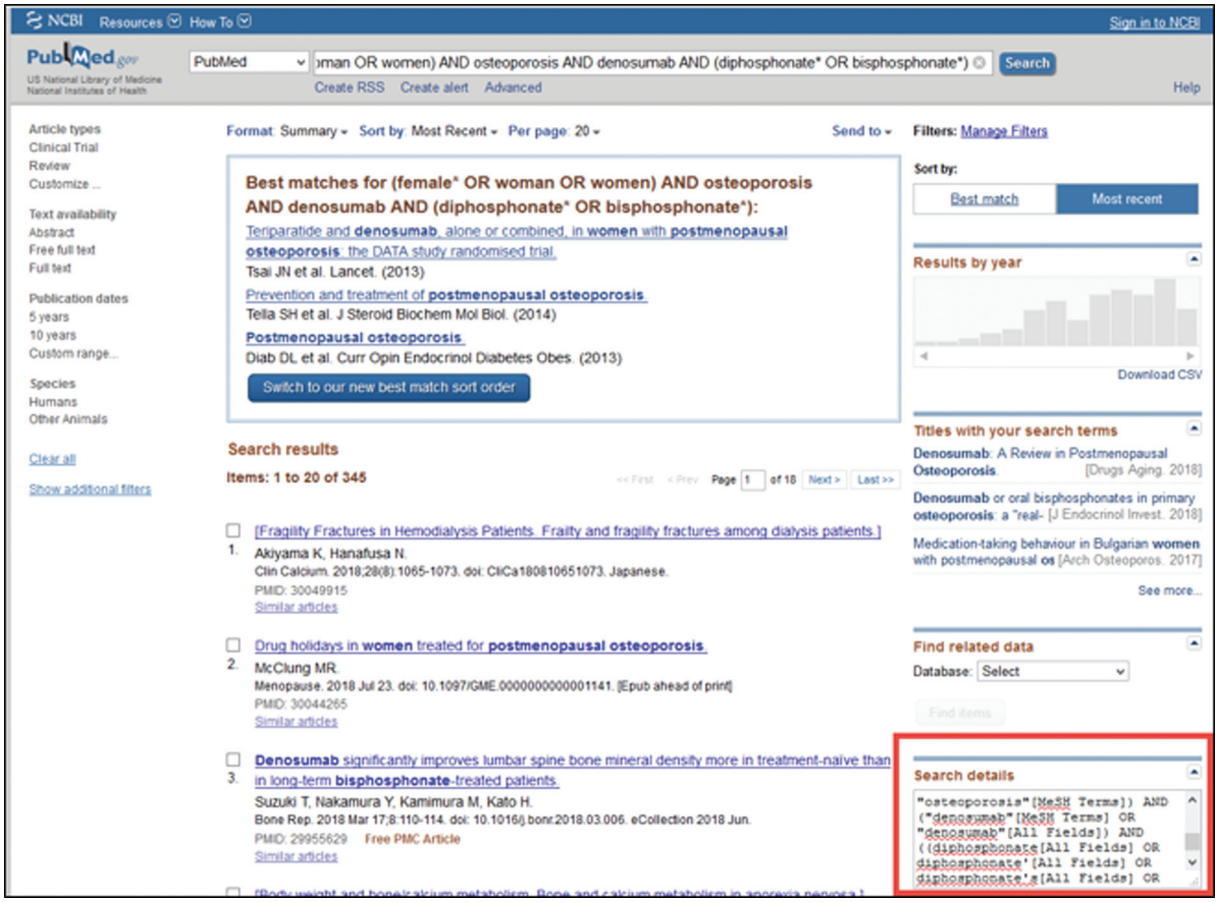


Figure 7 Automatic term mapping function in PubMed.

match or "map" the keywords in the search strategy to the applicable MeSH terms. The "search details" box shows this feature in action.

Note: When applying truncation to a keyword (e.g. female*), this turns off the automatic term mapping feature on that particular keyword, so keep this in mind when building your searches.

If your keyword search has not "mapped" to the appropriate MeSH terms, then you will have to look in the MeSH thesaurus yourself, to find the applicable MeSH terms to add your search. Figs. 8–10 demonstrate how to find MeSH terms using the MeSH thesaurus. If you are conducting a literature search for a publication, like a systematic review, you should build a search strategy, which is comprised of *both* keywords and MeSH terms, so that you construct a truly comprehensive search for all possible literature.

After clicking "search," (Step 4 in Fig. 8) you are presented with a list of potential MeSH terms (Fig. 9). Click on a term to read more about it and to decide if it will add value to the search strategy.

The next screen depicts the MeSH term record (Fig. 10), where you will often find a definition, the year the term entered the MeSH thesaurus, the additional terms the MeSH term will search for automatically (entry terms) and where the MeSH term fits in the MeSH hierarchy of terms. By looking at this hierarchy, you can determine if you would like to select a broader or narrower term to use in your search.

Once you find your applicable MeSH terms, you can incorporate them into a search strategy. A potential combined MeSH and keyword search would look as follows:

(female[MeSH] OR female* OR woman OR women) AND (osteoporosis[MeSH] OR osteoporosis)
AND (denosumab[MeSH] OR denosumab) AND (diphosphonates[MeSH] OR diphosphonate* OR bisphosphonate*)

Enter your search strategy into the PubMed main search box and make sure the drop-down menu to the left of the main search box says "PubMed." Once you have your results, you can apply filters (Fig. 11), like publication type, date range, and language (found under "show additional filters"), to further narrow the amount of results.

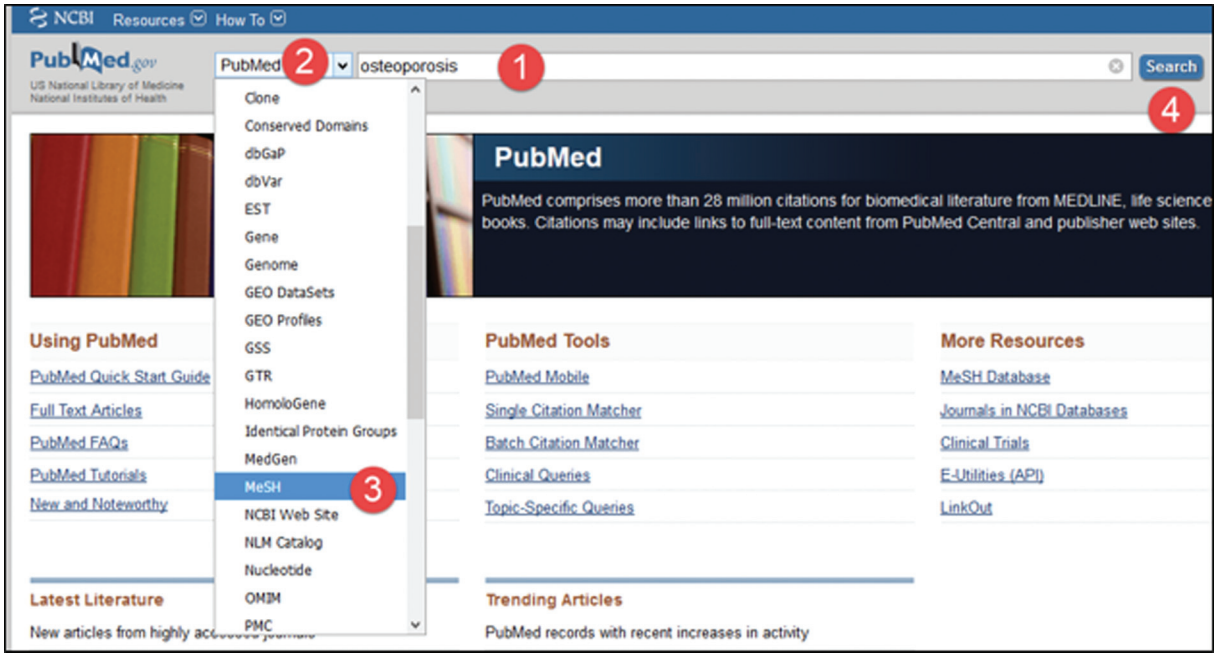


Figure 8 How to search for a MeSH term.

Tips to Consider

A useful tip is to input the title of a relevant article you have already found through another source into PubMed (MEDLINE) and take a look at the MeSH terms, which have been applied to that article (Fig. 12). This may provide you with additional terms you can add to your search strategy.

Additionally, you can use the "similar articles" option to view a list of other possible articles of interest (Fig. 13).

Lastly, always save your search strategies. You can create a free "MyNCBI" account with PubMed and save your searches in your account permanently. You can login at a later date and rerun the search again, or set up email alerts, in order to receive emails every time a new article is added to PubMed on your search topic.

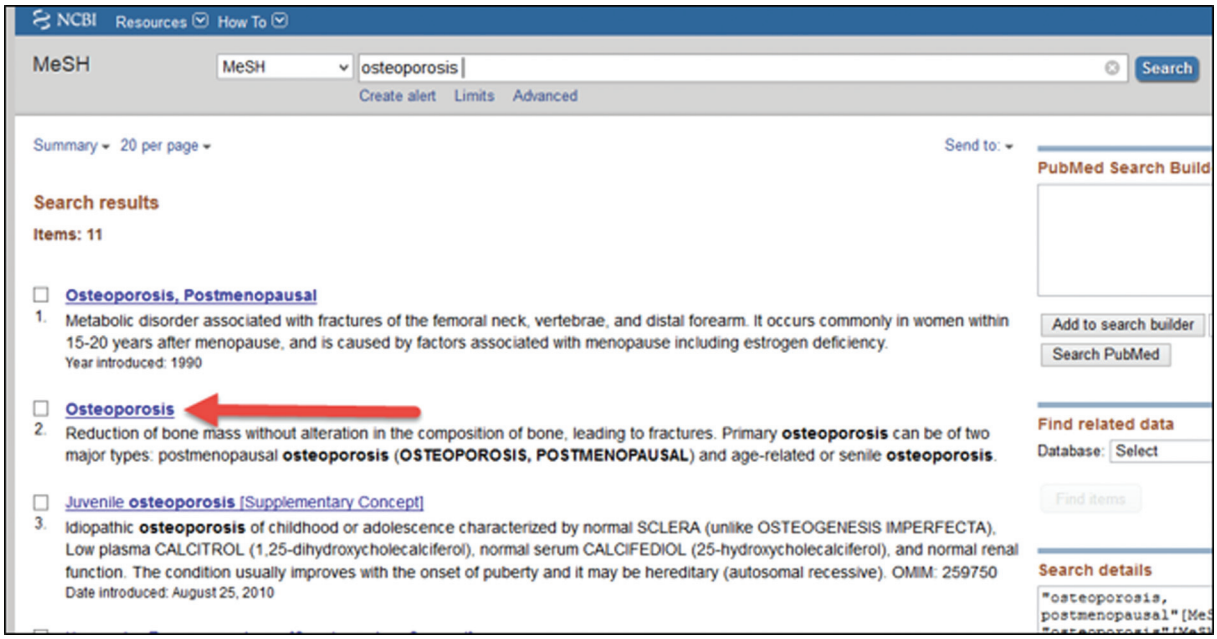
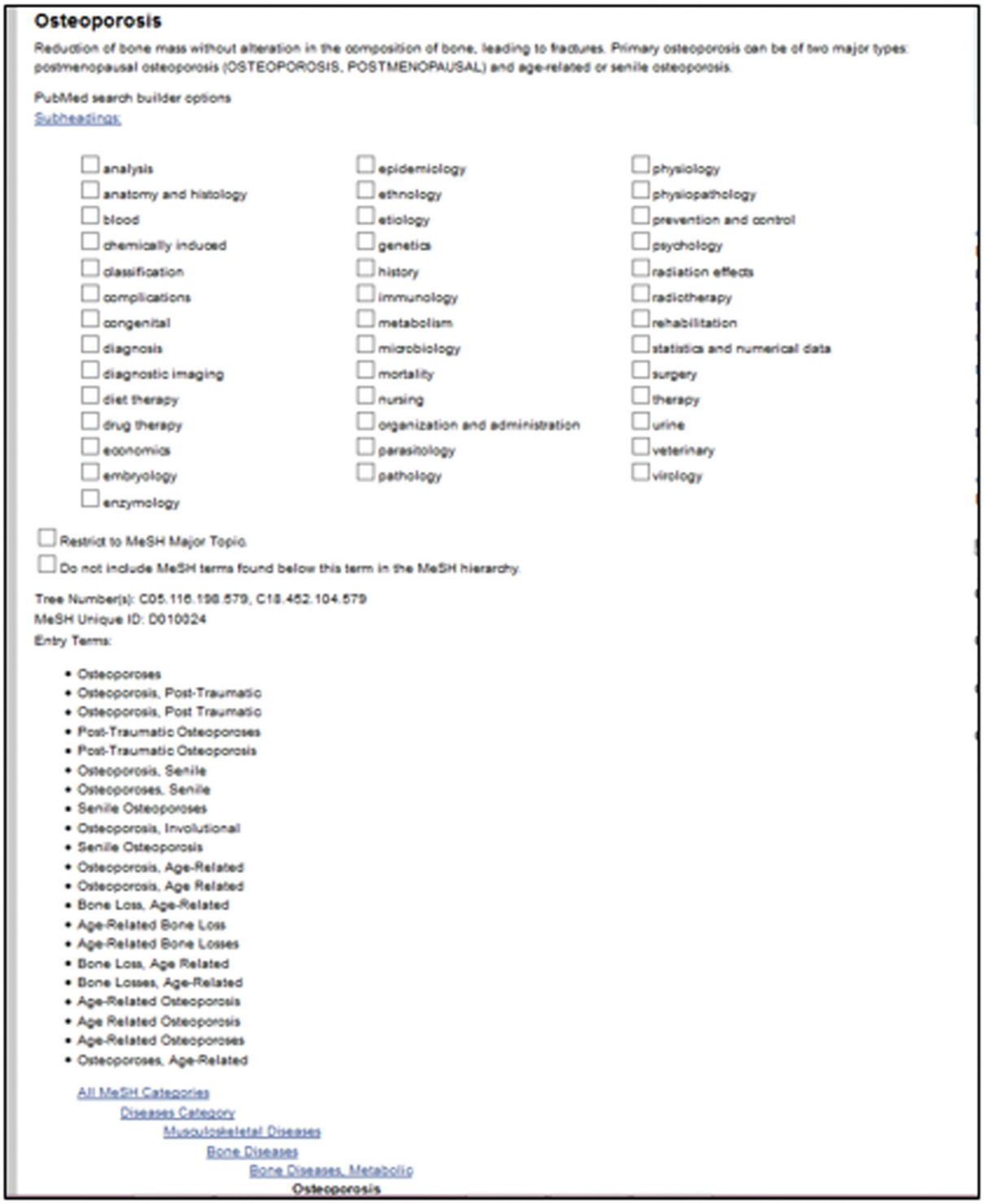


Figure 9 List of MeSH terms.



Osteoporosis

Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis (OSTEOPOROSIS, POSTMENOPAUSAL) and age-related or senile osteoporosis.

PubMed search builder options

Subheadings:

analysis	epidemiology	physiology
anatomy and histology	ethnology	physiopathology
blood	etiology	prevention and control
chemically induced	genetics	psychology
classification	history	radiation effects
complications	immunology	radiotherapy
congenital	metabolism	rehabilitation
diagnosis	microbiology	statistics and numerical data
diagnostic imaging	mortality	surgery
diet therapy	nursing	therapy
drug therapy	organization and administration	urine
economics	parasitology	veterinary
embryology	pathology	virology
enzymology		

Restrict to MeSH Major Topic.

Do not include MeSH terms found below this term in the MeSH hierarchy.

Tree Number(s): C05.116.198.579, C18.452.104.579

MeSH Unique ID: D010024

Entry Terms:

- Osteoporoses
- Osteoporosis, Post-Traumatic
- Osteoporosis, Post Traumatic
- Post-Traumatic Osteoporoses
- Post-Traumatic Osteoporosis
- Osteoporosis, Senile
- Osteoporoses, Senile
- Senile Osteoporoses
- Osteoporosis, Involutional
- Senile Osteoporosis
- Osteoporosis, Age-Related
- Osteoporosis, Age Related
- Bone Loss, Age-Related
- Age-Related Bone Loss
- Age-Related Bone Losses
- Bone Loss, Age Related
- Bone Losses, Age-Related
- Age-Related Osteoporosis
- Age Related Osteoporosis
- Age-Related Osteoporoses
- Osteoporoses, Age-Related

All MeSH Categories

Diseases Category

Musculoskeletal Diseases

Bone Diseases

Bone Diseases, Metabolic

Osteoporosis

Figure 10 MeSH record.

Clinical Queries

A unique feature of PubMed (MEDLINE) is the "clinical queries" function, found on the homepage (Fig. 14). This feature can be used to quickly find clinical studies, systematic reviews, and genetic studies. Simply enter in your search terms in the search box and click "search." After the results are returned, you have the option to change the "category" of the search topic and the "scope" of

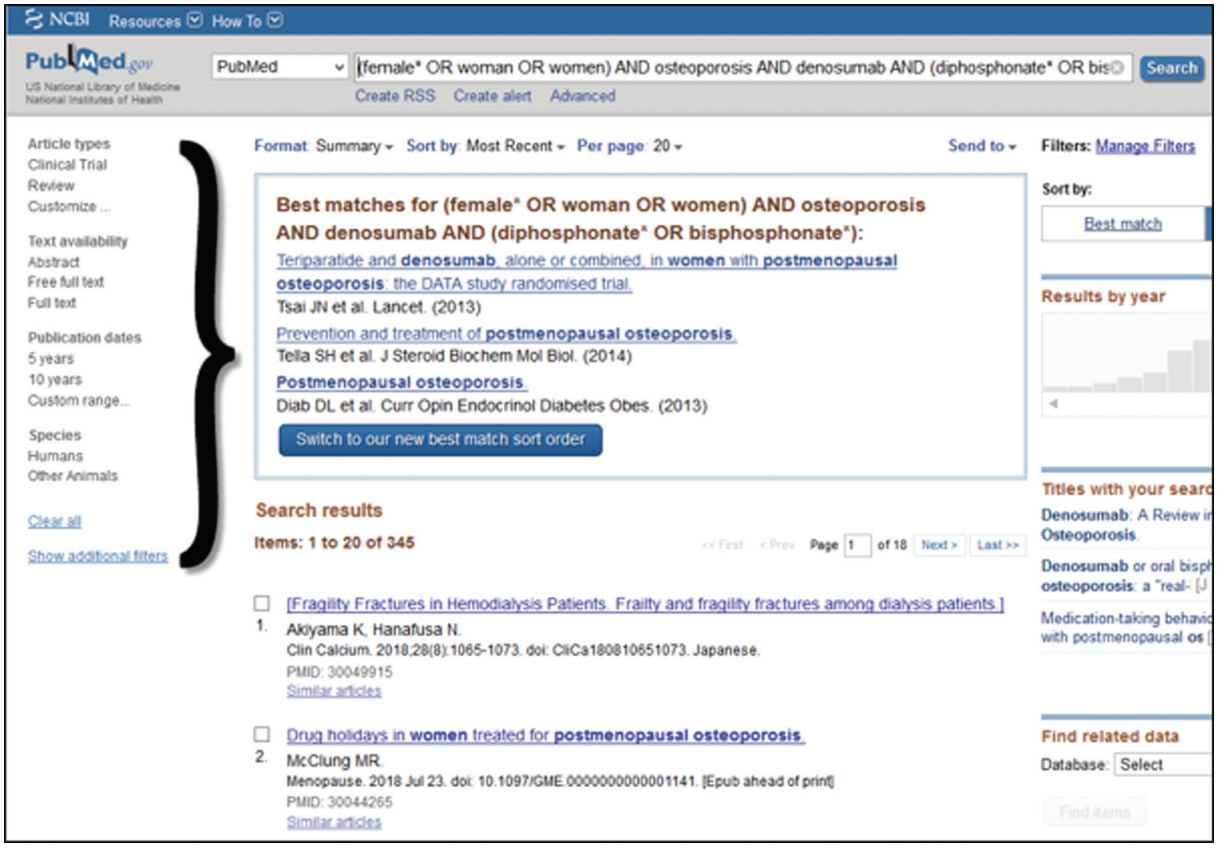


Figure 11 Limiting your search results with filters.

the results from broad to narrow. The "scope" automatically defaults to broad, so that the user is able to assess the relevancy and amount of results, before choosing to narrow the results instead.

Other Databases

In addition to PubMed (MEDLINE), there are several other databases a pharmacist will want to consider searching, in order to obtain a comprehensive overview of all of the literature on their subject. Table 2 outlines some of these databases of relevance.

Clinical Practice Guidelines

CPGs are used by health care practitioners in order to assist with making decisions related to the diagnosis and treatment of specific medical conditions. CPGs are often created by multidisciplinary teams and are defined as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of benefits and harms of alternative care options" (Institute of Medicine, 2011, p. 4). Not all guidelines are created equally, some are more credible than others, due to heavier reliance on research evidence and less on expert opinion. CPGs may be retrieved via a database search, but they can also be found through guideline-specific websites. Table 3 lists a few of these commonly used websites.

Gray Literature

There will be occasions when no, or very little evidence-based information can be found to answer a clinical question. Sources considered to be "gray literature" may offer a solution in this type of situation, as gray literature is often niche research. Gray literature includes information which is not typically peer-reviewed, challenging to find, and is inaccessible via traditional or commercial publishing (Mahood et al., 2014, p. 222). Examples of gray literature include, but are not limited to, reports from organizations, companies, or associations, government publications, unpublished clinical trials, PowerPoint presentations, conference proceedings, theses and dissertations, white papers, policy briefs, and blogs.

Simple keyword searches can be used in search engines, such as Google, to search for gray literature, but this is difficult, as most searches yield hundreds of thousands, if not millions, of results. As it is impossible to go through this many results, it is best to target

Table 2 Useful databases for pharmacy and medicine

Databases	*Content*	*Subscription required*
Embase	• Biomedicine and pharmacology • Includes 1000's of journals not indexed by MEDLINE • International, with significant European coverage • Includes abstracts from conferences	Yes-through various vendors
International Pharmaceutical Abstracts	• Pharmacy literature covering topics like biopharmaceutics, pharmacokinetics, drug reactions, ethics, liability, drug delivery, drug interactions, toxicity, and much more • International coverage • Includes abstracts from conferences and major pharmacy meetings	Yes-through various vendors
The Cochrane Library	• Collection of six healthcare databases: CDSR; CENTRAL; DARE; CMR; HTA; and EED	Yes, but full-text access may be free for your country or region—see the Cochrane Library's website for more information on countries with free or reduced cost access
TRIP	• Simultaneously searches for high-quality research, such as systematic reviews, evidence-based synopses, clinical practice guidelines, primary research articles, and much more • Offers a PICO search option on the homepage, which allows the user to structure a search query using the PICO formula	No, but a subscription-based version with additional content and search features is also available. See the TRIP website for more information on countries with free or reduced cost access.
BMJ Clinical Evidence	• Systematic reviews of the best available evidence on the effects of treatments • Evidence is formatted to answer key clinical questions and categorized by level of effectiveness	Yes-see BMJ Clinical Evidence's website for more information on pricing for shorter time periods, like 48 h or 30-day access

CDSR, Cochrane Database of Systematic Reviews; *CENTRAL*, Cochrane Central Register of Controlled Trials; *CMR*, Cochrane Methodology Register; *DARE*, Database of Abstracts of Reviews of Effects; *EED*, NHS Economic Evaluation Database; *HTA*, Health Technology Assessment Databases; *TRIP*, Turning Research Into Practice.

Table 3 Practice guideline websites

NICE	• A UK-based website of NICE-authored guidelines on a number of health conditions • Includes summaries of the best available evidence on medicines (NICE Advice) and flowcharts which bring together everything NICE has prepared on a topic (NICE Pathways)
CPG Infobase	• A Canadian-based website of guidelines authored by Canadian health organizations
NHMRC Clinical Practice Guidelines	• An Australian-based website of guidelines specific to Australian practice • Offers a guideline registry, so authors can register guidelines in development

NHMRC, National Health and Medical Research Council; *NICE*, The National Institute for Health and Care Excellence.

websites of important organizations, associations, or government agencies, as well as online academic institutional repositories, in order to search them individually for potentially useful gray literature.

When conducting gray literature searches, it is important to remember that you must assess the quality of any research you find. There are checklists available to assist with this process, such as Jess Tyndall's AACODS checklist (2010), which can be used to identify the authority, accuracy, coverage, objectivity, date, and significance of gray literature.

For drug-related clinical questions, various clinical trial websites may be relevant. These websites often provide access to clinical trial data, which was not published because the trial was suspended, terminated, or the results did not meet the researchers' expectations. Table 4 lists websites, which can be used to find unpublished clinical trial data.

EBM Step 3: Critical Appraisal of the Results

Before the results from the articles found during your literature search can be applied to the patient, they must be critically appraised for validity and reliability, as publication in a journal does not automatically guarantee a high level of quality. Before delving too far into the specifics of a study's validity, it is important to think about some general overarching questions from the outset. The following list includes some points to consider, derived from Greenhalgh's checklists (2014, pp. 243–44):

- Who authored the study? What are their credentials?
- Was the study peer-reviewed?
- Is the research original?

Figure 12 Locating MeSH terms applied to a relevant article.

Table 4 Clinical trial websites

The World Health Organization's ICTRP search portal	• An international database of clinical trial registration data • Includes data, such as recruitment status, sponsorship, study type, inclusion/exclusion criteria, outcomes, and links to the original records
The US National Institutes of Health (ClinicalTrials.gov)	• A US-based international trial registry • After a study is registered, more information is added to the study's record as the trial progresses; and in some cases, even the final results
ISRCTN.org	• A UK-based international registry and database of trial results • Not all registration records contain study results, or publication and dissemination plans
UMIN-CTR	• Japanese-based international registry and database of trial results • Not all registration records contain study results
PACTR	• A registry for all clinical trials conducted in Africa • Records may include a link to a publication
EU Clinical Trials Register	• Registry of trials conducted in the European Union • Includes important trial data, such as subject disposition, baseline characteristics, adverse events, trial amendments, interruptions, or limitations

ICTRP, International Clinical Trials Registry Platform; *PACTR*, Pan African Clinical Trials Registry; *UMIN-CTR*, University Hospital Medical Information Network Center.

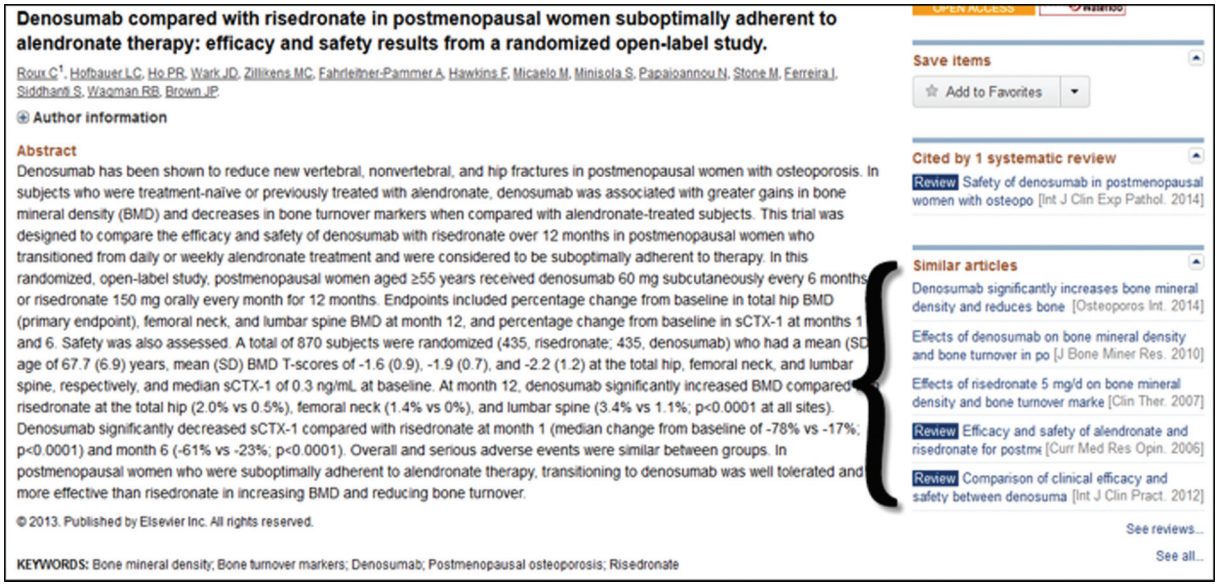


Figure 13 Similar articles feature.

- What is the purpose of the study? What problem is the study attempting to solve?
- Is the study's methodology described? Was the appropriate study design used to address the study question?
- How long was the study? How large was the sample size? Will this information have an effect on the applicability to your patient?
- What are the study's results? Have the right statistical tests been used to analyze the results? Do the results look like they may be applicable to other patients?
- Have the authors of the study met ethics standards and disclosed any possible conflicts of interest, like support from pharmaceutical companies?
- Do the conclusion(s) support the study's main objective(s)?

If you are satisfied with the answers to the above questions, you can proceed to a more critical examination of the articles and their results. Take into account that not all study designs can be appraised using the same questions, as some questions will be more relevant to certain study designs compared to others. For example, different criteria will need to be used to critique a systematic review, or meta-analysis, versus a RCT. As these study designs are of the highest rigor, the following is a list of questions

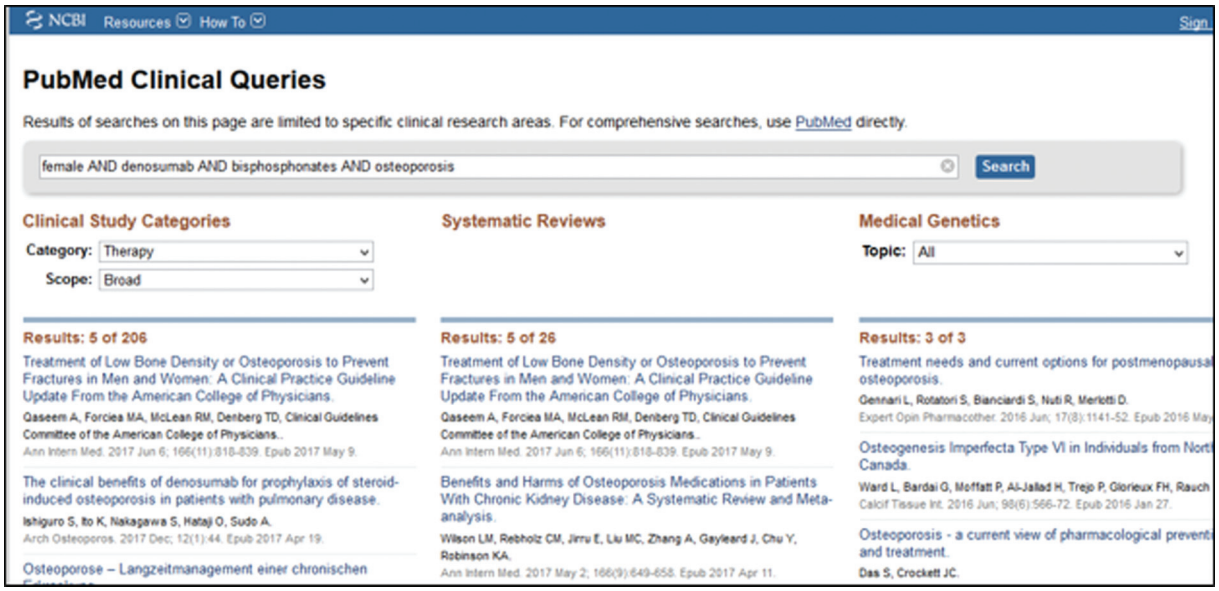


Figure 14 PubMed clinical queries feature.

specific to systematic reviews, meta-analyses, and RCTs. These questions should be considered in addition to the more general questions listed earlier.

Systematic Reviews/Meta-Analyses

Derived from Oxman and Guyatt (1993, p. 128)

- Was the main clinical question, or objective, narrow and focused?
- How thorough was the literature search? What is the likelihood that it has captured everything? Does the search strategy contain both MeSH terms (where applicable) and keywords? Have search "limiters" been used appropriately (e.g., publication date range, study type)?
- Can you identify the inclusion criteria used to determine eligibility?
- Was the process for screening and including eligible articles documented?
- Were each of the included studies critically appraised?
- How many individuals performed the critical appraisal and extracted the data?
- How homogenous was the data? Was it similar enough to perform a meta-analysis? If so, was the data combined and presented in the appropriate manner (e.g., forest plot)?
- How precise are the results? Do the results support the author's claims?
- What was the "overall scientific quality?" Will this influence or change how you practice as a pharmacist?

Randomized Controlled Trials

Derived from Walsh, Perkovic, Manns, et al. (2015, p. 61)

- Were the intervention and control groups similar at the start of the trial?
- How were the patients randomized? Was their allocation to treatment groups concealed?
- Was the study blinded? Did the patients or researchers know who was receiving which treatment?
- Were patients analyzed in the groups to which they were randomized?
- Were the patients in the intervention and control groups treated differently?
- Was follow-up complete? Did any patients drop out of the study?
- How large and precise was the treatment effect? Can you apply the results to the patients in your care?

Describing Study Results

While a review of statistical tests used in pharmacy research is beyond the scope of this chapter, readers of EBM resources should be familiar with the values commonly used to describe the magnitude of effect observed in quantitative research.

Quantitative research results are generally reported in the format of *point estimate* (*variability*), where *point estimate* is defined as "the single value that best represents the value of the population parameter" (Guyatt et al., 2015a, p. 667) and *variability* is a measure of the amount of consistency within the data—essentially, a measurement of how broadly or narrowly the data points are dispersed from the point estimate.

Measures of Central Tendency and Precision

Clinical and physiologic parameters among populations often result in data that follows a bell-shaped curve, or normal distribution. In this distribution, the most frequent values are those observed in the midpoint of the total range observed, with reducing frequency as one moves to each end of the range. When data follow a normal distribution, the *mean* (or average) is the most commonly used measure of central tendency, and the *standard deviation* is the common measure of variability used, as illustrated in Fig. 15.

When the data follows a skewed distribution, where the resulting curve is not symmetrical around the measure of central tendency, but rather is more gathered at one end of the range, the *median* (mid-point value when all observations are listed in order from smallest to largest) is the most commonly used measure of central tendency, and the *interquartile range* is the corresponding measure of variability used. Unlike the standard deviation, which is defined by cut-points at equal distance from the mean in

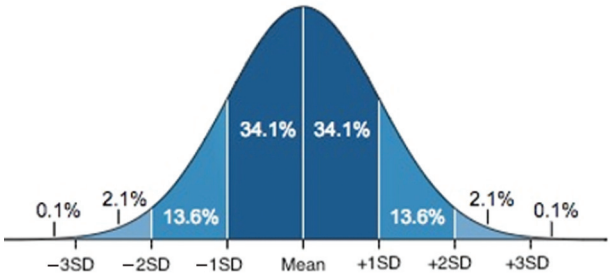


Figure 15 Standard deviation. Adapted from Toews, M.W., 2007. Standard Deviation Diagram. Available from: https://commons.wikimedia.org/wiki/File:Standard_deviation_diagram.svg.

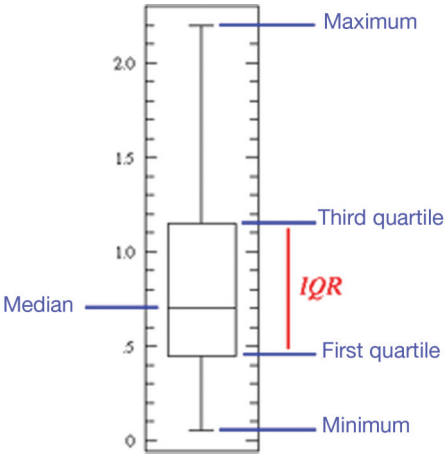


Figure 16 Box plot. Reprinted with permission from Kirkman, T.W., 1996. Display of Statistical Distribution—Box Plot. Available from: http://www.physics.csbsju.edu/stats/display.distribution.html.

each direction, the interquartile range instead presents the difference in the values that form the 75th and 25th percentile of the data. Therefore, the distance between the 25th percentile value and the median may or may not be the same as the distance between the median and the 75th percentile value, as illustrated by the box plot below (Fig. 16).

Describing Results in Relation to a Comparison Group

When a study involves an intervention group(s) and a comparison group (e.g., a placebo control, or comparison to another active agent or intervention) the difference in the observations across each group or exposure is most valuable to clinical decision-making.

Even in a placebo-controlled study, some study subjects may still experience the event of interest. The *control event rate* (CER) is the proportion of subjects in the control group who experience the event (or outcome) of interest, while the *experimental event rate* (EER) is the proportion of patients in the experimental (or intervention) group. Fig. 17 provides readers with an example of the CER and EER calculations, as well as all other calculations mentioned in this section.

The *relative risk* (RR) of the event occurring is "the ratio of the risk of an event among an exposed population to the risk among the unexposed" (Guyatt et al., 2015a, p. 671). An RR of 1 represents an equal event rate in both groups, while an RR >1 represents a greater event rate in the exposed population versus the control, and an RR <1 represents a lower event rate in the exposed population versus the control.

Absolute risk reduction (ARR) is the difference between the CER and the EER. In the event that the ARR calculation results in a negative value, it can instead be termed as an *absolute risk increase* by that magnitude. For example, an ARR of -0.25 actually represents an absolute risk increase (ARI) of 0.25 or 25%.

Many EBM resources further translate the absolute risk reduction into another value called the *number needed to treat* (NNT). This value is calculated as the inverse of the ARR (1/ARR) and represents the number of patients who need to be treated over a specific period to achieve one additional good outcome (Guyatt et al., 2015a, p. 665). The lower the NNT, the more effective the intervention is for that outcome. In the event that the intervention has a negative effect in relation to the control, the *number needed to harm* (NNH) can be similarly calculated (1/ARI) and represents the number of patients who need to be treated over a specific period in order to observe one negative outcome. In this case, a higher NNH is preferred as it means that more subjects can receive the intervention before the negative outcome is observed.

Another measure of association reported in EBM is the *odds ratio* (OR). A discussion on the specifics of comparing OR to RR and the specific uses and differences in interpretation among each are outside the scope of this chapter, but readers are provided with an article by Schechtman as a reference at the end of this chapter, for further reading. The OR is a ratio of the odds of an event in an exposed group to the odds of the same event in an unexposed group (Guyatt et al., 2015a, p. 665). Odds differ from relative risks in that the value is calculated as a comparison of the probability of an event compared to the probability of a nonevent in odds, while a relative risk calculates the proportion of subjects experiencing an event versus the total number of subjects. In situations where the event or outcome is rare, the OR and RR produce similar results; however, as an event becomes more frequent, OR generally overestimates the RR. For this reason, some recommend reporting both measures (Schechtman, 2002, p. 435).

Checklists

Many organizations have created critical appraisal checklists, which are freely available online. Table 5 lists several examples of these checklists, which can be used to assess the quality of various types of evidence. These checklists help to organize and structure the critical appraisal process, ensuring that the most important questions are addressed. This permits an easier comparison of the results from many research articles.

A 2x2 table can be helpful with these calculations, where the intervention and control arms occupy the first and second rows, respectively. Unfavorable and favorable outcomes occupy the first and second columns, respectively. The values in the cells represent the number of subjects in the study experiencing each outcome under each exposure.

	Unfavorable Outcome	Favorable Outcome	Total Patients
Intervention	a	b	a + b
Control	c	d	c + d

A randomized controlled trial evaluated the prevalence of fatigue among users of a drug versus a placebo control, with the following results:

	Adverse Event	No Adverse Event	Total Patients
Drug	349	23	372
Placebo	584	154	738

Experimental Event Rate (EER) = $\left[\frac{a}{a+b}\right] = \left[\frac{349}{372}\right] = 0.938 = 93.8\%$

Interpretation: 93.8% of subjects receiving the drug experienced fatigue

Control Event Rate (CER) = $\left[\frac{c}{c+d}\right] = \left[\frac{584}{738}\right] = 0.791 = 79.1\%$

Interpretation: 79.1% of subjects receiving placebo experienced fatigue

Relative Risk (RR) = $\left[\frac{EER}{CER}\right] = \left[\frac{0.938}{0.791}\right] = 1.186 = 118.6\%$

Interpretation: A subject on the drug had 118.6% of the risk of experiencing fatigue compared to a subject on placebo. Put another way, a subject on the drug has 1.18 times the risk of experiencing fatigue compared to a subject on placebo

Absolute Risk Reduction (ARR) = CER – EER = 0.791 – 0.938 = -0.147 = -14.7%

Interpretation: The absolute difference in event rates between subjects on the drug versus placebo is -14.7%. Put another way, the difference between the rate of fatigue among subjects on the drug versus on placebo is an Absolute Risk *Increase* of 14.7%

Number Needed to Treat (NNT) = $\left[\frac{1}{ARR}\right] = \left[\frac{1}{-0.147}\right] = -6.8$

Interpretation: As this result is a negative number, it actually represents the Number Needed to *Harm*. This means that for every 6.8 subjects taking the drug, 1 of them will experience fatigue from the drug.

Odds Ratio (OR) = $\left[\frac{a/b}{c/d}\right] = \frac{a*d}{b*c} = \frac{349*154}{23*584} = 4.00$

Interpretation: The odds of experiencing fatigue on the drug are 4 times higher than the odds of experiencing fatigue on placebo

Figure 17 Sample calculations for a study on adverse events from a drug.

EBM Steps 4 and 5: Applying the Evidence to Your Patient and Evaluating Your Results

After completing the critical appraisal, the next step is to determine whether the results apply to your patient and if so, how this information will be communicated. It is important to note that not all study recommendations can be applied to your particular patient, no matter how promising they may be, as every patient has different characteristics and experiences different circumstances (Fuller, 1997, p. 516). For example, an article demonstrating a positive drug treatment effect for young adult males may not be that helpful for elderly female patients. In addition, the route of administration, or differences in drug dosing, can affect the relevancy of the results for your patient. Factors such as age, race, ethnicity, and gender can all play roles in the applicability of evidence. Other factors such as the patient's socioeconomic status, lifestyle, support from family, religious beliefs, and potential for medication adherence can influence the relevance, or practicality of the evidence to the patient's situation (Haynes

Table 5 Critical appraisal checklist resources

Organizations or titles of checklist	*Descriptions*	*URLs*
SIGN	• Checklists for systematic reviews and meta-analyses, randomized controlled trials, cohort studies, case-control studies, etc.	www.sign.ac.uk
CASP	• Checklists for systematic reviews and meta-analyses, randomized controlled trials, cohort studies, case-control studies, etc.	http://www.casp-uk.net/casp-tools-checklists
Dartmouth Biomedical Libraries	• Checklists for systematic reviews and meta-analyses, randomized controlled trials, practice guidelines, etc. • Applying the evidence worksheet	www.dartmouth.edu/
Duke University Library and Archives	• FRISBE checklist for evaluating therapy studies • Worksheets for cohort and case-control studies, practice guidelines, systematic reviews, etc.	http://guides.rnclibrary.duke.edu/ebm/appraise
CEBM	• Worksheets for systematic reviews, randomized controlled trials, etc., in English, German, Spanish, and Lithuanian • PICO worksheet	http://www.cebm.net/critical-appraisal/
AMSTAR	• A checklist of criteria for assessing a systematic review/meta-analysis	http://amstar.ca/Amstar_ Checklist.php
STROBE	• A checklist of criteria for assessing cohort, case-control, or cross-sectional studies	https://strobe-statement.org/
AGREE II	• An instrument which can be used to assess the quality of guidelines	www.agreetrust.org

AGREE II, The Appraisal of Guidelines for Research and Evaluation; *AMSTAR*, Assessing the Methodological Quality of Systematic Reviews; *CASP*, Critical Appraisal Skills Programme; *CEBM*, Centre for Evidence-Based Medicine; *FRISBE*, follow-up, randomization, intention-to-treat, similar baseline characteristics, blinding, equal treatment; *SIGN*, Scottish Intercollegiate Guidelines Network; *STROBE*, Strengthening the Reporting of Observational Studies in Epidemiology.

et al., 2002, p. A13). Before attempting to apply evidence to your patient, it is crucial that you can identify similarities between your patient and the study participants.

The patient's opinion and feelings toward the evidence should be gauged and strongly considered before any integration of new information into the treatment plan. As mentioned earlier, patients come from diverse backgrounds and do not necessarily possess similar concerns, or views, when deciding on the best course of action. For example, one patient may indicate that it is not worth taking a medication because the side effects are too unpleasant, while another patient may not be bothered at all about the possible side effects. Ultimately, the patient should have the final say as to the treatment plan and should not be subjected to a treatment simply because the evidence states it is the best option.

Patients may expect certain results based on what they have seen in the media, or read on the Internet, which the pharmacist will need to take into account and discuss (Wiffen et al., 2013, p. 325). Communicating with the patient can pose various challenges. Health literacy, as well as comfort level with numerical information can affect patient understanding and it is important that the pharmacist provides an explanation in a clear manner, using the least amount of technical concepts or medical terminology. Various communication strategies can be used to assist with the facilitation of the exchange. Montori, Elwyn, Devereaux, et al. (2015, p. 550) encourage the use of a "talk model" approach, which emphasizes the partnership between clinician and patient in the decision making, while ensuring understanding of all possible therapy options and determining what is most important to the patient.

Once a decision has been made, you can look at the overall process and assess your work. Are you satisfied with how you performed each step of the EBM process? Were there steps that you were more comfortable performing, as opposed to others (e.g., literature searching vs. critical appraisal)? Perhaps the most important question you can ask yourself is how effective was the treatment option you decided upon with the patient and did it change how you practice (Johnson, 2008, p. 170)?

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Patient Counseling and Education: Models and Methods in Pharmacy Practice

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Objectives

By the end of this chapter, learners will be able to:

1. List five theoretical models relating to patient counseling and education
2. Apply theoretical models of behavioral change to develop targeted educational interventions
3. Compare and contrast communication norms from an international perspective
4. Explain patient counseling and education challenges and strategies relating to pregnancy and lactation, pediatrics, and mental health

Introduction

There are many images that come to mind when considering the phrase, "patient education in pharmacy practice" (Paolini and Rouse, 2010). A typical image may be a traditional drug store with medication usage information being communicated "over the counter." This image may also include details, such as a printed leaflet and/or warning labels appearing on the dispensed medication. A second image may be of a pharmacist approaching a patient in the aisles of a pharmacy to offer assistance in self-selection and self-treatment of minor ailments. Perhaps, one may envision a private counseling area for more detailed-patient interactions, a pharmacist's office in a primary care clinic, or space designated for group education sessions. Or it is possible, that one may remember seeing a pharmacist in a hospital setting providing education to admit patients and/or their primary caregivers. Finally, the image may be of pharmacists at an outreach event, educating the public about disease prevention, awareness, or medication safety. No matter what image comes to mind, they all share the same common theme: a pharmacist attempting to translate information into learning the health and safety of the patient or public.

This chapter will introduce different theoretical perspectives related to patient education, while introducing specialized educational models and strategies for international comparisons and special populations. The specialized knowledge and skills that pharmacists provide will only be effective if communicated appropriately and in a manner that supports end-user learning and behavior change (Hargie et al., 2000). Therefore, pharmacists must be aware of theoretical models of education, in addition to considerations of unique populations outside the usual communication norms. After providing an example-based approach to introduce the educational theories and models, this chapter will relate these concepts to special populations (international comparisons, pediatrics, pregnant and lactating women, and mental health patients) that may require greater emphasis on sensitivity, cultural humility, and use of nonverbal communication strategies when providing patient education. The information provided in this chapter adds to the existing health education literature by providing a theoretical, yet practical approach to patient-education models and also provides a platform for the development of future pharmacy-practice-research initiatives to better understand the role of communication and education methods, especially when considering special populations with unique communication needs.

While common images of patient education in pharmacy practice are associated with information giving (dosage instructions, expected benefits, adverse effects, etc.), the term patient education should be the thought of facilitation of behavior change, rather than transfer of knowledge or skills (Bellamy, 2004). This means education is much more than simply providing information from one person to another. It is a complicated process, such as counseling or instruction that aims to influence how patients act, make choices, and follow through with intended therapeutic plans. Any educational intervention is dependent not only on the pharmacist, but on the patient themselves (Marcus, 2014). This team's approach to behavioral change is essential to consider while designing the educational interventions targeted toward achieving better patient health outcomes.

In order to gain a better understanding of patient education in pharmacy practice, one must be familiar with theoretical approaches to how behavior can be changed. This includes awareness of the theoretical models applicable to patient counseling and education for pharmacy practice. Examples, throughout this chapter will be used to highlight the key points and areas of controversy, when encountered. The chapter will also highlight considerations for international perspectives of patient counseling and education. Finally, models of counseling and education will be discussed using three examples, arising from pharmacy practice initiatives in special populations.

Theoretical Models of Patient Education

As discussed previously, education refers to more than simply providing information to patients. As such, many theoretical models based on behavioral change have been developed to explain a patient's health-related behavior. The following sections will provide an overview of the most relevant models for patient education and discuss applicability to pharmacy practice, using examples commonly encountered in educational activities.

Health Belief Model

The health belief model is a theoretical model that attempts to explain health-related behavioral changes across three different concepts (Rosenstock et al., 1988):

1. There need to be sufficient motivation or health concern to ensure that health-related issue is relevant.
2. There need to be existence of a perceived threat, for which one is susceptible in developing a disease or a complication of a specific illness or condition.
3. A belief must exist that by following a recommendation or advice, the perceived threat can be avoided and it can occur with minimal barrier to the individual in terms of time, cost, or other factors.

The best way to explain this model is to use an example. A common educational initiative encountered by pharmacists in community practice is to improve adherence to prescribed therapeutic plans. This is especially important for chronic-disease education, such as hypertension. Imagine a 55-year-old patient, prescribed with two antihypertensive medications, Ramipril and hydrochlorothiazide. The patient is not adherent (misses doses at least 3 times weekly). He has no relevant past medical history but his father died of a heart attack at the age of 60. His blood pressure is rarely monitored but usually is stable around 160/100 mmHg. Based on this patient case, we can use the health belief model to design an educational intervention that may best support this patient's adherence to medications.

First, we must consider the patient's motivation or how he conceptualizes the severity of the disease itself. Perhaps he requires background information on the disease and/or its complications. Secondly, we need to determine the perceived individualized threat of the disease on the patient himself. In this case, discussions on the patient's consistently elevated-blood pressure or the relevant family history could assist in modifying the patient's overall disease beliefs. Finally, instruction regarding the benefits of medications, including discussion of clinical study results, may modify the health beliefs of the patient and motivate behavioral change. It is likely that a combination of all these factors work together to promote patient understanding and engagement with the therapeutic plan.

The concepts discussed previously translate into six key dimensions of the theory (Glanz et al., 1997):

1. Perceived susceptibility
2. Perceived severity
3. Perceived benefits
4. Perceived barriers
5. Cues to action
6. Self-efficacy

Pharmacists must design educational interventions along the spectrum of dimensions listed previously, in order to maximize success of uptake. For example, they may need to provide individualized epidemiological information in order to confirm susceptibility, yet need to provide more practical instruction if the patient is already "cued to action." Recognition of these dimensions and how patients perceive their own health related progress and risks, is essential for promoting healthy behavior change.

Table 1 Transtheoretical model of behavioral change stages (Prochaska and Velicer, 1997)

Stage of change	*Definition*
Precontemplation	Not serious about change and not seeking help to change
Contemplation	Aware of consequences of negative actions and may start to consider the possibility of change
Preparation	Made commitment to change but are attempting to gather information to determine what is required for change
Action	Believe in own abilities to change and take active steps to modify behavior
Maintenance	Successful avoidance of temptations to return to negative behavior

Transtheoretical Model of Behavioral Change

A second common model used for patient education is the transtheoretical model of behavioral change (Prochaska and Velicer, 1997). This model attempts to explain a patient's behavior through a temporal process that involves progress through different stages of change. The five different stages of change and their definitions are provided in **Table 1**. Relapse (or re-initiation of negative behavior) may occur at any time during any stage.

The most well known example that relates to pharmacy practice that can be explained using the Transtheoretical Model of Behavioral Change is that of smoking cessation (DiClemete et al., 1991). Pharmacists, as primary healthcare providers, are well suited to lead smoking cessation initiatives yet achieving success with patients is not an easy task. Consider a 27-year-old female patient, who smokes one pack per day for the last 10 years. Upon routine questioning when dispensing a refill of her oral contraceptive, the pharmacist discovered her smoking history and approached the subject of quitting. It soon became quite clear to the pharmacist that she is currently "precontemplative" as she appeared disinterested and somewhat defensive throughout the interaction. At this stage, any educational intervention should be designed to create awareness and self-evaluation for eventual openness to change, rather than suggesting any immediate actions (personalizing risks, information provision). As the patient moves into the contemplative stage, the pharmacist should focus on promoting evaluative behaviors, including personal pros and cons identified by the patient herself. During the preparation phase, the pharmacist would be most effective by helping to identify and assist in the solving of barriers to the change, as well as encouraging small steps for the patient to take to ensure optimal readiness (building social supports, removal of triggers). If the patient is motivated and moves to actually implementing the change (i.e., stop smoking), the pharmacist needs to be ready to support through education to identify and overcome obstacles and to focus the patient on the benefits of the change, especially if the patient experiences feelings of loss or relapse (peer pressure, social pressure, stress/anxiety). Finally, the maintenance phase of the behavioral change should be supported by plans for follow-up, reinforcement of personalized rewards/beneficial outcomes, identifying and removing newly emerged triggers, and continued discussions of coping with the ongoing threat of relapse. As demonstrated by this example, it is very important for pharmacists to recognize specific education needs of their patients, in order to provide the most effective care. The transtheoretical model can be used collaboratively with patients to discuss progress along the continuum of change and to help recognize when positive or negative change is occurring (Miller, 2016).

Locus of Control

The concept of locus of control originates from personality psychology and refers to the extent to which people believe they can influence outcomes in their lives versus external forces acting beyond the individual's control (Lefcourt, 1991). While this construct relates to many aspects of society (i.e., religion, politics, employment), it also relates to health and education (Adolfsson et al., 2005; Brincks et al., 2010). More specifically, it has been found that those with a higher internal locus of control adapt healthier behavior more frequently and more successfully (Steptoe and Wardle, 2001). These patients are likely to respond better to educational interventions designed to promote patient autonomy and empowerment. Those with a high-external locus of control, however, likely to have difficulty in implementing behaviors based on their own choices, and require more direct guidance and action promoted by those perceived to be respected or in a powerful societal position. In order to be effective educators, the pharmacist must recognize how a patient responds to instructions and whether or not they value being engaged as a decision-maker within the active therapeutic plan.

Adult Learning Theory—Andragogy

Adult learning theory was established in the 1980s as to describe the way the adults approach and succeed in learning experiences (Knowles et al., 2015). The main point from this theory is that adults and children learn differently, resulting in "pedagogy" transforming into "andragogy." This theory is based on both assumptions and principles. Assumptions include, self-concept (one's self-concept moves from being dependent toward self-directed with time), adult learner experience (accumulated experiences contribute to learning potential), readiness to learn (readiness to learn becomes focused on personal social roles), orientation to learning (orientation shifts from subject-centered to problem centered), and motivation to learn (maturity promotes internal motivation to learn). Based on these assumptions, one can recognize that learning must be tailored toward an individual's specific needs and should be outcome-oriented, rather than simple provision of information.

The principles of adult-learning theory are the following:

1. Adults need to be involved in the planning and evaluation of their instruction
2. Experience provides the basis for the learning activities
3. Adults are most interested in learning subjects that have immediate relevance and impact to their job or personal life
4. Adult learning is problem-centered rather than content-oriented

For example, if we consider a typical over-the-counter interaction between a pharmacist and patient, we can use adult learning theory to increase the chances of achieving the intended outcomes. Instead of simply spewing information at a patient and assuming they will understand and implement the behavioral considerations of taking a new medicine, the pharmacist must tailor this information and involve the patient in the plan of care. Considering the first principle, a pharmacist may engage a patient to determine the most appropriate time of day to take a daily dosed medication (instead of automatically assuming morning time). Perhaps the patient is a shift worker or has an altered lifestyle routine. Using the second principle, the pharmacist may dwell on the patient's health-history to relate the instruction specifically to their past experiences. If adherence is the goal of taking a diuretic consistently for heart failure, the pharmacist may discuss past times when the patient was experiencing adverse effects from fluid overload and then relate these experiences to the benefits expected with regular diuretics use. For principle three, a pharmacist may choose to educate the patient on surrogate markers, that can measure impact of the medication on their health status in a shorter time than perhaps more long-term benefits, such as prolongation of life. An example could be educating on expectations for fasting glucose or hemoglobin A1c values for patients with diabetes. Finally, principle four speaks the individualization of patient's health-needs. Instead of listing benefits and risks of therapy, the pharmacist may choose to instead engage the patient about their expectations and fears of therapy, in order to recognize and overcome potential barriers to successful treatment. As demonstrated through these examples, adult learning theory can be applied in most typical pharmacist-led educational sessions to improve overall effectiveness of educational interventions (Peeters, 2011).

Self-Efficacy Model

Self-efficacy, otherwise referred to as confidence, is the optimistic belief that one is able to successfully accomplish a task to produce a favorable outcome. Pharmacists are actively involved in disease prevention and lifestyle interventions, which require education of patients to change unhealthy behaviors into healthy ones. Bandura (1994) introduced a model that aims to describe four sources of efficacy beliefs. The first source of self-efficacy is stated to come from mastery beliefs. Consider a patient who had quit smoking 2 years ago for a period of 18 months but then relapsed. Self-efficacy may play a major role in the patient's current need for behavioral change, as he or she may have confidence from this past success. The second source of self-efficacy comes from vicarious experiences. These are ones that we observe from people around us, including mentors and role models. Witnessing successful accomplishments of others can stimulate the confidence needed for one to complete the task on their own. The third source of self-efficacy is verbal persuasion. This directly relates to pharmacist education, as persuasion can be used to modify behavior by attempting to instill confidence for patient success. Finally, the last source proposed by Bandura is emotions and physiological stress. Stress and its related symptoms can directly affect how one perceives their abilities to complete the task. Therefore, education regarding stress management and coping skills can greatly contribute to self-efficacy. A fifth source was proposed that suggests visualization as a tool to improve self-efficacy (Williams, 1995). Pharmacists may utilize this technique when providing patient education in hopes of maximizing success of achieving target outcomes.

International Perspectives

Patient-pharmacist interactions occur all around the world. These interactions are essential for the delivery and uptake of health services worldwide (Ha and Longnecker, 2010; Simpson et al., 1991). Provision of diagnostic testing or treatments without effective and safe communication with patients can lead to poor-health outcomes and mistrust in health systems. Pharmacists, professionals that almost entirely relying on communication for professional service are commonly the first access point for many patients seeking care. Therefore, it is vital that pharmacists are safe and effective communicators (Shah, 2006). It should be noted, however, that the same communication standards or rules should not apply in all settings, as communication norms greatly differ between regions.

Let us explore this from a theoretical perspective. In 1976, Edward Hall published a book entitled *Beyond Culture* that introduced the terms of high- and low-context cultures. The concept describes, how people relate to one another in both social and communicative aspects. Hall's view was that high-context culture is defined as one that is intimate, hierarchical, and communicates through simple messages with deep meaning. Conversely, low-context culture is defined as highly individualized, somewhat fragmented, and one that has little involvement between others. Communication in low-context cultures is more explicit and less personal (Kim et al., 1998).

It is well established that cultural context can affect the way people interact and communicate. Persons originating from high-context cultures, such as Asian and Arab populations, place great emphasis on nonverbal components of interactions, use implicit and indirect verbal messages, and personalize disagreement. In order to effectively communicate, messages must be placed in the appropriate context or environment for the receiver to understand the intended meaning (Kim et al., 1998). Conversely, persons from low-context cultures (primarily Western) do not emphasize nonverbal components, use explicit and direct verbal messages,

and depersonalize disagreement. The importance lies on what was said, not how it was said or the environment in which it was said (Onkvisit and Shaw, 1993).

Although Hall's theory only accounts for ethnicity and does not factor other aspects of culture (gender, sexual orientation, religion, etc.), the general premise of cultural contexts does appear to have weight. Hofstede's Cultural Dimensions Theory attempts to further breakdown culture into different components, namely power distance, uncertainty avoidance, masculinity/femininity, individualism/collectivism, and long-term orientation (Hofstede, 1983). Whichever theory is used to explain cultural differences in communication, it can be recognized that not all individuals communicate in the same way and these differences occur both across and within global populations.

For the purposes of an example, let's use both of the theories described aforementioned to explore international differences in patient education. Consider a patient been newly prescribed a narcotic for advancing cancer pain but who has reservations about initiating, such a "powerful" and "addictive" medication. A pharmacist working in the Middle East (i.e., Qatar) versus Europe (i.e., Switzerland) will likely approach this situation quite differently. According to Hofstede (1983), Arab patients originate from high-context cultures and respond better to affective communication strategies with simple messages that may come people in positions of power (high-power distance). These patients may also prefer to have family involvement in the decision-making process (collectivism). Pharmacists need to recognize these preferences and tailor education accordingly. Instead of spending time providing detailed verbal messages, it may be more effective to focus on developing relationship with the patient and their family members. Conversely, a pharmacist practicing in a European setting may instead choose to focus on the "facts" and provide detailed information without an emphasis on nonverbal communication strategies. Tailoring information to make the message more simple and meaningful, may make the patient distrust the pharmacist by believing some information is being with-held.

As we are currently living and working in an age of globalization, pharmacists must be ready to interact with patients from many different cultures and backgrounds. Recognition of times of cultural conflict and being able to subsequently reflect and learn from these interactions is the key to stimulating the self-awareness and personal growth required to be effective educators. Promoting these practices within training experiences and continuing professional development opportunities will help to equip pharmacists with the necessary attitudes and skills for achieving optimal patient educational outcomes.

Models and Methods of Patient Education in Special Populations

Pharmacists are front-line caregivers and require the knowledge, skills, and attitudes to provide counseling and education to all types of patients. As such, background information and theory regarding interventions within different populations needs to be discussed. This section provides an overview of models and methods of patient education relating to women's health, pediatrics, and mental illness.

Patient Education for Pregnancy and Lactation

Since more than 90% of women require at least one medication in pregnancy and lactation, healthcare practitioners have a significant role in educating pregnant and breastfeeding women about their drug therapy (Temming et al., 2016). The added risks of medication exposure to the fetus in pregnancy, or the infant in lactation can greatly impact medication safety and adherence (Temming et al., 2016). Women often question the value of their drug therapy once pregnant and consider discontinuing their medications to avoid fetal risk. Without proper medication counseling regarding fetal safety, and the potential consequences of untreated maternal medical conditions, the health of both mother and fetus may be at risk (Temming et al., 2016; Trønnes et al., 2017). Over 70% of women, who require medication during pregnancy, use this medication at the most critical time, organogenesis (Kaplan et al., 2017; Temming et al. 2016). In addition, medications with limited data and/or greater fetal risk are used more frequently in women with chronic medical conditions in pregnancy, thus timely medication counseling can have a major impact on maternal and fetal health (Temming et al., 2016; Trønnes et al., 2017).

A recent cross-sectional survey that included 102 pregnant women demonstrated that medication counseling significantly reduced women's own perception of teratogenic risks and probability of termination (Kaplan et al., 2017). Women in this study were motivated to find medication safety information in pregnancy and called a teratology counseling service. These women were primarily in first trimester (7.5 weeks gestation), and were taking an average of 3.3 medications that were not known to be teratogenic. The most common medications women sought counseling for were nonsteroidal antiinflammatories, antibiotics, central nervous system, and gastrointestinal therapies. This study confirms that a patients' understanding of the potential increase in teratogenic risk from medication use in pregnancy is higher than the actual risk and that intervention and education regarding the actual risks can impact the health of both the woman and the fetus.

Another interventional counseling-based survey confirmed that medication counseling could impact women's attitudes toward and understanding of medication use in pregnancy (Devkota et al., 2017). This study included 229 women that were prescribed at least one medication at the out-patient obstetrics ward in Nepal. The majority of women in this study were primigravida (59.4%) and in third trimester (58.6%). A structured knowledge, attitude, and practice (KAP) questionnaire was administered prior to medication counseling and at the next follow-up visit. Prior to medication, counseling 65.9% of women knew that not all medications are safe in pregnancy, 71.6% knew that unnecessary medications in pregnancy could cause harm, and 30.6% knew

that unwanted medications could affect organogenesis and development. Interestingly, 75.6% of women felt they should ask their physician or pharmacist about their health condition and medications, and 75.9% felt that medication harms in pregnancy could be reduced with help from a healthcare provider. In addition, 64.2% of women reported self-medicating. After medication counseling, 100% of women knew that not all medications are safe in pregnancy, 99.1% knew that unnecessary medication in pregnancy could cause harm, and 95.6% knew that unwanted medication could affect organogenesis and development. Furthermore, 97.4% felt that medication harms in pregnancy could be reduced with help from a healthcare provider and thus only 2.2% of women reported taking medication without advise. Thus medication counseling can greatly impact women's KAP of medication use in pregnancy.

Finally, the medication safety assessment in pregnancy must also consider the physiologic changes in pregnancy and how these changes affect the efficacy and safety of drug therapy (e.g., absorption, metabolism, and elimination) (Temming et al., 2016). Patients need to be counseled that their medications might require dose adjustments in pregnancy and again in postpartum to ensure efficacy and safety in both pregnancy and lactation.

Far too commonly, women are given misinformation and advised to cease breastfeeding in order to treat a maternal medical condition (Davanzo et al., 2015; Nice and Luo, 2012; Schirm et al. 2004). Knowing that breast milk is the preferred nutrition for infants and that 65.9% of breastfeeding women require at least one medication in lactation, medication counseling and optimization of therapy to avoid interruption of breastfeeding is key.

A survey, based in the Netherlands, revealed that 30% of women with children under 6 months of age hesitated to take a medication because they were breastfeeding, 16.9% of women would have taken a medication if they were not breastfeeding and 11.5% of women did not breastfeed because they had to use a medication (Schirm et al., 2004). A review article by Hussainy and Dermele (2011) identified some of the key reasons why women may be hesitant to breastfeed while taking drug therapy by examining healthcare professionals' and women's KAP toward medication used in lactation. This review highlighted that physicians and pharmacists had limited knowledge of medication suitability in lactation and often provided inconsistent advice about medication suitability in lactation. In addition, physicians and pharmacists often based their advice on potential risks to the infant, rather than data in lactation. Thus, women were frequently disappointed with the advice they were given and either stopped breastfeeding or choose not to take drug therapy (Hussainy and Dermele, 2011).

In response to similar findings in clinical practice and a lack of quality data guiding drug safety decisions in lactation, numerous organizations and journals have published articles to increase the general knowledge of medication safety in breastfeeding (Davanzo et al., 2015; Hussainy and Dermele, 2011; Nice and Luo, 2012; Temming et al., 2016). In addition, these organizations and journals have recommended a unified approach to assessing medication safety in lactation and counseling the patient (Davanzo et al., 2015; Hussainy and Dermele, 2011; Nice and Luo, 2012; Temming et al., 2016). Specialists in lactation are encouraged that with proper education of healthcare providers, drug therapy can be optimized to treat maternal health condition(s) while supporting breastfeeding (Davanzo et al., 2015; Hussainy and Dermele, 2011).

Healthcare practitioners have a significant role and responsibility in educating pregnant and breastfeeding women about the benefits and risks of their drug therapy. Based on the available data, the education provided will have a lasting impact on the health and well-being of both mother and child.

Pediatrics

Effective communication with children is dynamic and complex that often involves three people: a healthcare provider, the child, and the child's parents or caregivers. Special consideration of the level and depth of interaction with a child must be adapted to the child's cognitive developmental level as to efficiently convey their intended messages.

A patient-centered interaction framework of communication with children about their medications is an important model to adopt in all interactions with this population. This model of communication fosters the child's opinions about treatment while empowering them to seek information about their medications and illness. Strategies for promoting a patient-centered interaction with children may include: asking the child about priorities for improved quality of life, assessing how well the child perceives their medication working, and directly interacting with the child whenever possible, and allowing opportunities for the child to ask questions throughout the interaction (Sleath and Bush, 2012). The inclusion of the child in the treatment decision process is empowering and influences the child to seek information about various aspects of their illness (Holmström and Röing, 2010).

Healthcare professionals must consider the cognitive development level of the child when communicating with pediatric patients. Pediatric cognitive development has been classified into four stages: the *sensory motor* stage, the *preoperational* stage, the *concrete operational* stage, and the *formal operational* stage (Piaget, 1932). To gain insight into the child's stage of cognitive development, healthcare professionals must consider age as well as ask open-ended questions in early communications (O'Brien and Bush, 1999). In the *sensory motor* stage (birth to roughly 2 years of age), all learning is child centered with little connection between self and external factors. At this stage all patient-centered communication about medications is difficult and likely ineffective. The *preoperational* stage (age 2 through 6 years), a child's reasoning is connected to the present now. The connection between what they do in relation to their health, such as taking a medication, needs to be presented in a very simplistic format (i.e., this medicine will make you feel better) (Lau and Klepper, 1998). The *concrete operational* stage (7 through 12 years of age) occurs when children begin to distinguish between internal and external influences on their health, and develop the understanding that disease is preventable through actions taken that affect one's own health (O'Brien and Bush, 1999). Children in this stage might able to understand what is

causing their illness and how medicine can help them. As children move into adolescence, they begin the *formal operational* stage (age 13 years through adulthood) where they can reason through their decisions and develop awareness of the degrees of illness. The understanding that they have control over their own decisions continues to develop. It is imperative to determine the cognitive developmental level of a pediatric patient in order to effectively tailor communication methods and foster understanding. It can be argued that age appropriate information and participation were prerequisites for allowing children to make competent decisions about their own health (Mårtenson and Fägerskiöld, 2007).

While challenges may arise, such as parents taking a protective stance toward children and thus may choose to limit the child's involvement, effective communication with children about their medications may potentially improve adherence and overall clinical outcomes (Coyne and Harder, 2011; Curtis et al., 2004). Healthcare professionals must use a patient-centered approach to communication with children while acknowledging their cognitive development level.

Mental Health

Patient-counseling and education becomes intricate and complex when dealing with mental-health patients. Cognitive deficits and side effects associated with medications often times interfere with educational sessions leaving healthcare providers and patients feeling frustrated (Hatonen et al., 2008). Lack of adequate training and comfort level of healthcare professionals contribute to limited provision of counseling mental-health patients (Bell et al., 2006; Hatonen et al., 2008; Phokeo et al., 2004). Nevertheless, patient education has been shown to be beneficial among mental-health patients in terms of medication adherence, lifestyle regularity, and ability to cope with their disease (Hatonen et al., 2008).

Privacy and having a sense of security and trust is important for patients with mental-health disorders. For example, a schizophrenic patient who has paranoid delusions may not accept the information being provided by a healthcare provider. It is important in this case to make the patient feel safe and gain trust from the provider. Nonverbal communication, such as maintaining eye contact, being close without invading personal space, speaking calmly, and showing positive facial gestures plays a significant part in provision of patient care for this patient. Likewise, a patient coming to pick up a new psychotropic medication from a community pharmacy would value having a private counseling area to be able to communicate openly with a pharmacist is a safe environment.

Mental-health patients consider respect to be an important aspect when communicating with providers (Hatonen et al., 2008). Although most healthcare professionals do not intentionally display stigma, it may often be expressed through their body language, facial expressions, and verbal comments making patients feel undervalued (Calogero and Cale, 2017). Engagement in continuing education opportunities by healthcare professionals is one way to overcome mental illness stigma. These professional development opportunities should not only address education related to mental disorders, but should provide the healthcare professional with the ability to understand and relate to mental-health patients and the effect the disease has on their daily life. This method has been shown to be effective in reducing stigma toward depressed patients as reported in a study using consumer educators during a pharmacy continuing education session (Liekens et al., 2013).

Patient education must be a team-based approach for mental health patients. The role of the pharmacist among this team is crucial to ensure the safety and efficacy of psychotropic medications to improve patient outcomes (Finley et al., 2003).

Conclusions

Patient-counseling and education are vital roles of the pharmacist and they must be ready to adapt to the ever-changing needs of patients, including those of special populations. The shift in focus of pharmacists as educators, rather than simple providers of information, also comes with greater responsibility to take ownership of their role within the healthcare team to do their part to support the patient's achievement of intended outcomes. Pharmacists must recognize a patient's needs and tailor interventions accordingly. Familiarity with educational theory, such as the models discussed in this chapter, will facilitate effective communication, establish therapeutic relationships, and promote provision of optimal patient care.

Moving forward, pharmacy practice research must focus on how pharmacists can optimize therapeutic relationships through communication and education strategies that will allow for provision of effective patient care. Changing landscapes in terms of immigration and diversity are especially important considerations for pharmacists and pharmacy programs that will require continual evaluation and modification of practice and training to ensure the profession is able to address the needs of those it serves. As many (if not most) professional pharmacy activities are largely based on communication, there is an urgent need for researchers to study the most effective ways to address diversity in patient care and how to optimally train students and practitioners to fluently employ such methods.

This chapter provided an overview of theoretical models relating to patient education, including evidence-based methods of working with populations that have special communication needs. Key concepts discussed included the need for an informed and systematic approach to patient education, as well as highlighting difficult situations that may require more emphasis on responding and adapting to a patient's individual needs. Daily patient encounters in pharmacy practice cannot be predicted, therefore pharmacists must be prepared to identify a patient's educational needs and consequently tailor their communication strategies accordingly. Doing so will allow for provision of better patient care with a goal of ultimately achieving better patient health outcomes.

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Technology and Social Media Applications in Pharmacy Practice

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Introduction

Pharmacy is navigating a time of enormous technological advancement, both inside and outside the workplace. The rapid evolution of personal computing and social networking has major implications for patients and health-care providers alike. In particular, pharmacists can now find the answer to almost any question with a quick search online. They can produce patient information and share it with other pharmacists, health-care professionals, patients, and their local, national, and international communities. At the same time, individuals can use the Internet to identify possible causes of illness or medication side effects by connecting with other individuals who have similar illnesses or medical conditions. Handheld devices such as smartphones and tablet computers are also ubiquitous and can be used to access and create social media throughout the day. However, with great change comes great upheaval. The challenge for pharmacists is to navigate social media both at home and in clinical practice. In particular, it is becoming essential for pharmacists to understand how to make the most of the increasingly connected world while also being mindful of the risk. The following chapter will review the evolution of social media over the last decade, the research on social media use in pharmacy and pharmacy education, and the safe use of social media in health care.

Overview of Social Media

Social media refers to material that is created, edited, and shared online (Kaplan and Haenlein, 2010). Social networks, by comparison, refer to online communities where social media are shared (Boyd and Ellison, 2008). Facebook is the most popular social networking site worldwide (Statista, 2018), with active users numbering in the billions. The video sharing website YouTube has over a billion users worldwide, as do the immensely popular instant messaging applications such as Facebook Messenger and WhatsApp (Statista, 2018). Other popular social networking sites with hundreds of millions of users worldwide include Twitter, Snapchat, Instagram, LinkedIn, and QQ (Statista, 2018).

Across social networks, the social media that are shared include text-based posts, photos, videos, and links to resources such as published research papers, practice tools, and news articles. What differs is how users create, share, and interact with the information on the various networks, and this process has evolved over time. In early social networking sites, users could develop a profile and connect with other users—usually individuals that they already knew. For example, in 1997, the first social networking sites were "Six Degrees," which allowed users to create profiles and "friend" each other, and America Online (AOL) Instant Messenger, which allowed users to connect with friends and converse online in real time (Wikipedia, 2018). This was quickly followed by the first blogging website, Open Diary, which allowed users to write posts that could be shared with and commented on by friends.

Over the next decade, social networking sites were developed to allow users to connect in new ways and to share audio and video content (Varis, 2015; Wikipedia, 2018). For example, 2003 brought the launches of Myspace for sharing music and videos, LinkedIn

for professional networking, and Skype for video messaging. The following year in 2004, the photo-sharing site Flickr was launched, as was Facebook that allowed users to make a profile and share their status with friends. In 2005, the video sharing site YouTube and the news aggregation/discussion site Reddit were both launched. The microblogging sites Twitter and Tumblr launched in 2006 and 2007, respectively, to allow users to post short-form blog posts. Around this time in 2006 and 2007, MySpace was the most popular social networking site, but it was quickly overtaken by the popularity of Facebook in 2008. Facebook has consistently remained the most popular social networking site over the last decade (Statista, 2018). More recently, the photo and video-sharing site Instagram launched in 2010 followed by Snapchat in 2011 (Wikipedia, 2018).

Uptake of Social Media

The Pew Research Center (2018a) reports that as of 2017, over two-thirds of all adults in many developed countries are consuming social media, including the United States (US, 69%), Australia (69%), South Korea (69%), Canada (68%), Israel (68%), and Sweden (67%) (Pew Research Center, 2018a). Social media use is also high in some developing countries, such as Jordan (75%) and Lebanon (72%), and lower in some developed counties such as Italy (48%) and Germany (42%). While Facebook is generally the most popular social networking site across demographic groups, research from the US shows that young adults aged 18–24 are more likely to use Snapchat, Instagram, and Twitter compared to older cohorts, including those in their mid to late twenties (Pew Research Center, 2018b). Further, younger users are more likely to use multiple social networking sites, while older users are more likely to only use one to two sites (Pew Research Center, 2018b).

Common Features of Social Networking Sites

Over time, many social networking sites have evolved to share similar features (Varis, 2015). Most sites allow users to create a profile where they can post content and follow the content of other users or organizations to generate a "content feed." For sites such as Facebook, Twitter, and LinkedIn, the content feed contains text, videos, images, polls, and links to websites that users can "like," comment on, or share. Posts can also be organized and searched by hashtags (e.g., #pharmacy), which are a form of meta-data that allow text to be findable (Zappavigna, 2011). Users can also use many of the sites to exchange private messages with other users. Instagram and Snapchat are similar to the platforms mentioned above, but their content is limited to photos and videos. The launch of Snapchat was also notable because it was the first mainstream social networking site that allowed content to be posted for a short time before it disappears. Finally, YouTube operates slightly differently. On YouTube, users generate a video feed by subscribing to video channels and can like, dislike, or comment on individual videos.

Notably, Facebook allows users to make private groups, such as for a group of pharmacists in a single state or a group of students in a single-year cohort of a pharmacy school. Facebook also offers a "pages" feature, where businesses can develop a profile that users can follow without friending the organization. This is particularly advantageous for pharmacies and pharmacy undergraduate course instructors who may not want to "friend" customers or students, for example. Instead, business owners and instructors can create a page to share information, organize events, host discussions, and post live video feeds. Followers can follow the information in their content feed and engage with it by posting reviews, questions, or feedback. The page feature also allows administrators to moderate comments to remove offensive or inaccurate information, to answer questions, and to track analytics such how often the various content is viewed.

Creating Social Media Content

At present, the users of social networking sites have two roles: content creators and content consumers. Individuals and organizations may have both roles or may simply create content or consume content. For creators, social media content can be created either on or off of a social networking site. For example, a video can be developed using private video-editing software and posted directly to Facebook, Twitter, YouTube, and Instagram. Alternatively, the video can be posted to YouTube and the YouTube link can be shared on other social networking sites. A video can also be filmed directly using Instagram and shared to Facebook, or vice versa. Similarly, some social networking sites allow users to connect their social networking sites to automatically post across multiple sites at the same time, so a video shared to Twitter can be automatically posted on Facebook. As described above, content consumers then access the content through their content feeds, where they can like, share, and comment on the material.

The roles of content creator and consumer can also overlap. Memes are popular example. A meme is defined as "an image, video, piece of text, etc., typically humorous in nature, that is copied and spread rapidly by Internet users, often with slight variations" (Oxford Dictionary, 2018). With memes, users often add text to adapt a photo or video to their own context. For example, a pharmacist meme could contain the words "beta-blockers make me lol" over a photo of a famous actor laughing. Other users may then take the same words and apply them to a picture of an animal that appears to be laughing. Alternatively, they may take the same photo of the actor or animal and apply new, unrelated words. Memes offer a good example of social media, in that they are continuously being adapted to new contexts. The graphics interchange format (GIF) videos are another example of adaptable content. GIFs are very short, repeating videos that are often added to posts in social networking sites to convey additional meaning. For example, a post about a busy day at the pharmacy may be accompanied by GIF of someone falling onto the floor or falling into bed.

Finally, the term "viral" is often used to describe content that is shared and spreads rapidly across a single social networking site or multiple sites (Varis, 2015). In their paper on social media virality, Varis and Blommaert (2015) point out that "'liking' is a responsive uptake to someone else's activity while 'sharing' is the initiation of another activity directed at another (segment of a) community." In this process, information can be liked and shared in its original format or it can be slightly modified over time, as seen with the popular examples of memes. The information can also be shared or commented on with other forms of media such as GIFs. Thus, with the enormous popularity of social media, the constantly evolving nature of the individual social networking sites, and the evolution of the social media content itself, social media is changing the way the world communicates. The following section will focus on how social media is being used in pharmacy in relation to other health-care providers, pharmacists, patients, and the broader public.

Social Media in Health Care

Over the last decade, a growing number of consumers have been accessing health information online, including through social networking sites. In the US, over 70% of people who use the Internet look up health information online (both through websites and social networking sites), including 60% who look up drug information, 57% who look for a diagnosis based on symptoms, 52% who look for information on supplements, and 49% who look for treatment options based on a diagnosis (Gandhi and Wang, 2015). As with the US, it can be assumed that patients in most developed countries and some developing countries are also accessing some health-care information through social networking sites.

The wide availability of health-care information online is having a direct impact on the patient–clinician relationship. Tan et al. (2017) found that the growth of online information is shifting the traditional information balance, forcing health-care providers to develop new ways to make treatment decisions with patients—specifically, patients are now more informed and may require a more collaborative decision-making process (Tan and Goonawardene, 2017). Smailhodzic et al. (2016) also noted that social media use by patients can have several beneficial effects such as improved self-management, control, and subjective well-being while also having some risks such as social media addiction, loss of privacy, and being targeted for advertising.

For health-care providers, the benefits to using social media can include facilitated communication within teams, support for education and training, and access to updates on health-care news and professional development (Chan and Leung, 2018). In particular, health-care providers appear to use social networking sites to develop virtual communities and share expert knowledge (Rolls et al., 2016). However, research also suggests that health-care providers prefer to use social networking sites to connect with their own profession—a form of "tribalism"—that can limit information sharing across different disciplines or specialties (Rolls et al., 2016).

Social Media in Pharmacy

For pharmacists, one of the clearest advantages of social media is that it facilitates networking outside the workplace—both within pharmacy and with other health-care professions (Royal Pharmaceutical Society, 2018). The benefits of social media address some of the key barriers pharmacists face when adopting new services and practice models, including the culture of pharmacy, time constraints, and difficulty keeping up with daily workflow (Rosenthal et al., 2016).

In the early days of social media, some pharmacists avoided the expectations of professionalism by creating anonymous profiles. These early accounts occasionally mocked patients, used profanity, and were critical of the profession (Clauson et al., 2010). However, in recent years, the pharmacy profession's use of social media has expanded to include many pharmacy organizations, students, pharmacists, and researchers from around the world. In the last decade, the evolution of pharmacist Facebook groups and pharmacist-specific social networks such as Skipta (https://pharmacistsociety.com/) now offer pharmacists a platform to ask questions and share experiences, advice, or mentorship. Similarly, pharmacists can use social media to keep abreast of continuing professional development opportunities, such as through the social networking profiles of the Centre for Postgraduate Education in the United Kingdom (https://www.cppe.ac.uk) or the American College of Clinical Pharmacy (https://www.accp.com) in the US.

As the use of social networks expands, pharmacists need to exercise a certain degree of caution. Research on pharmacists and social media have found that while use is growing, little is known about the best ways for pharmacists to engage with social networking sites (Benetoli et al., 2015; Grindrod et al., 2014). When building a profile, for example, pharmacists and other professionals need to decide if the profile will be for professional use, personal use, or a hybrid of the two. A pharmacist creating a personal account on a social networking site must decide if they will also identify as a pharmacist in their profile. Similarly, a pharmacist creating a professional account must decide if they will share any personal details, such as details about family, sports interests, or hobbies. In a qualitative study with pharmacists around the world, Benetoli et al. (2017) noted that many pharmacists address this dichotomy by either having two separate accounts or by being a "dual citizen" on a single account. It should be noted, though, that regardless of whether pharmacists are creating personal accounts, professional accounts, or dual citizen accounts, there is an expectation that they will abide by the professionalism standards set out by the profession (Royal Pharmaceutical Society, 2018).

e-Professionalism and Social Media

As described in the previous section, pharmacists may choose to engage with any of the social networking sites or communities using either an anonymous or an identifiable handle. The challenge is to build an online identity that aligns with their professional identity.

Professional behavior online is often referred to as "e-professionalism." Cain and Romanelli (2009) define e-professionalism as the "attitudes and behaviors reflecting traditional professionalism during the use of digital media." In other words, e-professionalism is the expectation that members of a profession behave online as they would in their place of work. Oftentimes, these tenets of professionalism will be outlined for pharmacists through codes of ethics, standards of practice, and workplace policies from regulatory bodies and employers. By the definition outlined above, all pharmacists who use social networking sites are expected to behave according to the professional standards of their own jurisdiction regardless of whether a social network account is private, personal, anonymous, or identifiable.

Beyond professional development, pharmacists may also wish to use social networking sites to advertise their services to the public. Some social media polices have emerged to provide guidance. For example, the social media policy from the Pharmacy Board of Australia cautions pharmacists to adhere to both the professional and advertising guidelines that apply in their jurisdictions (Pharmacy Board of Australia, 2018). Similarly, the National Association for the Boards of Pharmacy in the US routinely monitors social media to identify pharmacies that are advertising and selling products outside of the current regulations (National Association of Boards of Pharmacy, 2018). As the use of social media by pharmacists matures, greater attention will be paid to monitoring pharmacists' use of social media and e-professionalism.

Another aspect of e-professionalism is the relationship between the pharmacist and patient. Pharmacists can be disciplined by their regulatory bodies for unprofessional behavior, such as using an instant messaging site to pursue a romantic relationship with a patient or sharing private patient information on a social networking site such as Facebook. Both in response to and in anticipation of unprofessional conduct, some pharmacy organizations have developed guidelines to support pharmacists in using social networking sites safely. The guidelines are typically written for pharmacists in a single jurisdiction or country, but many of the principles apply universally. For example, the Royal Pharmaceutical Society in the United Kingdom advises pharmacists to be aware of the rules of their employment and of liability, copyright, and data protection laws (Royal Pharmaceutical Society, 2018). They also caution pharmacists against providing specific medication advice to patients on social networking sites. Similarly, the Pharmaceutical Society of Australia urges pharmacists to keep online information, such as that created on blogs or on pharmacy websites, up-to-date and to clearly communicate how the information was developed, including the sources of information and any relevant government regulation that applies to the medications being discussed (Pharmaceutical Society of Australia, 2018).

Pharmacy Communities Online

When used professionally, social networking can be a powerful tool for connecting with both the larger pharmacy community and with the general public. Individual pharmacists can use social networks to connect with colleagues, both in pharmacy and other health-care professions. For example, on Facebook, there are many closed pharmacy groups that are organized based on location. In the Canadian province of Alberta, for example, pharmacists established the "Pharmacists of Alberta Unite" Facebook page to organize protests and discussion around funding cuts by government. Over the years, the group evolved to support pharmacists in managing drug shortages, prescription billing, and to navigate new or emerging information on clinical topics such as the administration of drugs by injection or in response to updated clinical practice guidelines. On Instagram, for example, Hindman et al. (2017) observed that the most common posts shared with the hashtag #pharmacy were celebrating pharmacy or relating a work experience, with around 10% of posts related to education in pharmacy.

Health-care professionals tend to use social networking sites as a one-way communication platform, where information is consumed, rather than an interactive forum where users engage in discussions over content (Campbell et al., 2016; Rolls et al., 2016). As such, professional social network accounts may appear to have low engagement but may actually be closely read by individuals in practice. For example, the Royal Pharmaceutical Society is very active on Twitter with over 20,000 followers. The account frequently shares information on professional development and leads discussions on topics such as gender in the profession and interprofessional collaboration.

Other communities that connect a more general health-care community include Skipta (https://skipta.com/), which was founded by a pharmacist, and the "Figure 1" mobile application that allows health-care providers to share images of interesting patient problems such as rashes or radiographs and seek guidance from the community. Pharmacists can also participate in topic-specific communities, such as the Free and Open Access Medical Education (identified by the hashtag #foamed) community, which shares information related to emergency medicine and pharmacy across social media sites.

Social Media in Pharmacy Education

One of the most important reasons to integrate social media into pharmacy education is to teach and model professional social media behavior. Social media has been explored in several pharmacy programs, with positive results (Benetoli et al., 2015).

Examples include the use of Twitter to support classroom engagement and reflection (Desselle, 2017), and the use of Facebook to provide updates on current events (Kostka-Rokosz et al., 2014) and to support exam preparation (Mawdsley and Schafheutle, 2015). Social media is also being studied to support education in other health-care professions. In medicine, for example, instructors have provided senior medical students with credit to update medical and health-care pages on Wikipedia (Azzam et al., 2017).

In addition to supporting education, the incorporation of social media into the pharmacy curriculum also supports students in developing social media literacy and e-professionalism skills. For example, a study of young rheumatologists and basic scientists identified that 30% of those who do not use social networking sites struggle with a lack of knowledge of the platforms (Nikiphorou et al., 2017). Other research has also identified that low uptake can result from the one-way flow of information in an educational setting and a lack of trainee engagement (Chan and Leung, 2018). Thus, effective learning opportunities will likely need to encourage students to participate and to provide technical support for those who have less familiarity with the platforms.

Unlike more experienced pharmacists, pharmacy trainees are likely to have been using social media before joining the pharmacy profession. For health-care trainees, the opportunities to develop e-professionalism skills occur both in the classroom and during experiential learning opportunities. Trainees who enter a health-care professional program as active users of social media may need to routinely audit and refine their social media presence as they learn about the various facets of professionalism. For example, after it was identified that 60% of medical schools faced challenges related to the inappropriate social media use by medical students (Chretien et al., 2009), one US medical school developed a two hour social media education program that led almost two-thirds (64%) of students to make changes to their social media account (Gomes et al., 2017). A 2017 study of medical residents also identified that while students can learn e-professionalism behaviors in school, exposure to unprofessional behavior during their third-year experiential rotations can erode their professionalism, especially as it relates to information security (Mostaghimi et al., 2017).

Teaching Pharmacy Students to Use Social Media

The American College of Clinical Pharmacy outlines the tenets of professionalism for pharmacy students in the following way: altruism (unselfishness), honesty and integrity, respect for others, professional presence in both professional and personal settings, engagement in the profession and community, and dedication and commitment to excellence (American College of Clinical Pharmacists, 2009). These same principles apply for students' use of social media. Several recent surveys of pharmacy student perceptions of social media have noted that students have high adoption rates, use social media as part of their education, but have little concern about unprofessional content being shared on social media such as posts including profanity or representing drug or alcohol use (Augustine et al., 2015). Thus, pharmacy educators and trainees must continue to find opportunities to incorporate social media and e-professionalism education into the pharmacy curriculum.

The Safety of Social Media

Over the last two decades, social media has become ubiquitous. As the various social networking sites have become established in our daily lives, society has grown more aware of the challenges. From a health-care perspective, patients and health-care providers must pay close attention to privacy and security. Most social networking sites are not designed to be used to convey sensitive health-care information and do not meet the requirements of privacy legislation. As seen in recent years, the information can be aggregated, stolen, and sold to private organizations. In 2017, it was revealed that researchers in the United Kingdom were able to download or "scrape" the personal information of 50 million Facebook users and sell them to a political campaign in the US. This led to a series of hearings in Europe, with the British Information Commissioner's Office concluding that "Facebook contravened the law by failing to safeguard people's information . . . and failed to be transparent about how people's data was harvested by others" (Satariano and Frenkel, 2018). The CEO of Facebook was also required to apologize to the European Parliament (Frenkel, 2018).

At the same time, Europe recently enacted tighter privacy laws that are changing the way information is collected about users online, including through social networks. The new General Data Protection Regulation (GDPR) has several impacts, including the requirements for better transparency around data collection and use; stricter controls around the collection of information on race, political affiliation, and sexual orientation; and even ensures that users must be able to delete photos from social media that were posted when they were a minor (Tiku, 2018). There is also a growing interest in the sharing of false information, often called "fake news" and hate speech, with Germany being among the first countries to pass legislation allowing them to fine sites that do not remove fake news and hate speech up to 50 million (Zhou, 2018).

Conclusion

Social media has changed the way society communicates. With the majority of adults in developed countries using social media, it is no longer optional for health-care providers to understand how and when to participate in social media. In the coming years as social media continues to evolve, pharmacists, pharmacy students, and pharmacy educators will need to continuously develop and refine the expectations of how the profession will engage. Particular attention must be paid to help pharmacists and trainees develop social media literacy and e-professionalism skills and behaviors.

Glossary

e-professionalism the expectations and standards ascribed to professionals during the use of digital media
Social media online content that is created, modified, and shared
Social network an online space where users connect with others to share information that has been created
Meme an often humorous image, video, or piece of text that is copied and rapidly shared online with slight changes or variations

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Pediatric Pharmacy Practice

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Providing pharmaceutical care to pediatric patients relies on the application of specialized pharmacy knowledge including pharmaceutics, pharmacokinetics, therapeutics, drug information, safety practices, and communication skills as an active member of the health-care team. This chapter provides an overview of pediatric pharmacy practice that includes the role pharmacists play in the delivery of pharmaceutical care to pediatric patients including information and examples of pharmaceutical calculations, pharmacokinetics and therapeutic drug monitoring (TDM), and special considerations required to care for this unique population.

Responsibilities of All Pharmacists Working Within a System That Cares for Pediatric Patients

A child is not a scaled down version of an adult. All pharmacists who work with pediatric patients must keep this in mind when delivering care. Pharmacists working in pediatric settings have adopted the pharmaceutical care practice model (Cipolle et al., 2012). However, beyond following this defined process of delivering care, pharmacists practicing with pediatric patients must maintain a foundational knowledge of how age impacts all aspects of medication management services and the patient care process. Beyond this, a day in the life of a pediatric pharmacist includes understanding how child development, medication dose availability, and the child's family circumstance may impact the pharmacist's approach to applying the pharmaceutical care process.

All pharmacists are accountable to deliver the best care possible to their patients. A pharmacist working with pediatric patients must also practice with the recognition that their decisions may have long term impacts to the health, wellness, and development of the child. In addition, pharmacists will need to consider recommendations that may also impact siblings and family members.

In this chapter, we consider some of the prescription focused (e.g., accurately auditing prescriptions) and patient-centered activities (e.g., TDM, medication education) to caring for infants and children.

Roles of the Pharmacist Caring for Pediatric Patients

The medication use process involves the management of prescribing, dispensing, administering, and monitoring of drug therapy. The roles of pharmacists have evolved in the field of pediatrics requiring application and development of specialized knowledge and skills. The common practice is one that is accountability for the delivery of the knowledge and skill that is provided. Traditionally pharmacists have worked in the role of a Dispensing Pharmacist, a staff pharmacist role that is primarily

responsible for the auditing of prescriptions, entry of the prescription into the medication delivery management system, and dispensing of the medication product to the patient. Over the past 25 years, pharmacists have evolved to an advanced practice model, working in the role of Clinical Pharmacist, a clinician who primarily works directly with patients actively involved in the assessment, decision-making, prescribing, monitoring, and counseling of patients.

Examples of other specialized pediatric pharmacist roles are listed below.

- Drug Information
- Drug Use Evaluation Pharmacist
- Compounding Pharmacist
- IV Resource Pharmacist
- Parenteral Nutrition Pharmacist
- Subspecialty Pharmacist (i.e., Cardiology, Critical Care, General Pediatrics, Hematology/Oncology, Infectious Diseases, Neonatal Care, Neurology, Nephrology, Transplant, Stem Cell Transplant, Surgical Services, others)
- Medication Safety Pharmacist
- Antimicrobial Stewardship Program Pharmacist
- Informatics Pharmacist
- Administrative Leaders (e.g., Director, Manager, Clinical Coordinator)
- Clinician Scientists

Working in these specialized fields often requires additional training (i.e., residency training) or education (i.e., Masters of Science, Masters in Business Administration), postgraduate training (i.e., Leadership training) or several years of work experience.

Age Terminology and Definitions

Age is an important factor to consider when dosing medications as it serves as a surrogate delineation for growth and development. The definitions of each age group can vary depending on the resource used and this may vary among countries.

Dosing guidelines may require the health professional to consider age definitions before recommending a dose (or drug) due to differences related to development, pharmacokinetics, and pharmacodynamics in children compared to adults. When employing a recommendation from a resource or literature to practice, imprecise use of age terminology may result in an inaccurate application.

The United Nations Convention on the Rights of the Child defines child as "a human being below the age of 18 years unless under the law applicable to the child, majority is attained earlier" (United Nations Human Rights Office of the High Commissioner, 1990). The practice of pediatrics may continue up to the age of 21 years and beyond in some countries; however, arbitrary limits for transition to adult care may depend on funding models such as health-care insurers or health-care policy. Pediatric pharmacy practice should consider the appropriate age of transition to adult care with the health-care team to best serve the individual patient.

Pediatric age group classifications have been proposed by different organizations including the World Health Organization (Knoppert et al., 2007), resulting in some variability of age categories depending on the source used. In 2009, the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD) Pediatric Terminology Harmonization Initiative aim to standardize terms to promote consistency in the reporting of age-related data in child health research (**Table 1**) (Williams et al., 2012). This classification is the most differentiated and will be used in for the purposes of this chapter.

It is essential for the pediatric pharmacist to be knowledgeable of key periods of development as it relates to achieving desired outcomes in patients. The perinatal period, the timeframe just before and after birth, is a time when there is rapid developmental growth and is further defined considering gestational age. The American Academy of Pediatrics (Engle et al., 2004) provides definitions to aid in the calculation of age (**Table 2**). The neonatal period is a critical time frame where prematurity is a leading cause of death in newborns. Specifically, morbidity and mortality data show maternal and neonatal adverse outcomes differ over the neonatal period. **Table 3** is a summary of terms used in the neonatal period that are based on gestational age. Birth weight is a

Table 1 Age stages defined according to NICHD pediatric terminology stage definitions

Preterm neonatal: The period at birth when a newborn is born before the full gestational period
Term neonatal: Birth to 27 days
Infancy: 28 days to 12 months
Toddler: 13 months to 2 years
Early childhood: 2–5 years
Middle childhood: 6–11 years
Early adolescence: 12–18 years
Late adolescence: 19–21 years

NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development (Williams et al., 2012).

Table 2 Summary of age terminology recommendations by the American Academy of Pediatrics Committee on Fetus and Newborn, 2004.

Neonatal age term	*Definition*	*Recommendation*
Gestational age	Time elapsed (in weeks) between the first day of the last menstrual period and the day of delivery	If pregnancy was achieved using assisted reproductive technology, gestational age is calculated by adding 2 weeks to the conceptional age
Chronological age	Time elapsed (in days, weeks, months, years) since birth	
Postmenstrual age	Gestational age plus chronological age (in weeks)	Preferred term during hospital stay to describe the age of preterm infants
Corrected age	Chronological age (in weeks or months) reduced by the number of weeks born before 40 weeks of gestation	Preferred term after the perinatal period This term should only be used for children up to 3 years of age who were born preterm

(Engle et al., 2014)

Table 3 Neonatal age definitions based on gestational age

Neonatal term based on gestational age	*Definition*
Extreme prematurity of newborn	<28 weeks
Preterm	<37 weeks or 259 days gestation
Early term	37 weeks to 38 6/7 weeks
Full term	39 weeks to 40 6/7 weeks
Late term	41 weeks to 41 6/7 weeks
Post-term	≥42 weeks

(ACOG, 2013; Spong, 2013; WHO, 2018).

Table 4 Neonatal definition based on birth weight

Neonatal term based on birth weight	*Definition*
Extremely low birth weight (ELBW)	<1000 g
Very low birth weight (VLBW)	1000 to <1500 g
Low birth weight (LBW)	1500 to <2500 g

(WHO, 2018).

predictor of neonatal health and survival thus neonates as a group can be further divided into groups based on weight as defined by the World Health Organization (WHO, 2018) (**Table 4**).

Dosing in the perinatal group requires special attention to definitions of weight and gestational age. Careful calculations are often required to determine the appropriate dose for pediatric patients for safety and effectiveness.

Fundamentals of Pediatric Pharmaceutical Calculations

Working with pediatric patients requires an additional level of focus as there is no "one size fits all" approach to dosing medications. It is good practice to check a minimum of two dosing resources particularly when encountering a medication for the first time. It is also good practice prior to auditing a prescription or recommending a medication dose for a pediatric patient to minimally consider the age and weight of the patient. This is important because pediatric drug handbooks provide medication dosing recommendations based on age and weight (dose of medication in milligrams or grams per kilogram of body weight). A decision about the accuracy of a medication dose cannot be calculated without these two crucial pieces of information. In addition, for some potentially toxic medications (e.g., cyclophosphamide, methotrexate), the height/length of the patient is also required. This is because height is needed to calculate body surface area to allow for accurate dosing of some medications.

To determine the patient's BSA, use a pediatric nomogram and the following equation to double check your work:

$$\text{Patient's BSA } (m^2) = \text{square root } (\text{patient's height [cm]} \times \text{patient's weight [kg]}/3600) \quad \text{(Mostellar, 1987)}$$

Additional information that the pharmacist must consider prior to auditing a prescription or recommending a patient specific dose includes the following:

- What is the referenced recommended dose for the specific indication the medication is being prescribed?
- Is the dose consistent with treatment or prophylaxis doses?
- Is treatment or prophylaxis necessary for siblings or other close family contacts?
- Is the infant or child's weight accurate, up-to-date, and provided in pounds or kilograms?
- Has the patient had a recent growth spurt or weight gain?
- Is the prescribed medication available in the appropriate dosage form required for the age and condition of the patient?
- If the medication is available in a fixed dose combination, what is milligram strength of each component (e.g., milligram per milliliter of solution/suspension)?
- On what component of the fixed dose combination is the dosing recommendation based?
- What is the maximum recommended single dose?
- What is the maximum recommended total daily dose?
- Is the daily dose recommendation provided in divided doses?
- If only an intravenous solution is available, can the product also be given orally?

These are some of the fundamental questions that the pharmacist must address to ensure accurate dosing in the pediatric population.

Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

An understanding of age-related developmental changes is required to appreciate the rationale for some of the differences in dosing among different age categories. A pharmacist's role relies on application of this knowledge in order to achieve desired outcomes.

Pediatric Pharmacokinetics and Pharmacodynamics

Age-related changes in pharmacokinetics and pharmacodynamics can, in part, be explained by physiologic differences between children and adults. Historical examples that highlight pharmacokinetic and pharmacodynamic differences unique to children (Table 5). Changes in body water, body fat, plasma proteins, hormonal composition, and organ function occur during aging and influence drug disposition in absorption, distribution, metabolism, and elimination. In addition to growth and maturation considerations, children are also exposed to medicines from transplacental transport and from breast milk. Knowledge of these differences is required for the pharmacist to rationalize dosing recommendations between age groups, aid in the assessment of alternatives for pediatric patients, determine appropriate dosing when a recommendation does not exist, as well as for extrapolation from adult literature for novel therapies. Comprehensive reviews of pediatric pharmacokinetics have been published elsewhere (Kearns et al., 2003a; Pai and Nahata, 2017), and application of this knowledge is imperative for the pediatric pharmacist clinician.

Pharmacodynamics is the study of how a drug may affect the body. The developing nature of a child may pose a changing target for a drug. Examples include tetracyclines staining developing enamel, and thalidomide causing phocomelia during limb formation. Pharmacodynamic factors that may affect response in early life are not well defined, and studies investigating new therapies in pediatrics should focus on understanding these factors. When recommending or assessing drug therapies for pediatric patients, the pharmacist's role involves an assessment of risk based on the patient's stage of development.

Therapeutic Drug Monitoring

TDM can offer insight to individualized drug concentration and response. Given the many challenges with changing development, dosage form limitations, and limited pediatric evidence, TDM serves as a tool to help individualize dosing by interpreting drug concentrations to achieve surrogate efficacy and safety endpoints. Indications for TDM are to ensure dosing is within range for agents with a narrow therapeutic window (e.g., digoxin, phenytoin, aminoglycosides, and vancomycin), adherence, change in route of administration, influence of concurrent medications, or distribution to site of infection. Knowledge of pediatric pharmacokinetic and pharmacodynamics changes during development assists in the interpretation of bodily fluid concentrations and how this relates to therapeutic endpoints. With advanced training (i.e., TDM certification), it is common practice for pharmacists to lead TDM programs with the ability to monitor pediatric patients and adjust regimens independently with the use of expanded scope and medical directives for prescribing. Pharmacists are also involved in determining timing and number of samples (i.e., when trough or peak levels should be drawn, determining the area-under-the-curve estimations for selected therapies), recommended sampling sites, repeated sampling when feeding status or routes of administration may influence achieving desired endpoints. It is also important to liaise with laboratory staff in understanding limitations with drug assays, sampling, and processing.

Table 5 Historical examples of adverse outcomes related to differences in pediatric pharmacokinetics and pharmacodynamics

Year	*Medication*	*Indication*	*Adverse patient outcome*	*Pathophysiological mechanism*	*Regulation/Recommendation*
1956	Sulfisoxazole (Harris et al., 1958; Silverman et al., 1956)	Antibiotic	Kernicterus in premature neonates Mortality	Displacement of bilirubin in plasma Decreased glucuronidation of bilirubin due to decreased glucuronyl transferase activity Free bilirubin crossing immature blood–brain barrier in neonates	Not recommended in infants < 2 months of age
1959	Chloramphenicol (Cummings et al., 2017; Mulhall et al., 1983; Nahata and Powell, 1983; Sutherland, 1959)	Antibiotic	Gray baby syndrome (lethargy, abdominal distention, hypoxemia, decreased perfusion, cardiovascular collapse, mortality) in neonates	Decreased hepatic glucuronidation Decreased renal elimination	Therapeutic drug monitoring (Mulhall, 1983)
1961–1962	Thalidomide (Rehman et al., 2011)	Hypnotic and antiemetic	Embryonic teratogen causing phocomelia (limb and bone abnormalities) when used in pregnant women for morning sickness	Potential oxidative stress, antiangiogenesis in utero	Withdrawn from market 1961 Later studied under strict regulations for other indications (i.e., erythema nodosum leprosum (1965), graft-versus host-disease (1988))
1982	Benzyl Alcohol (CDC, 1982; Gershanik et al., 1982; Liston, 1983)	Bacteriostatic preservative in intravenous products	"Gasping syndrome" (acidosis, respiratory distress, circulatory failure, seizures), death	Immature liver of neonate is unable to oxidize benzyl alcohol to benzoic acid	Avoid use of benzyl alcohol or other preservatives in intravascular flushes (Liston AJ. 1983)
1993	Ceftriaxone (Martin et al., 1993)	Antibiotic	Kernicterus	Displacement of bilirubin in plasma Free bilirubin crossing immature blood brain barrier in neonates	Contraindicated in neonates

Medications where TDM is commonly utilized are listed below:

- Aminoglycosides
- Antiretroviral agents (amprenavir, atazanavir, darunavir, efavirenz, etravirine, indinavir, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, ritonavir, saquinavir, and tipranavir)
- Antituberculosis medications (cycloserine, ethionamide, isoniazid, p-aminosalicylic acid, pyrazinamide, and rifampin)
- Carbamazepine
- Cyclosporine
- Digoxin
- Methotrexate
- Mycophenolic acid
- Phenobarbital
- Phenytoin
- Sirolimus
- Tacrolimus
- Valproic Acid
- Vancomycin
- Voriconazole

Pediatric pharmacokinetic data can lead to further understanding about the ontogeny of physiologic parameters that may affect metabolism and elimination of substances. Recommendations for pharmacokinetic research in children have been published (Barker et al., 2018). Moreover, a decision-making algorithm has been published to help clinicians critically assess the drug concentration and response for agents with limited literature to aid in determining the utility of clinical pharmacokinetic monitoring as a surrogate marker of outcome for selected agents and patients (Ensom et al., 1998). These approaches are welcome in a pediatric practice when medications are not well studied outside of an adult population, and an understanding of drug disposition and attainment of therapeutic endpoints can be tailored to patients.

Pharmacogenomics

Differences in drug responses in the pediatric population also include those that may be explained by genetic variation. An example is that of codeine. Codeine is metabolized to morphine for its therapeutic effect. Safety risks associated with the genetic polymorphism of CYP2D6 (rapid metabolizers), such as in the case for a 2-year-old child (Ciszkowski et al., 2009) and in nursing mothers (Health Canada, 2008), have led to an institutional recommendation to avoid use of codeine (Chen et al., 2011). This example highlights the role pharmacogenomics could play in the prevention of predictable adverse outcomes for individual pediatric patients.

Advances in the field of pharmacogenomics may result in significant impact in areas of childhood cancer, psychiatry, hematology, asthma, seizure disorders, and use of biologics for a variety of diagnoses to better predict potential outcomes of therapy. As medication therapy experts, pharmacists have an opportunity to incorporate pharmacogenomics into daily patient care practice. The role of pharmacists can include providing education on, and active participation in, testing, clinical interpretation of results, and recommendations for personalized drug therapy to promote effective and safe medication use for children. This has been endorsed by the American Pharmacists Association (Owen, 2011) and the Pediatric Pharmacy Advocacy Group (Kennedy et al., 2011). Potential barriers to implementation have been also been identified (Cohn et al., 2018) and should be considered when expanding practice into this field.

Pediatric Dosage Forms

A pharmacist must ensure that patient's medications are indicated, effective, safe, and useable/feasible. After determining the appropriateness of a selected drug based on indication, effectiveness, and safety, and adherence, dosage form selection should also undergo a similar assessment.

Case Example:
Desmond is an 18-month-old (12 kg) male who requires treatment for his first episode of acute otitis media. He lives with both parents and a 3-year-old brother. He developed a fever while at daycare and was seen by his pediatrician. He is being prescribed amoxicillin 500 mg PO BID. He has no known allergies. Amoxicillin is available in 500 mg capsules and 50 mg/mL suspension. Which dosage form would be most suitable for Desmond?

Medications are manufactured in specific dosage forms during drug development. These include solid dosage forms (i.e., tablets, capsules), liquid dosage forms (drops, solutions, suspensions), topical (i.e., patches, creams/ointments), and injectable

Table 6 Enteral dosage form selection based on age

	Enteral dosage form selection				
	Liquids	Solids			
Age	Drops/Solutions/Suspensions	Dispersible tablets/powders/sprinkles	Chewable tablets	Gummies	Tablets/Capsules
Neonates	•				
Infants to Child (1 month to 2 years)	•	•			
Child (2–5 years)	•	•	•	•	
Child (6–11 years)	•	•	•	•	•
Adolescent–Teens (12–18 years)	•	•	•	•	•

(for IV admixture or IM/SC injection). Factors to consider when selecting a dosage form most suitable for a pediatric patient include:

- Patient acceptance (age (Table 6), development, palatability)
- Pharmaceutics
- Pharmacokinetics/pharmacodynamics
- Therapeutics (interchangeability and effectiveness for disease)
- Feasibility to measure intended dose
- Safety (hazardous medications)

Challenges with developing pediatric formulations have been published (Gupta and Khan, 2013), and there are situations when the commercially available dosage forms would not be suitable for pediatric patients where alterations of existing formulations or extemporaneous preparations are required. It should be noted that alterations of existing formulations are not without consequence since this is an unregulated practice and prone to risk for error. The NICHD and the United States of America Food and Drug Administration (FDA) have developed the Pediatric Formulations Initiative (PFI) to promote the development of pediatric-friendly formulations and to address barriers during drug development (NICHD, 2018).

Case Example:
Mathieu is a previously healthy 18-month-old (12 kg) male who requires treatment for an enterococcus urinary tract infection (UTI)/cystitis. The organism was susceptible to both amoxicillin and nitrofurantoin. He has a history of an urticarial rash with amoxicillin and is awaiting allergy testing. Your assessment is that nitrofurantoin is the treatment of choice given his allergy history. Based on weight, you determine that his dose should be nitrofurantoin 20 mg PO q6h (6 mg/kg/day). Nitrofurantoin is only available in 50 mg capsules.
How can the dose of nitrofurantoin 20 mg be delivered to Mathieu?

The above case highlights concerns related to limited dosage form availability. Will alterations of the dosage form affect its effectiveness, safety, or adherence?

In resolving this problem, assessments may include:

- Does the dosing frequency need to be every 6 h?
- Are there any published data with alterations of this dosage form?
- Can a suspension be compounded?
- Can the dose be prepared by compounding capsules to make the 20 mg dose?
- Does the drug interact with food?
- Will stability be compromised if the dosage form is altered?
- Will palatability be a factor?

Pediatric pharmacists are often faced with questions related to medication delivery to children and are responsible for offering solutions to such drug therapy problems. Knowledge, skills, and resources should be used to justify recommendations with an assessment of efficacy and safety. Special consideration should be made to address potential consequences of dosage form alterations. Examples of when altering dosage forms warrant some caution are listed later.

Drug Properties

Therapeutic interchangeability is a consideration for both the expected treatment outcomes as well as for formulary considerations for insurers and payers. To crush a sustained/controlled/extended-release product to be able to administer in a child may result in

loss of the sustained release (SR) property of the drug and consequently peak serum levels potentially toxic effect (e.g., sustained release morphine, controlled release oxycodone). The Institute for Safe Medication Practices (ISMP) organization has published recommendations for oral dosage forms that should not be crushed (ISMP, 2016). Like adult practice, pharmacists are expected to be resources for this type of dosage manipulation. In pediatric practice, awareness of sustained release products that can be altered (e.g., opening tamsulosin SR capsule to be sprinkled and not chewed) may aid in available dosage forms for children.

In the pediatric population, palatability is a factor that contributes to adherence (Baguley et al., 2012), consideration of products that result in poor taste is of value when recommending changes to dosage form (e.g., topiramate tablets, imatinib tablets). A common question is whether a medication can be mixed with food to aid with adherence. Awareness of changes to the stability or change in potency of the desired medication when mixed with selected foods is required. For example, ciprofloxacin is known to chelate with calcium-containing products, thus mixing doses of ciprofloxacin in a child's cereal, may result in decreased amount of drug available for systemic absorption. As a general principle, mixing medications with food is not recommended if there is a risk of the child not receiving the entire dose, the development of food aversions or decreasing the effectiveness of the drug.

Enteral Tube Administration

Enteral feeding tubes may also serve as an alternate route of enteral medication administration, particularly when children are unable to feed orally (i.e., developmental delay, risk of aspiration), require supplemental nutrition, or are receiving a medication that is poorly palatable. An assessment of the compatibility of a drug via the enteral tube route is required because there are situations when it would be not be recommended: administration of enteric coated products (due to risk of coating clogging the tube and/or risk for gastric irritation after product is crushed), viscous products due to the risk for blockage (e.g., ciprofloxacin suspension), drug properties known to clog small bore feeding tubes (e.g., pyridoxine), or where administration via enteral tube results in decreased absorption, particularly when patients are receiving enteral feeds (e.g., phenytoin). If this route is being used, appropriate resources such as texts (i.e., White and Bradnam, 2015), manufacturers, and/or primary literature should be consulted.

Short Bowel Syndrome

Short bowel syndrome is a condition when the body cannot absorb enough nutrients due to absent or poorly functioning portions of the bowel (i.e., congenital or acquired). Examples of conditions that can lead to short bowel syndrome in a child include necrotizing enterocolitis (more common in premature neonates), intussusception, volvulus, gastroschisis, intestinal atresia, or trauma. Symptoms may include diarrhea, bloating/gas, inability to gain weight, and vomiting. Complications can include dehydration, malabsorption, malnutrition, bacterial overgrowth, vitamin/mineral deficiencies, or diaper rash from frequent diarrhea. Medical therapy may include agents that aid in slowing transport in the gut to promote nutrient absorption (i.e., loperamide), antireflux medications due to increased gastric secretion in some patients (i.e., omeprazole), and antibiotics to prevent bacterial overgrowth.

Factors affecting drug absorption include intestinal length, presence of a stoma, mucosal integrity, gastric emptying, intestinal motility and transit, pH, and drug formulation (Sood et al., 2013). The dosing regimen and/or formulation may need to be modified to promote bioavailability in this population. Hyperosmolar agents or simple carbohydrates (often found in syrups and suspensions) may contribute to diarrhea, abdominal cramps. It is generally recommended that consideration is taken to the ingredients when selecting a dosage form for this patient population to prevent worsening diarrhea, cramping, and decreased absorption.

Ketogenic Diet

The ketogenic diet is a strategy to control refractory childhood epilepsy. It is a diet that involves high fat intake along with restricting carbohydrate and controlled protein intake. It's indication for epilepsy dates back to the 1920s (Bailey et al., 2005) and is used when patients have had unsatisfactory control with medications. It results in the body relying on fat as the sole energy source; rather than the brain using glucose as its primary energy source, fat is converted by the liver to ketone bodies which can cross the blood brain barrier and provide the brain with energy. The mechanism by which the ketogenic diet controls seizures is not well established; however, the theory is that ketones exhibit an anticonvulsant effect once they cross the blood–brain barrier (Runyon and So, 2012).

Case Example:
Neel is a 5-year-old (18 kg) boy with developmental delay, intractable epilepsy, and is g-tube fed with an enteral formula. He has failed multiple anticonvulsant regimens, and he was admitted to hospital to trial a ketogenic diet for seizure management. During the admission, he developed a fever and requires treatment for a possible pneumonia. After initial treatment with IV ampicillin, he will be deescalated to an enteral antibiotic. You review this patient with the Ketogenic Dietitian and note that you need to ensure minimal carbohydrate content of medications to optimize ketosis and seizure control. What are the additional factors to consider when recommending an enteral antibiotic in this case?

When selecting the dosage form, questions may include:

- Which medication dosage forms are compatible with enteral tubes?
- What is the carbohydrate content of the dosage forms available?

Pharmacists play an important role in ensuring medication therapies do not disrupt achievement of ketosis for seizure control. Pharmacists should review carbohydrate contributing nonmedicinal ingredients as part of the assessment of selecting the dosage form appropriate for the child's age, route of administration, as well as for ketosis. In general, carbohydrate content is typically highest in syrup and suspension dosage forms and lowest among tablets and capsules. For hospitalized patients, awareness of intravenous fluids containing dextrose or intravenous medication admixtures prepared in dextrose-containing solutions should be avoided (e.g., ciprofloxacin in dextrose 5%). Strategies to prevent the inadvertent administration of high carbohydrate-containing medications to patients are to list "carbohydrate restriction" or "ketogenic diet" to alerts in the patient chart. Communication with the medical team is also vital; explaining that the medications have been selected to ensure minimal carbohydrate content as to not disrupt ketosis and risk compromised seizure control, can assure nursing staff that the dosage forms to be administered have been selected with pharmacist input.

Hazardous Medications

Dosage form selection requires special consideration when dealing with hazardous medications (i.e., chemotherapy or cytotoxic medications). Special equipment or supplies (i.e., gloves, masks, gowns, and disposal containers) may be used to help protect inadvertent or unintended exposure to medications considered hazardous. Recommendations for the safe handling, administration, and disposal of chemotherapeutic agents have been published by the Pediatric Oncology Group of Ontario (POGO, 2016). Selection of dosage forms should consider ease of measurement and extent of exposure to hazardous substances. For example, dissolving tablets in water contained within an oral syringe versus crushing a tablet and then mixing in water is usually recommended to prevent risk for spillage and aerosolization of hazardous substances. When recommending therapies for patients, a pharmacist would be required to consider the dosage form appropriate for the patient age, route and with medication preparation factors in mind when children are required to take medications that may pose a hazardous risk to others and the environment. These medications should also be appropriately stored and labeled to ensure appropriate safe handling.

Patient Education

Due to the complexity of medication administration, differences in presentation, pharmacokinetics, and safety considerations, written information is often provided in addition to verbal counseling to best inform patients and their caregivers. During patient and family counseling, pharmacists have a role in the delivery of medication information, which may help with better understanding of therapies and disease states, the importance of adherence, accommodate schedules (i.e., school), and awareness of potential for side effects (El-Rachidi et al., 2017; Horace and Ahmed, 2015; Trivedi, 2017).

Counseling for pediatric patients should include communication that support:

- Medication information based on evidence (verbal and written)
- Medical information in lay language (verbal and written)
- Inclusion of children according to their level of development (i.e., demonstration)
- Adherence (i.e., medication schedules/calendars, mobile device applications)
- Expanded scope for pharmacists (i.e., pharmacist demonstration of devices, monitoring)
- Measurement devices and tools with instruction upon dispensing to ease dosage delivery (i.e., syringes with clear markings, pill splitters, pill crushers)

Drug Information

In general, drug information for the pediatric patient is vastly limited in comparison to information available for adults. This is due to a multitude of factors primarily related to limited research performed for pediatric patients. A pharmacist may be asked to share information on medication use for pediatric indications when there is limited published literature and may need to perform detailed literature searches, contact manufacturers, work with other drug information centers to collate available data and apply to the clinical setting. The availability of drug information sources specific to this population continues to grow, and use of pediatric-specific dosing reference guides, clinical practice guidelines and resources is strongly recommended.

Pediatric drug information services may also serve as resources to institutions for direct patient care and/or to support medication management (i.e., Drugs & Therapeutics Committee, Antimicrobial Advisory Groups), provincial centers, pharmaceutical companies, and the community. The responsibility may vary between answering a general drug information question, review a class of products for inclusion on the institution's drug formulary, provide therapeutic alternatives in the case of drug shortages, perform drug-use evaluations, participate in committees evaluating drug use, development of standardized patient information leaflets, and/or produce a drug dosing guideline handbook. The skill set required to provide evidence-based pharmaceutical care to pediatric

patients is one that can navigate and exhaust information resources, apply knowledge specific to the pediatric population, and communicate it to the stakeholder(s).

Common pediatric specific drug information resources include:

- AboutKidsHealth (www.aboutkidshealth.ca)
- Canadian Pediatric Society (www.cps.ca)
- American Academy of Pediatrics (www.aap.org/en-us)
- Pediatric & Neonatal Lexi-Drugs database (online.lexi.com)
- NeoFax and Pediatrics (neofax.micromedexsolutions.com)
- Red Book: Report of the Committee on Infectious Diseases (www.redbook.solutions.aap.org)
- Handbook of Drug Administration via Enteral Feeding Tubes (White and Bradnam, 2015)

Medication Safety

It is understandable that by virtue of the calculations, pharmacokinetic considerations, frequent need to manipulate dosage forms which may be required to deliver drug therapy, the pediatric population is vulnerable and at high risk for medication errors. This risk can exist at each stage of the medication use process: prescribing, order entry, dispensing, administration, and monitoring. Examples have been published in the community (Poon and Ho, 2011) and hospital (ISMP, 2015) with the aim to learn from these cases.

Strategies recommended to improve patient safety include:

- Dose-range checking software
- Use of an institutional drug formulary
- Separation of sound-alike and look-alike medications
- Use of barcoding
- Clinical Pharmacist's participation in interdisciplinary rounds and direct patient care
- Single concentration of high-risk medications (electrolytes, heparin, opioids) in hospitals
- Removal of concentrated electrolytes on nursing units
- Double checks for reconstituted products and extemporaneous preparations
- Use of referenced extemporaneous formulations
- Pharmaceutical compounding standards (USP, 2018)
- Prohibiting use of error-prone abbreviations (ISMP, 2017)
- Demonstration of device use
- Use of calibrated measurement utensils
- Medication reconciliation

Medication Reconciliation

Pediatric pharmacy practice includes the involvement of pharmacy professionals in the process of obtaining and reviewing medication histories of patients. Medication reconciliation is the formalized process of obtaining a best possible medication history in collaboration with patients, families, and care providers and to ensure continued care involves evaluation of each medication added, changed, or discontinued. The process of medication reconciliation has become a requirement for accreditation standards in some countries (Accreditation Canada, the Canadian Institute for Health Information, the Canadian Patient Safety Institute, et al., 2012). The intent is to ensure accurate communication at each transition points of care.

In pediatrics, specific attention is devoted to:

- Inclusion of dosage forms, details of compounded preparations (references, correlation to clinical outcomes), units of measure
- Use of multiple sources of information (i.e., all caregivers, contacting all pharmacies)
- Prompting for herbals, vitamins, topicals, inhalation
- Use of tools (medication lists, calendars), storage (original vials, locked cabinets for hazardous medications)
- Assessment of patient/family understanding of medication use, adherence, side effects

Special attention is required to be aware of dosage form differences and interchangeability, assessment of doses, decimal places, and units of measure to actively identify and resolve drug therapy problems during this process.

Expanded Scope of Practice

In Canada, pharmacists can practice with an expanded scope with prescriptive authority to initiate selected therapies, adapt or manage (e.g., renew, refuse to fill, adjust or substitute), injection authority (with some limitations on age and drug products),

order and interpret laboratory tests. The extent of the scope varies between the provinces (CPA, 2018) based on regulatory and legislative bodies.

For pediatric patients, pharmacists can make changes in dosage form, recommend treatments for minor ailments, provide the annual influenza vaccine (and other vaccines), in some regions. In hospital settings, pharmacists can utilize their expanded scope with medical directives or collaborative practice agreements to monitor patient's drug therapies with the ability to order lab tests and tests for TDM. As the medication expert on the team, the role of the pharmacist continues to evolve to better apply the specialized knowledge and skill to direct patient care.

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Use of Complementary/Alternative Medicines in Pharmacy Practice

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What is Complementary and Alternative Medicine?

Defining CAM

Complementary and alternative medicine (CAM) refers to a set of medical practices, services, and products usually considered outside of or complementary to standard care (WHO, 2018). Standard care, in this context, is considered accepted medical practices that are fully integrated into any given country's dominant health care system (WHO, 2018). Often, standard care is considered interchangeable with Western medicine practices since many of these practices have been adopted worldwide. CAM, therefore, would be considered outside of these practices and is not usually fully integrated into the health care system in terms of guidelines and funding models. CAM can be classified into five main domains (Tabish, 2008) that include the following:

1. Whole medical systems: naturopathic medicine, homeopathic medicine, and traditional medicine systems (i.e., traditional Chinese medicine [TCM], ayurvedic medicine, indigenous medicine, etc.)
2. Mind–body medicine: meditation, prayer, and mental healing as well as creative therapies using artistic outlets (e.g., dance);
3. Biologically based practices: herbs, foods, vitamins, and dietary supplements
4. Manipulative and body-based practices: chiropractic, osteopathic manipulation, rolfing, and massage
5. Energy medicine: biofield therapies (Qi Gong, reiki, therapeutic touch) or bioelectromagnetic-based therapies (pulsed fields, magnetic fields, and current fields)

Within whole medical systems, it is important to highlight the guiding principles between the commonly identified systems. Naturopathic medicine is a primary care practice focused on identifying the root cause of symptoms and disease and supporting the body's innate ability to heal itself; this is done through various therapeutic approaches, including use of herbs and nutrients, clinical nutrition, physical medicine (i.e., hydrotherapy), and others (CCNP, 2018). TCM incorporates philosophical worldviews of Taoism, Confucianism, and Buddhism (NIH, 2013). This medical system emphasizes the significance of Qi (pronounced "chee"), which is defined as a vital energy that manifests physically, mentally, and spiritually in all individuals (NIH, 2013). Through various therapeutic approaches, including acupuncture, acupressure, moxibustion, cupping, and other herbal and dietary interventions,

the overarching goal of TCM is to reestablish and maintain an orderly flow of Qi since this system believes that disturbances in the flow of Qi manifests as disease (NIH, 2013). Ayurvedic medicine is one of the oldest medical systems in the world and even today remains a dominant health care system in India (NIH, 2015). Ayurveda focuses on healing approaches that consider the interconnections between people, their health, and the universe as well as the constitution of the body and life forces, referred to as *prakriti* and *dosha*, respectively (NIH, 2015). This is carried out using compounds of herbs and other materials, physical activity, diet, and other treatments (NIH, 2015). Homeopathy was developed by a German physician and is based on the guiding principles that a disease or symptom can be cured by giving an individual a substance that causes similar symptoms in an otherwise healthy individual and that the lower the dose of the substance given, the greater its effect (NCCIH, 2015). Homeopathic medicine systematically dilutes an active substance and believes that the remaining liquid or solid retains the energy of the medicinal product originally used that can then create a therapeutic effect (Tabish, 2008; NCCIH, 2015). While the whole medical systems described here are examples of the most common systems used worldwide, others also exist and may play a strong role in influencing an individual's health practices and beliefs. One such example, significant in North America and Australia, is indigenous traditional healing principles and practices (Robbins and Dewar, 2011; Dudgeon and Bray, 2018).

Chiropractic, osteopathic manipulation, and massage therapy are all considered manipulative and body-based practices. Chiropractic focuses on the critical interrelationship between the spine and the nervous system, believing that a degradation of the integrity of the spine can affect surrounding neurological tissue and cause health consequences for an individual (NCCIH, 2012). Chiropractors, referred to as musculoskeletal experts, perform manual adjustments and manipulations on the spine to restore such integrity (NCCIH, 2012). Chiropractic also incorporates lifestyle and nutritional recommendations into their individualized treatment plans (NCCIH, 2012). Massage therapy manipulates soft tissues to influence the surrounding musculoskeletal, circulatory, lymphatic, and nervous systems to enable the body to heal itself (College of Massage Therapists of Ontario, 2018). Massage incorporates different techniques to deliver treatment, including compressing or stretching soft tissues, as well as reflexology, which is based on the idea that pressure on one part of the body can affect another part of the body (College of Massage Therapists of Ontario, 2018; NCCIH, 2017a). Osteopathic medicine utilizes a diagnostic assessment skill called a palpation that is able to detect scarring, stiffness, density, hydration level, mobility, and other states of tissues and systems being examined (Campbell et al., 2012; AACOM, 2018). The osteopathic practitioner, who in some countries such as the United States are also licensed medical doctors with additional training, will then proceed to use pressure, resistance, and stretching to restore balance in the body (AACOM, 2018).

The practice of acupuncture encompasses the strategic insertion of solid acupuncture needles into the skin at particular points on the body to induce a therapeutic effect (Berman et al., 2010). Acupuncture is often classified as a type of energy medicine, however, is commonly incorporated within different CAM domains. It is commonly practiced as a part of TCM, since it also follows the guiding principles of restoring the balance of Qi, as well as in naturopathic medicine (NIH, 2013; CCNP, 2018). This is similar to biologically based practices such as herbs and dietary supplements, which are commonly utilized in a number of different CAM medical systems and practices.

The Regulation of CAM Practices and Products

Regulation of CAM Practitioners

Access to the various products and services that encompass CAM is greatly influenced by how such practices are regulated in a particular country or jurisdiction. When considering CAM practitioners who offer specific services, the quality of their practice relies heavily on the regulations set out in the jurisdiction they practice in. Whether or not a CAM profession is governed by a set of regulations varies considerably across the world, and even within a country itself. For example, in Alberta, Canada, naturopathic doctors (ND) are governed by the College of Naturopathic Doctors of Alberta; this professional college mandates standards of practice that must be adhered to and restricts membership and the use of a reserved professional title to only those individuals who have completed a certain level of education from an accredited institution, passed national licensing exams, and carry malpractice insurance (CNDA, 2018). In this sense, individuals who visit a ND can be assured that there is a professional board governing the services provided to them. It also prevents unqualified individuals from using this reserved title (ND), as such action would be subject to discipline by a court of law (CNDA, 2018). Without this professional regulation, any individual can refer to themselves as a ND and provide services that they may not be qualified to which is a risk to the public. Interestingly, within Canada, only 3 of 13 provinces and territories regulate naturopathic doctors by a professional college (CNDA, 2018; CNPBC, 2018; TCNO, 2018); currently, other provinces are in the process of such level of regulation and many others attempt to regulate the profession through a professional association, such as Saskatchewan (SANP, 2018). In the United States, only 20 states regulate naturopathic doctors by a state board similar to a professional college in Canada (The American Association of Naturopathic Physicians, 2018). Likewise, naturopathic doctors are not yet considered a regulated or registered health profession in Australia (CMA, 2013). The regulation of naturopathic doctors is one example of a CAM practice; the regulation of other CAM practitioners is also varied and even less common for certain practices such as homeopathy. Since the regulation of such professions aims to protect the public and ensure high-quality, safe medical care, it is important for individuals and health professionals to be aware of what regulations exist in their jurisdiction and how appropriate care can be sought when considering CAM.

Regulation of CAM Products

Products prescribed by many CAM practitioners and used inherently within a number of CAM domains are called natural health products (NHPs), dietary supplements, or herbal medicines (Briggs, 2002; Government of Canada, 2015; FDA, 2018)—various names are used across different countries. Such products encompass a broad category of health products that are available without a prescription from a medical doctor and most commonly include vitamins, minerals, herbs, homeopathic remedies, traditional medicines, probiotics, amino acids, and fatty acids (Government of Canada, 2015). Marketing approval processes differ significantly across countries, leading to a wide variety of products available to patients for use. In many developed countries, NHPs are considered medicinal products and are regulated as a subset of other medicines or under their own separate regulations. NHPs in Australia are called herbal medicine products (HMPs) and are regulated by the Therapeutic Goods Administration as medicines or registered medicines based on their premarket assessment of ingredients, dosage forms, efficacy claims, and safety risks (Briggs, 2002). Similar processes are followed in the European Union by the Committee on Herbal Medicinal Products and in Canada by the Natural and Non-prescription Health Products Directorate within Health Canada (CHMP, 2018; Government of Canada, 2018). In Canada, a Natural Health Product Number (NPN) is provided to those products that have undergone an efficacy and safety evaluation and are deemed appropriate to be sold on the market (Government of Canada, 2016). Contrary to processes followed by the countries described above, the United States regulates NHPs under the Dietary Supplement Health and Education Act of 1994 as a subset of food and refers to them as dietary supplements (FDA, 2018). Manufacturers of dietary supplements do not have to apply for premarket approval and the United States Food and Drug Administration is only involved in repercussions for unsafe dietary supplements that are already available on the market (FDA, 2018).

While Europe and Canada outline a premarketing approval process for NHPs, it is important to point out that the criteria required for approval and the rigor applied to this process vary across products. Applications for products may be submitted through a traditional use pathway, which specifies that products that have been used traditionally for 30 years or longer do not require clinical trials on efficacy or safety for approval. In the European Union, for example, products seeking approval under the "traditional use registration pathway" only require the demonstration of "sufficient safety data and plausible efficacy" (European Medicines Agency, 2018). Likewise, in Canada, NHPs that seek approval through the "traditional use pathway" are asked to submit evidence of efficacy through "two independent references supporting efficacy based on belief /theories/experiences within a single system of traditional medicine" (Government of Canada, 2012). Of particular concern, it is often unknown or unclear to which extent such submitted data are reviewed and the quality assurance mechanisms in place to protect consumer safety. An example of this was highlighted recently in a Canadian television show titled "CBC *Marketplace*" in which a fake homeopathic product claiming to treat fevers in children was approved for licensing (Grundig, 2015). This action was highly criticized given that the only effectiveness claim for this product was based on a 1902 homeopathy textbook of ingredients (Grundig, 2015).

Complementary and Alternative Medicine Use

Prevalence of CAM Use

Complementary and alternative medicine use is prevalent worldwide (NHPD, 2011; Walji et al., 2011; Vicki Wood, 2012). Greater than 70% of the population reports CAM use in many countries around the world, including Canada, the United States, and Europe (WHO, 2013a). This use has increased significantly over the past decade (WHO, 2013a). CAM use is often sought for the management of acute conditions such as pain and headaches (Barnes et al., 2009a) but is also commonly used by individuals living with serious and chronic diseases. For example, the rate of CAM use by individuals with multiple sclerosis is 41%, 70%, and 82% in Spain, Canada, and Australia, respectively (Skovgaard, 2012). In patients living with cancer, global rates of CAM use ranges from 6–91% and has grown significantly in recent years (Werneke et al., 2004; dams et al., 2013; Bonacchi et al., 2014).

The rates of specific CAM practices vary worldwide. CAM practices such as massage, chiropractic, and acupuncture are commonly used around the world; in fact, over 50% of countries in the world utilize and recognize the use of acupuncture within the health care system (WHO, 2013b). One of the most commonly reported CAM therapies is NHPs. Over 70% of Canadian adults reported the use of at least one NHP in 2010 (NHPD, 2011); utilization data are similar across other countries such as the United States, Europe, and Australia (Xue et al., 2007; Corazza et al., 2009; Barnes et al., 2009b). NHPs are also commonly used in children, with such use being largely influenced by whether or not their caregiver or parent use CAM (Sawni-Sikand et al., 2002; Barnes et al., 2008; Kim et al., 2012). It has been reported that over three-quarters of children with type 1 diabetes mellitus use at least one NHP (Haliloğlu et al., 2011). In Norway, nearly 40% of pregnant women report utilization of herbal products (Nordeng and Havnen, 2004).

Traditional medicines, including TCM and Ayurveda, are deeply rooted within the cultures of many countries such as China, Africa, and India (WHO, 2013b). These medicine practices have been passed along from generation to generation and are widely accepted amongst individuals of these cultures (WHO, 2013b). For example, nearly one-fifth of all medical visits in China in 2009 were to TCM practitioners; in fact, 90% of publicly and privately funded hospitals in China have a traditional medicine department and both conventional medicine and traditional medicines are offered concurrently in all institutions (SATCM, 2009; Government of China, 2011; WHO, 2013b). In Singapore, where more "Western" conventional practices are commonly accepted and utilized, three-quarters of the population still report using traditional medicines (WHO, 2012). Traditional medicine use has been reported to be as high as 60–90% in Africa and 70% in India (Bach Hernán et al., 2014). It is important to recognize that given the extensive use of traditional medicine in certain cultures around the world, immigration patterns may also impact the use of CAM in other

countries that do not integrate such practices to the same extent. In the United States, immigrants from China accounted for the second highest proportion of all immigrants between 1986 and 2016, and India was the third highest (USDHS, 2018).

Homeopathy, despite current controversy around the lack of efficacy surrounding such practices, is still prevalent in many countries. Given its development by a German physician in 1796, its use tends to be greater in Europe and countries within close proximity to Europe (Relton et al., 2017). While rates of use across Canada, the United States, the United Kingdom, and Australia have remained quite consistent over nearly 30 years at 0.2–4.4%, countries such as Italy and Switzerland report much higher use (Relton et al., 2017). In Italy, 8.2% of the adult population and 7.7% of children used homeopathy in 1999 (Relton et al., 2017). The highest rates of use are reported in Switzerland where, interestingly, the cost of homeopathy treatment is covered by health insurance (Relton et al., 2017).

Reasons for CAM Use

Reasons for CAM use are complex and often multifactorial, based on values and different sources of information. Many consumers utilize CAM in their health care based on traditional cultural values, as discussed previously. Outside of cultural traditions, individuals often link the assumption of a product being "natural" to inherently mean it is safe, and therefore it is a healthier or safer alternative to conventional drugs used in the Western medical system (WHO, 2013b). In fact, one in five Canadians believe that NHPs do not have any adverse effects associated with them (NHPD, 2011). Since NHPs are available over-the-counter (OTC) without a prescription in most countries, patients often self-select and incorporate NHPs into their treatment plans based on information gathered from sources such as the Internet, media sources, popular health-focused talk shows, and friends/family (Felix, 2009; NHPD, 2011). Additionally, much of the world's population, especially in more developed countries, are demonstrating a drive to focus on health prevention and increased attention to natural approaches for overall health (NHPD, 2011). Within less developed countries such as Africa, access to traditional healers who use CAM is much greater than to medical doctors (Abdullahi, 2011). Data from the World Health Organization show that there is one medical doctor for every 40,000 people in Africa, compared to one traditional healer per 500 people; as a result, traditional medicine is more accessible and often costs less money (Abdullahi, 2011).

The treatment approach practiced by many CAM providers often differs from that which individuals are accustomed to in the Western medical system; in turn, this often leads to an improved sense of client-centered care and acceptance by patients to engage in CAM treatment strategies (Kaptchuk, 2002). For example, a patient may get to see a medical doctor for 5–10 min for a typical encounter, depending on the practice setting, whereas with a CAM provider that interaction may be upward of 60 min of time. This increased time together with what may be perceived to be a more complete history gathering often leads to improved patient satisfaction with care and willingness to engage in treatment options recommended by a CAM provider (Kaptchuk, 2002). In fact, a strong therapeutic relationship that results from the entire therapeutic encounter, not just the specific treatment modality itself, has been demonstrated to improve treatment outcomes based on the concept of the placebo effect (Kaptchuk, 2002). A placebo is defined as a "harmless, unmedicated treatment used for its psychological effect, often as a comparison with other treatments" (Wall and Wheeler, 1996). It has been proposed that a placebo effect is likely impacted by the therapeutic relationship itself, especially one that focuses on care rather than just cure, and may directly result from a patient's perception of their provider's qualities instead of just the treatment itself (Wall and Wheeler, 1996). Likewise, individuals who are dissatisfied with the care they have received by conventional health professionals, or with the therapies they have received, may likely seek care from a CAM provider in an attempt to better manage their medical condition (Chao et al., 2006).

Complementary and Alternative Medicine and Pharmacy Practice

Sale and Marketing of NHPs in Pharmacies

Pharmacies are a common retail source of NHPs. Canadians spent over $1.5 billion in 2015 on over 70,000 licensed NHPs in Canada; within pharmacies, NHPs are the top-selling OTC products, even when considered next to commonly used OTC product categories such as pain relievers (Felix, 2013, 2015; Smith et al., 2014). Similarly, in the United States, consumers spent over 7 billion dollars on herbal dietary supplements in 2016, which was a 7.7% increase from 2015 (Smith et al., 2017). Such growth in NHP sales has been reported in many other countries around the world as well, such as Asia, Europe, and Australia, and the global market is expected to reach US$115 by 2020 (Ung and Harnett, 2017). Interestingly, pharmacists who have been surveyed admit to feeling required to increase OTC inventory of NHPs to meet the growing demands by their clients (Boon et al., 2009). As a result, many pharmacy chains worldwide have a large number of aisles dedicated to NHP sales due to both consumer demand and the significant potential for generating revenue. Such a profit-driven environment surrounding NHP sales has led to an abundance of NHPs available within a community pharmacy setting or used by patients in other pharmacy settings (Gunawan et al., 2016; Stub et al., 2016; Ogbogu, 2017).

Role of the Pharmacist in CAM

CAM undoubtedly impacts pharmacy practice given the prevalence of use of such therapies worldwide, and the availability of NHPs in retail pharmacies. Pharmacies and pharmacists are very much involved in the sale, marketing, and education of NHPs. Research

has found that 89% of community pharmacists report spending at least 30 minutes a day counseling patients on NHPs (Charrois et al., 2007). Similarly, other studies demonstrate that consumers of pharmacies frequently ask pharmacists for information and advice on NHPs (Robinson and Lorenc, 2011; Volmer et al., 2011). While pharmacists are taking on a larger role in the NHP industry, a defined scope of practice has yet to be established to guide exactly which responsibilities pharmacists should be incorporating into their practice (Ung and Harnett, 2017). The World Health Organization's International Pharmaceutical Federation states that "pharmacists should take steps to update their knowledge and skills about complementary and alternative therapies in order to maintain and improve professional practice" (World Health Organization, 2011). A majority of the literature highlights the need for pharmacists to inquire about NHP use and document such use in a person's medication record, as well as to take an active role in preventing drug–herb interactions and educating individuals on the safety risks associated with NHPs (Miller et al., 2000; Chavis, 2001; Abahussain et al., 2007; Olatunde et al., 2010; Ung and Harnett, 2017). Pharmacy consumers value pharmacists' expertise in medicines and strongly support the role of pharmacists in providing safety information about NHPs (Braun et al., 2010). A growing body of research, however, also suggests that pharmacists should have the knowledge to advise patients on the efficacy and use of NHPs and major stakeholders consider a pharmacist's role in CAM products to be a "legitimate extension of their established roles in pharmaceutical care" (Miller et al., 2000). Likewise, major stakeholders, such as professional colleges and national organizations, also feel that pharmacists should be able to educate individuals on NHPs in the same way they do with OTC medications (Miller et al., 2000). In practice, this is likely what is occurring given the extensive sales of NHPs within pharmacies and the consumer demand on pharmacists for information. A study out of Alberta, Canada, surveyed community pharmacists about practices related to NHPs and found that nearly one-fifth of pharmacists recommend NHPs often to patients, and almost half report doing so at least sometimes (Ogbogu and Necyk, 2016). Recommending a product for use entails more than general knowledge around safety and drug–herb interactions; up-to-date knowledge and a critical evaluation of the literature is required to ensure the product is efficacious for the desired indication, and that it is in fact the best alternative for the patient given other products on the market. Pharmacists require the training and confidence in order to provide such a scope of practice, and yet, they may have neither. Indeed, research has shown that pharmacists lack the adequate training and knowledge to deliver such care related to CAM, and as a result, they also lack confidence (Ung and Harnett, 2017). A comprehensive standard of practice is required at both a national and international level to outline both the ethical and professional responsibilities of pharmacists in this role, which would then inform undergraduate pharmacy education programs and professional organizations to train and support pharmacists in this area of practice.

Integrative Medicine Approaches

The National Center for Complementary and Integrative Health in the United States defines Integrative Medicine as "bringing conventional and complementary approaches together in a coordinated way" (NCCIH, 2016). Approaches to integrative medicine may differ based on the country and primary health system utilized. Ultimately, the goal is to combine the best evidence from all health systems in order to optimize health care for all patients. Such an approach can be found in disease-specific clinical practice guidelines that may incorporate CAM approaches supported by strong research infrastructure and evidence to the treatment algorithms. Examples of this are demonstrated in the inclusion of acupuncture and massage therapy into chronic noncancer pain treatment guidelines (Busse, 2017), as well as supporting the use of omega-3 fatty acids and yoga in depression treatment guidelines (Ravindran et al., 2016). Specific NHPs are also supported in the management of other medical conditions; examples of this include recommendations for calcium and vitamin B6 use in premenstrual syndrome management and the use of bulk-forming laxatives such as psyllium for constipation (Wyatt et al., 1999; Douglas, 2002; Williams et al., 2005; Longstreth et al., 2006; Whelan et al., 2009). The uptake of this approach to practice by pharmacists may be increasing, given that research has demonstrated that not only are pharmacists recommending NHPs for use, but 85% are recommending NHPs to be taken concurrently with prescription drugs and 31% are recommending NHPs as an alternative to conventional drugs (Ogbogu and Necyk, 2016). The evidence base behind such recommendations, however, is unknown and it is still unclear whether pharmacists are embracing an integrative medicine approach in their practice or whether external factors, such as consumer demand, potential for profit, and recommendations from other health professionals, play a role. Pharmacists should be aware of clinical guidelines and emerging literature that support the use of CAM, and specifically NHPs, with strong evidence backing their use in order to provide a holistic care approach for their patients. Likewise, pharmacists that do not possess the intricate knowledge behind the pharmacologic, pharmacokinetic, and safety profiles of NHPs should refrain from making recommendations outside of published guidelines and should collaborate with other health professionals trained in this area to prevent misuse of products and patient harm. This, again, supports the need for a pharmacists' role to be better defined around CAM in order to establish appropriate training and support mechanisms for the profession.

Safety of Complementary and Alternative Medicine

Safety of CAM Procedures

If pharmacists are involved in recommendations of CAM treatments, especially referrals of individuals to CAM practitioners, it is important to be aware of the efficacy and safety data that exists for such practices. First, this relates back to Regulation of CAM Practitioners in terms of being knowledgeable about the training and qualifications of CAM practitioners in their area and help guide

patients to those who are credible and guided by established scopes of practice by a professional college. This in itself, however, does not dictate whether such practices are considered efficacious and safe. It is important for pharmacists to educate both themselves and their patients on efficacy and safety data around a specific CAM procedure or practice (i.e., acupuncture, chiropractic, etc.), and for the specific indication it is being considered for. Pharmacists who make specific recommendations or referrals should do so with full knowledge of what they are recommending to a person and how it relates to their care plan; pharmacists who are approached by patients inquiring about this information should direct patients to where they can find credible information if they are not comfortable supporting such a recommendation or referral within their own scope of practice.

While CAM is often considered "natural" and, therefore, safe, procedures that fall under the common domains of CAM are not without risk (Walji et al., 2010). Acupuncture, for example, has been associated with adverse events (AE) such as bacterial infections, pneumothorax, central nervous system injury, syncope, and organ injury (Wu et al., 2015). One systematic review determined that reused needles were the most common source of hepatitis infection due to acupuncture (Lao et al., 2003); once again, this speaks to the need for standards of practice and standardization of practice protocols to govern CAM practitioners. While chiropractic is most often associated with mild and transient AEs such as vertigo or muscle pain, spinal manipulation has also been associated with more severe AEs, including dissection of the vertebral arteries, dural tear, nerve injury, disc herniation, and bone fracture (Ernst, 2007). It has also been suggested, with some controversy, that spinal manipulation in the cervical spine area should be avoided in any individual who present arteriosclerotic disease, calcified arterial walls, or tortuosities of the vessel as this may increase the risk of subdural hematoma (Cagnie et al., 2006).

Many other CAM procedures exist, all with their own potential risk profiles. While these risks may be further increased by inadequate training and regulation of CAM practitioners, it is critical that pharmacists are aware of such risks to be able to educate their patients and the public, especially when recommendations of CAM treatments and referrals to CAM practitioners are made. Literature is ever growing in this area as well, so it is also the responsibility of pharmacists to stay abreast of new knowledge when incorporating various aspects of CAM into their scope of practice.

Safety of Natural Health Products

The extent to which NHPs are being sold in retail pharmacies and the current demand on pharmacists to provide the public with information and guidance on such CAM products is well-documented. Much of the literature to date supports the role of pharmacists in assessing and educating on the safety of NHP use for individuals under their care or who visit the pharmacy. Indeed, it is critical that pharmacists are aware of the potential safety considerations of NHPs.

NHPs are pharmacologically active substances that have the potential to lead to adverse reactions (AR). An AR is defined as "a noxious and unintended response to a marketed health product, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function" (Health Canada, 2011). In the United States between 2000–07, NHPs were associated with one of the highest rates of hospitalization due to ARs reported to poison control centers (PCC) (Vassilev et al., 2009). Similarly, in 2003, 30% of all AR reports to PCC in the United States related to dietary supplements were considered moderate to very severe in nature (Perharic et al., 1994).

The causes of ARs may be complex and can be both intrinsic and extrinsic in nature. Extrinsic causes are those that may be related to the manufacturing process of NHP, such as contamination, adulteration, or incorrect preparation and labeling (Jordan et al., 2010). Contamination of NHPs through the growing and manufacturing process may lead to the presence of dirt, pesticides, pollutants (including PCBs), bacteria, molds, mycotoxins, processing impurities, and solvent residues in the final product that becomes available to consumers (Chan, 2003). Of particular concern is the potential for contamination of NHPs by toxic heavy metals. During the growing process, plants used to manufacture NHPs may accumulate heavy metals from the environment they are grown in (Street et al., 2008; Gasser et al., 2009). One type of Ayurvedic medicine, *rasa shastra*, entails the intentional addition of metals, minerals, and gems into herbs for therapeutic purposes (Saper et al., 2008). If manufactured and used properly, experts in this field feel that these products are both effective and safe; however, a large proportion of Ayurvedic products manufactured in India, South Asia, and even the United States have been found to contain detectable levels of lead, mercury, and arsenic that exceeded daily acceptable intake limits (Saper et al., 2008). Interestingly, one study found the prevalence of metal-containing Ayurvedic products to be similar whether manufactured in the United States or India (Saper et al., 2008). Perharic et al. reported that out of 1040 NHP-related reports to the National Poisons Unit in London, UK, 8 cases involved heavy-metal poisoning due to contaminated NHPs (Perharic et al., 1994). Adulteration of NHPs involves the addition of other pharmaceutical drugs, or their analogues; these drugs are undeclared for the purposes of monetary profit due to increased sales of products (Jordan et al., 2010). Weight loss products adulterated with sibutramine and sleep products adulterated with benzodiazepines are a few examples of adulteration that have occurred in NHPs (Jordan et al., 2010). The potential for harm is great with adulteration, especially given that these added products are undeclared and have the potential to reach the consumer. Another possible extrinsic cause of ARs related to NHPs involves species misidentification or substitution (Jordan et al., 2010). Black cohosh (*Actaea racemosa*) has been linked to hepatotoxicity in the literature, however, further analysis and evidence has linked this hepatotoxicity to a Chinese *Actaea* species present in the product rather than the *Actaea racemosa* itself (USNLM, 2018).

Intrinsic causes of NHP ARs are those effects that are related directly to the NHP itself, including its mechanism of action, pharmacokinetics, and interactions with other herbs and drugs (Perharic et al., 1994). NHPs such as bitter orange and ephedra can cause adverse events related to stimulation of the nervous system, such as increased heart rate and blood pressure (Jordan et al., 2010). Woolf et al. found that hazard rate of toxic reactions due to nonephedra herbal products was 96/1000, while the

hazard rate of products containing ephedra ranged from 250 to 267/1000 (Woolf et al., 2005). This rate has grown significantly over the years as well (Woolf et al., 2005). Other NHPs, such as fish oils and Gingko biloba L., can affect blood coagulation and or/platelet aggregation and have been associated with ARs related to bleeding events (Calder, 2004; Bent et al., 2005; Cohen et al., 2011).

Given their pharmacological activity, NHPs also contribute to both pharmacodynamic and pharmacokinetic interactions with other drugs. For example, St. John's wort increases serotonin levels and can increase the risk of serotonin syndrome when taken alongside other drugs that elevate serotonin, such as selective serotonin reuptake inhibitors, dextromethorphan, and triptans (selective serotonin agonists) (Henderson et al., 2002). Ginseng can worsen psychiatric conditions, such as bipolar disorder, due to its stimulating pharmacological profile (Joshi and Faubion, 2005). Other NHP-drug interactions continue to be debated, such as cranberry's effect on coagulation when taken alongside warfarin, but are critical for consideration when delivering patient-centered care (Ge et al., 2014). A scoping review was completed by Kutt et al. in 2016 that reviewed all literature related to NHP–drug interactions, both documented and theoretical (Kutt et al., 2016). Out of 29 NHPs included in the review, 28 were identified as having interactions with pharmaceutical drugs and in total, 97 clinically documented interactions were found (Kutt et al., 2016). Those NHPs with three or more clinical interactions documented are summarized in **Table 1**, along with the drug classes they have the potential to interact with (Kutt et al., 2016). Further details on the nature of the interactions are summarized in the publication (Kutt et al., 2016). Interestingly, St. John's wort was found to interact with 15 different drug classes (Kutt et al., 2016); such interactions are likely due to the pharmacokinetic profile of St. John's wort that is known to induce cytochrome P450 3A4, 2C9, and 1A2, as well as P-glycoprotein (Henderson et al., 2002). While **Table 1** reviews those NHPs with three or more interactions,

Table 1 NHPs with three or more clinical interactions documented

NHP	*Drug class*
Echinacea	Antiplatelet/anticoagulant drugs
	Sedative drugs
	Hepatotoxic drugs
Ephedra	Antihypertensive drugs
	Corticosteroids drugs
	Hepatotoxic drugs
Gingko	Antiulcer drugs
	Antiplatelet/anticoagulant drugs
	Diuretic drugs
	Analgesic drugs
	Antipsychotic drugs
	Antidepressant drugs
	Sedative drugs
	Antiretroviral drugs
Licorice	Diuretic drugs
	Sex hormones
	Antidiabetic drugs
	Antibiotic drugs
Milk thistle	Antihypertensive drugs
	Antidiabetic drugs
	Antiretroviral drugs
	Antibiotic drugs
St. John's wort	Antiulcer drugs
	Antiplatelet/anticoagulant drugs
	Lipid-lowering drugs
	Antihypertensive drugs
	Cardiac glycoside drugs
	Anti-allergy drugs
	Antipsychotic drugs
	Antidepressant drugs
	Antiepileptic drugs
	Sedative drugs
	Sex hormones
	Antifungal drugs
	Antiretroviral drugs
	Antidiabetic drugs
	Antiasthmatic drugs

Adapted from Kutt A, Girard L, Necyk C, et al., 2016. Natural health product–drug interaction tool: a scoping review. Can. Pharm. J., 149(2),75-82.

many other NHPs have clinically relevant interactions as well such as ginger and garlic with antiplatelets/anticoagulants and aloe vera with antihyperglycemic drugs (Kutt et al., 2016).

Given the high prevalence of NHP use worldwide, it is very likely that individuals are taking NHPs and drugs at the same time and are at risk of experiencing such interactions. In the United States, 38% of individuals take NHPs alongside prescription drugs, and 42% take NHPs alongside an OTC medication (Rashrash et al., 2017). In Australia, 87% of individuals over 50 years-old that took NHPs were found to do so concurrently with prescription drugs (Morgan et al., 2012). Of those, 14.2% were at risk of a potential NHP–drug interaction; when 5 or more products were taken in combination this risk increased to 23.7% and in 10 or more to 38.4% (Morgan, 2012). This is concerning, especially since we know individuals with chronic diseases such as cancer, diabetes, and heart disease, who are likely taking one or more prescription drugs, are also more likely to take NHPs as well (Rashrash et al., 2017). It is also important when we recall that up to 85% of pharmacists may be recommending concurrent NHP–drug use (Ogbogu and Necyk, 2016). Within Canada, nearly half of patients visiting community pharmacies take NHPs and prescription drugs concurrently and of those, 7.4% reported experiencing an AE as determined in a national Pharmacy SONAR (Study Of Natural health product Adverse Reactions) research initiative (Necyk et al., 2014). Pharmacists are highly trained to detect, prevent, and manage interactions occurring with pharmaceutical drugs, including those involving NHPs. In fact, Charrois et al. found that 47% of community pharmacists reported recognizing a potential NHP–drug interaction in their patient population (Charrois et al., 2007). Pharmacists should stay abreast with current and emerging literature identifying NHP–drug interactions and be able to apply such evidence to the patients in their care to reduce the AR rate in this population.

Monitoring and Reporting Adverse Events Involving Complementary and Alternative Medicine

Adverse Event Reporting for CAM Practices and Procedures

An AE is an event to which a patient experiences unintended harm and is related to the care or services provided to them, or to products consumed (FDA, 1995). An AE may not yet be determined to be causally associated with the service or product, with which it would then be classified as an AR. The monitoring and reporting of AEs related to specific CAM practices delivered by a CAM practitioner during a patient visit often depends on the extent to which the CAM practitioner is regulated in a particular country. Just as it is expected that conventional medical doctors and other health professionals disclose any AE experienced by a patient in their care to the patient themselves, and to whatever institutional and regulatory body is required to ensure a quality review process occurs to prevent further harms from occurring in the future (CPSA, 2018; TCMPA, 2009), CAM practitioners should be held to the same practice standard. AEs as well as inappropriate, unethical, or unprofessional practices are most often investigated by the professional college to whom the specific practitioner belongs to. Such complaints may come from the public or from another health professional. Investigations, when reports are made to the professional college, are undertaken for the purpose of ensuring that the professional standards of practice and codes of ethics were being followed when delivering patient care. It is for this reason, among many others, that professional colleges and the regulation of health professions aim to serve the best interests of the public.

As previously discussed in Regulation of CAM Practitioners, many CAM practitioners around the world are not governed by a professional regulatory body. As such, it is the responsibility of individual practitioners to monitor AEs that may arise and disclose it to the patient and any other professional body that may exist. Without any professional body overseeing such a process, it is unlikely that AEs or complaints from the public will be managed in a way that can accelerate widespread change.

Adverse Event Reporting for CAM Products

Typically passive surveillance, or passive reporting, of AEs by drug companies, health professionals, and patients are utilized in most countries around the world to capture AEs related to various health products, including prescription drugs (Pal, 2011). While product companies are mandated to report serious harms that occur during clinical trials or postmarketing surveillance, reporting by health professionals and consumers remains low. Unfortunately, we know that passive surveillance captures less than 1% of all ARs that occur (Wiktorowicz, 2010). While health professionals are mandated in their standards of practice to report all ARs identified in their practice, barriers such as time constraints and lack of confidence in completing AR reports prevent much of it from occurring (Wiktorowicz, 2010).

The issue of underreporting in passive surveillance AR reporting systems is further intensified when considering NHPs (Barnes, 2003). Many patients do not disclose CAM or NHP use to their conventional health professionals, such as physicians and pharmacists, and in return these health professionals often do not question about such use (Wiktorowicz, 2010; Pal, 2011; Morgan, 2012; Morgan et al., 2012). This reduces the likelihood that a patient will disclose an AE related to such products to their health professional. In addition, many individuals perceive NHPs to be safe since they are considered natural and therefore do not relate experienced AEs to a NHP itself (Raynor et al., 2011). It has been found that health care providers report NHP-related AEs to regulatory agencies, even when identified, less than drug-related AEs (Pal, 2011). Pharmacists, however, have been found to report AEs to regulatory bodies more than any other health care provider (van Grootheest et al., 2004); pharmacists likely do and should play an important role in reporting NHP AEs as well.

The Pharmacy SONAR research initiative across Canada aimed to identify rates of AEs associated with NHP use by implementing active surveillance strategies into community pharmacies (Vohra et al., 2012; Necyk et al., 2014). Active surveillance "seeks to

ascertain completely the number of adverse events via a continuous pre-organized process" (ICH, 2004). Different active surveillance approaches, such as electronic databases that track specific medical conditions or drug utilization, as well as strategies built into health clinics, have been found to markedly improve the frequency and quality of AE reports (Walley and Mantgani, 1997; Al-Tajir and Kelly, 2005; Talabi et al., 2009; NDB, 2013). Few active surveillance programs have been implemented for NHP-specific AEs. Pharmacy SONAR led such an aim, and the results were astonishing. When pharmacy staff systematically screened all individuals who visited the pharmacy about NHP AEs, the rates of such events identified were 3000 times greater than what had been captured by Health Canada through passive surveillance during the same time period (Vohra et al., 2012; Necyk et al., 2014). The SONAR protocol has been further applied to various specialty clinics, including mental health outpatient clinics, to identify NHP AE rates in individuals living with various chronic diseases (Necyk et al., 2016).

It is important for pharmacists to build active screening around NHP use and related AEs into their patient histories and discussions. This is especially true now that pharmacies are leading the sales of many NHPs and becoming a preferred source of information for individuals taking such products. All AEs related to NHP use should be reported to the respective regulatory agency in order to collect accurate safety data on such products. Since many NHPs do not require the premarketing clinical trials that prescription drugs do, monitoring and reporting of AEs is even more critical to improve patient safety.

Finding and Interpreting Evidence Surrounding Complementary and Alternative Medicine

Evidence-Based Medicine and CAM

Pharmacists are trained in evidence-based medicine, utilizing the most up-to-date and high-quality research to inform their practice decisions. This essential skill can become difficult to apply to CAM where much of the evidence pharmacists are accustomed to is lacking (Ung and Harnett, 2017). High-quality evidence surrounding CAM is lacking for various reasons, such as a lack of research funding dedicated to CAM to carry out the same premarketing clinical trials that pharmaceutical companies are able to do (Veziari et al., 2017). NHPs also do not require the same evidence base prior to marketing compared to pharmaceutical drugs, and in some countries, do not require any evidence at all, therefore, the need to conduct such research is not as urgent (Government of Canada, 2016; European Medicines Agency, 2018). Majority of studies exploring NHP efficacy and safety are observational in nature, and/or consist of small sample sizes that hinder the integrity and generalizability of the study results (Aickin, 2010). While randomized controlled trials (RCTs) are considered the gold standard level of evidence to be sought while assessing causality, it may be difficult to implement a placebo-controlled RCT for certain CAM treatments (i.e., acupuncture and chiropractic) (Aickin, 2010). While sham treatment procedures can be used in such a design, we must consider that part of the treatment effect that may be present when utilizing CAM lies within the placebo effect and the patient–provider relationship itself (Veziari et al., 2017; Spencer et al., 2018). It is also important to consider that this idea of situating RCTs at the top of the evidence pyramid is very much a Western medical concept. Countries and medical systems that follow more traditional belief systems do not necessarily hold this level of evidence to the same standard and, instead, value traditions and generations of treatments handed down through word of mouth and scripture (Aickin, 2010; Veziari et al., 2017). Pharmacists should practice evidence-based patient care, while simultaneously appreciating that the values and belief systems of such therapies may pose a challenge in this pursuit. Regardless, interpreting available evidence on CAM should be held to the same rigor as conventional treatments, assessing the validity, risk of bias, generalizability of the results while considering some of these nuances that may exist. In the same manner, evidence should be taken into consideration individually, alongside patient values and goals.

It has been reported that up to 80% of the public report using the Internet to gain health advice; many Internet sources are inaccurate and could lead to further patient harm (Williams, 2013). Given how accessible pharmacists that work in community settings are to the public, providing accurate education around CAM is an important public health initiative.

Resources for Locating Evidence on CAM Practices and Procedures

Pharmacists may need to identify up-to-date literature on various CAM treatments and procedures, such as chiropractic, massage therapy, and acupuncture, in order to provide integrative treatment plans or to educate the public. While extensive primary literature can be accessed through databases such as PubMed (NLM, 2018) and MEDLINE (Medline, 2018), not all health professionals have access to such resources. *BMC Complementary and Alternative Medicine* is the partnered journal for the International Society for Complementary Medicine Research and provides open access to all published articles within this journal (ISCMR, 2016; BMC, 2018). The United States' National Institute of Health (NIH) houses a National Centre for Complementary and Alternative Health that provides well-summarized descriptions and evidence on various CAM treatments, including scientific literature summaries on the effectiveness and safety considerations (NCCIH, 2017b). This resource is free to the public and all health professionals (NCCIH, 2017b). Also, out of the United States, Maryland Center for Integrative Medicine created Cochrane Complementary Medicine, an organization that aims to improve and disseminate quality systematic reviews related to CAM for widespread public use; this resource is also available at no cost to health professionals and the public and is beneficial since systematic reviews summarize and interpret available clinical trials in the literature (CCM, 2018).

Resources for Locating Evidence on CAM Products

A number of user-friendly databases and resources exist that summarize the most up-to-date evidence for thousands of NHPs. Free, comprehensive, and credible resources that are available to health professionals and the public include NIH's National Centre for Complementary and Alternative Health (NCCIH, 2017b) and American Botanical Council's HerbMed (HerbMed, 2018). An enhanced, more exhaustive version of HerbMed is also available at an additional cost through subscribing (HerbMed, 2018).

Pharmacists commonly report using the Natural Medicines Comprehensive Database (NCMD) to access such information, a database to which a subscription and associated cost is required (Ogbogu and Necyk, 2016; NMCD, 2018). Evidence and functions from both NCMD and Natural Standard have now been combined into the comprehensive database, Natural Medicines (TRC, 2018). The Natural Medicines team, which includes contributors from over 50 institutions, systematically collect data around mechanism of action, dosage, effectiveness, safety, and interactions on an extensive list of NHPs (TRC, 2018). Data are critically appraised and reported based on the relevance, validity, and quality of data available, and updated regularly; such a feature is exceptionally useful for pharmacists who are constrained by time pressures in their work environment (TRC, 2018). Natural Medicines provides practical information that is of interest and use to health professionals (TRC, 2018).

When accessing primary literature related to NHPs, tools utilized to critically appraise RCTs and observational studies such as the Cochrane Risk of Bias Tool (CRBT, 2018), STROBE checklists (STROBE, 2009), and the tools provided within JAMAevidence User's Guide to the Medical Literature: A Manual for Evidence-Based Clinical Practice (JAMAevidence, 2018) also apply and can be very useful. Specific tools for evaluating RCTs related to NHPs have been developed as well (Jurgens et al., 2009).

Where no evidence exists on particular NHPs or CAM treatments, it is important to have a discussion with the patient around the fact that a lack of evidence does not inherently indicate safety and that such products should only be used with caution and close monitoring for effect and toxicity. In the same manner, it is important to relay the message that a lack of available evidence also does not guarantee a lack of efficacy. It may be appropriate to engage in a benefit-risk discussion with the consumer to present alternative therapies, CAM, or conventional, which do have a solid evidence base backing them. Further discussion on how to communicate with individuals around CAM will follow in the next section.

Communicating with Patients about Complementary and Alternative Medicine Use

Before in-depth discussions can take place around CAM treatment options, patients must actually disclose such use or interest in use to their health professionals. Less than half of patients actually disclose NHP use to their physician for reasons including fear of judgment, immediate dismissal of concerns, and fear that their physician knowing may lead to halted access to NHPs on the market (Walji et al., 2010). Interestingly, the single greatest factor that led to disclosure of such use was the physician actually inquiring about NHP use (Busse et al., 2005); however, it has still been found that only 24% of pharmacists ask their patients about CAM use (Tiralongo et al., 2010). Pharmacists should always strive to collect a best possible medication history (BPMH) from all their clients in order to provide accurate, timely, and optimal care to each individual; BPMH guidelines clearly state the need to inquire about CAM use in addition to prescription and OTC drugs (OCP, 2007). CAM inquiries should be adopted as standard practice for all health professionals, but especially pharmacists since NHP use may significantly impact drug therapy.

When CAM use is disclosed or inquired into, it is appropriate for health professionals to engage in a shared decision-making care model when discussing CAM treatments with patients (Elwyn et al., 2012). Shared decision-making is defined as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences" (Elwyn et al., 2010). Often with CAM, health professionals assume that there is not enough evidence to support such treatment and may not actually take the time to search available databases and literature to support such a blanket recommendation. It is important to remember that we do not have to agree with our patients' choices to effectively communicate with them around that choice (Verhoef et al., 2008). If a client is considering CAM and taking the time to ask for advice, it is important to reciprocate with a fair search for available evidence in order to engage in an accurate discussion around the evidence. Listening to your patient and engaging in shared decision-making can go a long way in building a strong therapeutic relationship. It is through these actions and refraining from judgment that pharmacists can promote appropriate and safe use of CAM and prevent AEs related to specific products and interactions with other medications. Such an approach aligns with the WHO Traditional Medicine Strategy that advocates to "promote therapeutically sound use of appropriate traditional medicine by practitioners and consumers" (WHO, 2013b).

Conclusion

CAM use is prevalent and increasing each year worldwide. It is important for pharmacists and other health professionals to be aware of the regulations, safety considerations, and evidence behind such use in order to engage in shared decision-making models with their patients and to promote patient safety. Effective communication and adequate knowledge around CAM is pertinent to building strong therapeutic relationships with patients, as many individuals consider pharmacists frontline to providing accurate education around CAM use, especially NHPs. A variety of evidence-based resources and databases are available to pharmacists to gain additional expertise and information around CAM efficacy and safety.

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Prevention and Management of Substance Misuse and Addiction in Pharmacy Practice

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Introduction

The health burden of substance misuse and addiction are major causes of disability and premature loss of life globally (Peacock et al., 2018). Pharmacists play a key role in optimizing pharmacotherapy in the management of alcohol, nicotine, and opioid use disorders, as well as in the prevention, monitoring, detection, and treatment of medication use disorders that arise during the therapeutic use of pharmaceutical products, for example, opioids, benzodiazepines, and medical cannabinoids. Health professionals report frequently identifying addiction to medications among patients, including those with long-term pain, mental health problems, sleep disorders, and other substance use disorders, but also report that these addictions are often not addressed (Hagemeier et al., 2016). The prevalence of use of these substances is extremely high (Peacock et al., 2018); therefore, pharmacists can expect to be presented with opportunities to help people prevent or manage substance use disorders as part of everyday practice. The primary role of pharmacists in clinical practice is to prevent, identify, and resolve drug-related problems. With this unique knowledge, skills, and responsibilities, the profession needs to take a lead role and actively engage in being part of the solution to the clinical problem of substance misuse and addiction.

Terminology in the addictions field can be confusing. Certain terms can go in and out of favor and there are often no standardized definitions. The term "addiction" has a long history, is generally understood, and is used interchangeably with terms such as dependency or habit. However, it is important to recognize that addiction is more than the development of physical dependence (i.e., tolerance to a substance or the presence of a withdrawal syndrome when use is reduced). Addiction has features reflecting difficulties in controlling use, continuing use despite knowing it is causing harm, and use of the substance taking priority over other aspects of life. It may or may not include physical dependence (American Psychiatric Association, 2013). As understanding the nature of addiction has progressed, so has the acceptance of addiction being a health problem, rather than a moral or criminal issue. However, there remains a pervasive pejorative attitude toward addiction (van Boekel et al., 2013). The term is not used in diagnostic classification systems, instead it is referred to as dependence syndromes or substance use disorders. Likewise, the term "substance abuse" is no longer preferred since it implies the problem lies solely with the person (unlike other health conditions), rather than the reinforcing properties of the substance itself (Broyles et al., 2014). Therefore, terms such as use or misuse are being used, where misuse reflects use that is associated with greater risk of harm.

Although there is a limited repertoire of pharmacotherapy options for substance use disorders, focused research continues to expand the field. It is accepted in many jurisdictions that pharmacotherapy is primary in the treatment of opioid use disorder (e.g., methadone, buprenorphine), with psychosocial interventions having an important supporting role. For all other substance use disorders at this time, psychosocial interventions are primary, with adjunctive pharmacotherapy options available for some. These include medications for alcohol use disorder (e.g., acamprosate, naltrexone, disulfiram) and smoking cessation (e.g., varenicline, bupropion), as well as medications to manage withdrawal symptoms (e.g., benzodiazepines for alcohol and sedative-hypnotic withdrawal symptoms, nicotine replacement therapy for nicotine withdrawal symptoms). Pharmacists have important roles in the provision of methadone and buprenorphine services in several countries. Likewise, pharmacists have broadly embraced providing some level of service to assist with smoking cessation. These roles could be expanded both in availability and scope, as well as pharmacists could take on a more proactive role in supporting pharmacotherapy for alcohol dependence. In specialty settings for medically assisted management of withdrawal syndromes, pharmacists are involved in the development of protocols, help monitor and adjust withdrawal treatment, monitor and treat general medical needs, and assist in providing patient education on substances. Pharmacists have also provided urine drug testing consultation services to assist providers with interpreting complex results. The patient-centered, clinically focused pharmaceutical care practice model provides an excellent

framework for pharmacists to provide assessments, develop care plans, conduct follow-up evaluations, and work collaboratively with other members of the health-care team.

Several pharmaceutical products have psychotropic properties that are experienced as reinforcing, either by producing pleasurable effects or relieving negative states. Some people may use these medications specifically for these effects, or they may be exposed to them for therapeutic reasons. Pharmacists are at the interface of the supply of these medications and the health-care system. Depending on the jurisdiction, these include both prescription medications (e.g., opioids, benzodiazepines, stimulants, cannabinoids) and nonprescription products (e.g., low-dose codeine products, dextromethorphan, dimenhydrinate). This has resulted in the need for pharmacists to know how to recognize and manage complex patients who may be using medications for therapeutic purposes and developing an addiction to them. The expansion of prescription monitoring programs providing real-time information to pharmacists at point of care can be a significant help clinically in identifying problems, for example, the presence of multiple prescribers or drug–drug interactions. In addition, pharmacists have traditionally played a role in preventing the diversion of prescription medication through their training to detect forged or altered prescriptions. Unfortunately, health-care providers often find it easier to dichotomize people into either "legitimate patients" (assuming that if the patient has an identifiable indication, then they are not at risk of addiction) or "abusers" (assuming there is no therapeutic need). This may do a disservice to everyone. It is likely that most people fall somewhere in between these extremes. Patients may not be monitored for a developing problem, and those labeled as abusers may not have their health problem treated adequately. Pharmacists may be the health-care provider most frequently in contact with these patients. They must be familiar with factors that increase the risk of addiction, have the skills to identify the emergence of addiction, and not miss opportunities for engagement in treatment. In addition, the profession should take on public health stewardship roles for these medications, including, for example, limiting quantities to reduce unused leftover medication, actively promoting safe storage, and accepting returns of unused medication for proper disposal.

There are barriers to pharmacists fully engaging in practice in the area of addictions. These broadly include the presence of pervasive stigma and a lack of robust education on the scientific basis of addiction and clinical management. Taken together, these contribute to pharmacists avoiding the topic with patients, to not treating patients with respect and compassion, and to a lack of confidence in the ability to help (Hagemeier et al., 2016; Matheson et al., 2016).

Stigma refers to negative attitudes (prejudice) and negative behaviors (discrimination) toward people using substances. Negative attitudes may stem from long-standing beliefs and judgments that this is a self-inflicted problem and people are weak for allowing this to happen. As our understanding of the neurobiology of addiction improves, it is clear that exposure to these psychoactive substances causes neurobiological changes that contribute to compulsive use, that the acute rewarding effects are only part of the picture, and brain functions related to learning and memory are key contributors. Some people are more vulnerable than others, based on genetics as well as life experiences and stressors, including other psychiatric comorbidities (Volkow and Boyle, 2018).

There is a recognition that negative attitudes persist in part due to the language used in this field, which reinforces ideas that people are unworthy or "bad." This has led to recommendations for the use of alternative language and a message that "words matter." For example, rather than call someone an "addict" or "abuser," use first person language and say he/she suffers from addiction or a substance use disorder. They are more than their addiction. Do not refer to people as "clean" when they are successful in stopping harmful substance use—the implication is that they were "dirty" before. It is better to indicate they are in recovery. These words can have an impact on the person's self-perception, their willingness to seek help and on their clinical outcomes (Broyles et al., 2014).

Substance use disorders are generally not covered in most undergraduate pharmacy training programs, nor are they a focus of continuing education programs, despite the prevalence of these disorders. Pharmacists who report having education in the area are more likely to interact and feel more confident in their interactions with patients (Lafferty et al., 2006). Education must include the scientific basis of addictions, the evidence-base for pharmacotherapy and other treatment approaches, the development of good communication skills with other health-care team members, and the use of motivational conversations to help guide patients toward behavior change.

Of course, pharmacists are also susceptible to developing substance use disorders, and several aspects of the profession may actually increase the risk (Merlo et al., 2012). Most notably, access can be a key issue in the development and maintenance of an addiction to prescription drugs, in particular. Mechanisms for obtaining drugs from the pharmacy include taking expired drugs awaiting disposal or keeping patients' returned unused medications, changing inventory records to steal drugs, or forging prescriptions. This may be exacerbated by the pharmacist's perception that they are drug experts and can manage their use. Contributory factors may also be stressful work environments and reluctance to seek treatment due to potential professional consequences. Recognition of the problem and confidential access to assessments, treatment, and monitoring are important. A unique challenge in long-term recovery may be the return to a work environment that includes exposure and handling medications, which could serve as triggers for resuming use. In this case, pharmacists may need to seek out professional opportunities that do not involve dispensing, for example, drug information, medication reviews, or other clinical roles.

The follow sections focus specifically on pharmacy practice issues related to opioids, benzodiazepines, alcohol, and nicotine.

Opioids

Opioid medications including, morphine, hydromorphone, hydrocodone, oxycodone and fentanyl, have a significant role to play in the management of acute pain and cancer-related pain (World Health Organization, 2017). For many in developing countries

around the world, appropriate access to opioids for pain relief is often lacking. The vast proportion of all opioids used globally are accessed and consumed by a small subset of the population, particularly by those in North America. Concurrently, there is a need for improved quantity and quality of pharmacological and nonpharmacological options for pain management, particularly for chronic noncancer pain, across the world. However, with access to opioids comes exposure to opioids. All opioids have an inherent risk of misuse because of their ability to activate key reward pathways in the brain. For some people, an opioid addiction or use disorder may occur as a result of a complex interaction between genetic predisposition, concurrent psychiatric conditions, and/or psychosocial factors such as a history of trauma. Individuals who have a current or past history of substance use are likely at highest risk of developing problematic opioid use. As a preventative measure, pharmacists can proactively assess patients' risk prior to dispensing an opioid medication, particularly in a primary care setting. For example, the Opioid Risk Tool is a validated self-report questionnaire that stratifies opioid-naïve patients with pain to an estimated low, moderate, or high level of risk for developing problematic opioid use (Webster and Webster, 2005). This tool stratifies risk based on the patient's age, sex, personal and family history of psychiatric illness, and/or substance use. Clinicians can utilize the score to established individualized monitoring parameters to balance rational access to opioid medications while minimizing risk of iatrogenic opioid-related harms such as opioid addiction, or at least ensuring earlier detection of it (Webster and Webster, 2005). While the Opioid Risk Tool has sufficient sensitivity and specificity, it is worth noting that individuals stratified as being of lower risk can still develop an opioid use disorder, and those who are at high risk could still be provided access to opioids, depending on the indication (e.g., severe acute pain), within a more robust monitoring program.

To decrease acute and long-term harms associated with prescription opioids, pharmacists can recommend or initiate opioid stewardship strategies that promote safe and rational access to opioids. For example, depending on relative scopes of practice, pharmacists may wish to independently, or recommend to prescribers, reduce the quantity of opioids dispensed at a single time. In the context of acute pain, this could mean dispensing three to seven days' worth of medication instead of providing one month's supply of opioids. Similarly, for cancer-related pain management, consider dispensing one month's worth of medication at a time, rather than 3 months' worth. This supports the health and safety of the patient, their family, and their community as it minimizes the risk of overdose and/or diversion. Other examples of opioid stewardship include encouraging safe storage of medications and employment of a 'take-back' program of unused medications, with a particular focus on opioids and other narcotic or controlled substances.

In jurisdictions where access to codeine can be obtained without a prescription (frequently at low doses per dosage form), pharmacists may have an even more crucial role to play with respect to ensuring rational access to opioids and monitoring for effectiveness and safety. While codeine may be considered a "weak" opioid, problematic use does occur with its exposure. In fact, likely because of its relative low potency and lower risk in overdose, and thus the increased access or prescription of it relative to other opioids, codeine poses a significant public health issue that is frequently under recognized (Nielsen and Van Hout, 2017). Furthermore, medical complications can arise from its use and overuse as it is frequently combined with other analgesics that may produce gastric bleeding (when combined with nonsteroidal anti-inflammatory drugs) or hepatotoxicity (when combined with acetaminophen).

For all medications with abuse liability, including opioids, pharmacists should regularly monitor for requests for early refills, multiple prescriptions from different health-care providers, altering the medication's dosage form (e.g., chewing and swallowing tablet as opposed to ingesting it whole), and/or acquiring them from nonmedical sources. While these signs are not diagnostic of an opioid addiction or use disorder, they can be signals that a patient is having poorly managed physical or mental pain and/or problematic opioid use. When these signs are observed, wherever possible, pharmacists should take a patient-centred approach to care by providing an objective assessment of the behavior to appropriately triage and refer, where needed. This contrasts a paternalistic approach, which may be punitive, judgmental or stigmatizing. One way to prioritize the patient's health and well-being and maintain a therapeutic alliance is to ask "how" and "why" questions related to the behavior, as opposed to the individual. For example, asking the patient about why they think their opioid use has increased over a short period of time, or how much time per week they spend acquiring new prescriptions from various practitioners.

More formally, as with other substance use disorders, opioid use disorder (or addiction) is characterized by impaired control, social impairment, risky use, and physical dependence (i.e., tolerance and/or withdrawal) (American Psychiatric Association, 2013). For individuals who are using opioids under medical supervision, a diagnosis of opioid use disorder or addiction cannot be made based on the presence of physical dependence via withdrawal symptoms or tolerance (decrease in effects with continued use at the same dose) (American Psychiatric Association, 2013). Both are expected with regular use of opioids, regardless of reason for use. Opioid withdrawal is characterized by signs and symptoms such as sweating, increased pupil size, runny nose or tearing, gastrointestinal upset, tremor, and anxiety or irritability (American Psychiatric Association, 2013).

Pharmacists can support all patients receiving opioid therapy by distinguishing between physical dependence and an opioid use disorder or addiction. Fear of developing an opioid use disorder may prevent some individuals who have an appropriate indication for opioid therapy from using it, even with an appropriate monitoring plan in place. The risk of iatrogenic complications associated with opioid use needs to be balanced with under treatment of syndromes such as acute pain, which may then progress to chronic pain.

In individuals who develop a moderate to severe opioid use disorder to nonprescription or prescription opioids, and/or illicit opioids such as heroin, opioid agonist treatment with methadone or buprenorphine should be initiated as soon as possible and for as long as the treatment is beneficial for the patient. While adjunct psychosocial support is preferred, it should not be a stipulation of accessing pharmacological treatment given its strong evidence base. Given the high rates of relapse associated with abstinence based

therapy, simply managing an individual's acute opioid withdrawal symptoms does not equate treatment of the opioid use disorder. In fact, solely offering or promoting "detoxification" from opioids may elevate an individuals' risk of death when relapse to opioid use occurs in the context of decreased tolerance (Sordo et al., 2017).

Methadone and buprenorphine are considered first-line medications to treat opioid use disorders. Based on their evidence in reducing mortality, improving treatment retention, reducing spread of blood-borne illnesses, and decreased rates of illicit opioid use, both forms of opioid agonist treatment are considered essential medications by the World Health Organization. In fact, other than nicotine replacement therapy, methadone and buprenorphine are the only medications on the list of essential "medicines for disorders due to psychoactive substance use" (World Health Organization, 2017).

Methadone is a synthetic, long-acting, full agonist at key opioid receptors. Over decades of research and use, there is extensive clinical and epidemiological evidence supporting its role in improving individuals' physical and mental health, social functioning, and quality of life. Through once daily oral ingestion of methadone, once an effective individualized dose is achieved, methadone diminishes the effects of other opioids, and its long half-life breaks the cycle of negative reinforcement by preventing the onset of opioid withdrawal symptoms. For pregnant women with an opioid use disorder, methadone protects both the mother and the developing fetus from obstetrical and fetal complications associated with unpredictable yet frequent changes in opioid concentration (Terplan et al., 2018).

Buprenorphine is a relatively newer treatment for opioid addiction. It is a partial mu-receptor agonist that is frequently formulated with naloxone, an opioid antagonist, to minimize misuse via injection or insufflation. Due to safety benefits conferred by its mechanism of action as a partial-agonist, buprenorphine can be quickly titrated to a stable dose, and is preferred in individuals who might be at risk of experiencing adverse effects with methadone, a full opioid agonist. This would include individuals who have prolonged QTc intervals, baseline respiratory illness, severe constipation, and/or concurrently taking central nervous system depressant medications or substances. Anecdotally, buprenorphine is also considered to have less of an association with stigma. As such, buprenorphine may be used first when initiating pharmacotherapy for treatment-naïve individuals with an opioid addiction. Due to its partial mu-receptor agonist action, individuals should be in at least moderate opioid withdrawal before the first buprenorphine dose to prevent the risk of precipitated withdrawal. One frequently used scale to help in this assessment in clinical practice is the Clinical Opiate Withdrawal Scale (COWS) (Wesson and Ling, 2003).

Both methadone and buprenorphine treatment typically occur as part of a structured dispensing process. Specifically, patients usually present to a health clinic or pharmacy for daily observed doses, particularly during treatment initiation. While this structure likely minimizes the risk of diversion and supports closer monitoring of opioid agonist treatment effectiveness and safety, mandating individuals to present for daily doses can be viewed as stigmatizing, onerous on patients, and deter their motivation to participate in treatment. Wherever possible, arrangements should be made to promote easier access to methadone and buprenorphine, for example, for the patient to receive dosing at a nearby pharmacy or clinic of their choice as opposed to one that is physically geographically challenging to get to. Additionally, like any other patient, all patients with an opioid use disorder presenting to the clinic or pharmacy should be treated with respect. This is particularly important for patients with an opioid use disorder as they often have been stigmatized by their family, community, and by other health-care professionals who have written them off as "drug-seeking" or "weak" for not being able to "deal with their habit." Witnessed or observed doses can be particularly contentious as it may be perceived as mistrust between the medical community and the individual; the clinician may have to ask to look underneath the patient's tongue to check of dissolution of buprenorphine tablets, for example. To emphasize respect and empathy, individuals should be offered a seat in a private area to take their methadone or buprenorphine dose, while still being witnessed by a pharmacist or health-care provider (Isaac and Sproule, 2009).

As mentioned previously, the length of opioid agonist treatment depends on the patient and their goals of therapy. In general, longer durations of treatment are associated with better outcomes for patients (Barrio, 2017). It provides patients with an opportunity to build resilience and address contributing factors to their substance use disorder, including trauma or concurrent psychiatric illness. If or when patients wish to taper off of opioid agonist treatment, longer, flexible, and individualized tapers lead to better patient outcomes as compared to short tapers (Sordo et al., 2017).

Regardless of what individuals choose with respect to treatment for their opioid use disorder, harm reduction strategies should be offered in conjunction with pharmacological and nonpharmacological resources. Naloxone is a pure opioid antagonist that is indicated for use in emergency situations to temporarily reverse the potentially fatal effects of an opioid overdose. Evidence has shown that take-home naloxone kits decrease overdose mortality with minimal adverse effects (McDonald and Strang, 2016). In some jurisdictions where pharmacists can provide take-home naloxone kits pursuant to a prescription, or more independently via a medical directive, or without a prescription at all, pharmacists can provide crucial information related to opioid overdose prevention, along with how to respond to an opioid overdose. Take-home naloxone kits should also be recommended to caregivers of, and individuals who are taking opioids for pain management as they are at risk of experiencing an opioid overdose or poisoning as well, particularly if they are on other central nervous system depressants or using high doses of morphine or equivalent. Other harm reduction strategies are discussed in further depth later in the chapter.

Sedative–Hypnotics

Sedatives (drugs that tend to calm or soothe) and hypnotics (drugs that produce sleep) are widely used in clinical practice. They are also frequently used on a long-term basis with little evidence to support this practice. These medications include, for example,

benzodiazepines (e.g., lorazepam, alprazolam, diazepam), "z-drugs" (e.g., zopiclone, zolpidem), and barbiturates. The use of barbiturates for sedation has largely been replaced by benzodiazepines due to their better safety profile. By comparison, benzodiazepines are safer in overdose, have a less severe withdrawal syndrome, and have a lower abuse liability. Benzodiazepines are used therapeutically for sleep disorders, anxiety and mood disorders, alcohol withdrawal, and for aggressive behaviors in psychosis. They also have muscle relaxant and anticonvulsant properties. Although safer than older sedative-hypnotics, benzodiazepines can cause cognitive and coordination problems, psychomotor impairment, physical dependence, and addiction (Lader, 2011). They are frequently prescribed for patients at increased risk of adverse effects, including those with substance use disorders, or taking other CNS depressant medications (e.g., opioids) (Kroll et al., 2016; O'Brien et al., 2017). They are recommended primarily as adjunctive therapy short-term early in treatment to help acute symptoms while the primary treatments (both pharmacological and nonpharmacological) reach their full effect.

The question remains, why is long-term use so prevalent? Do they continue to be effective, or is it due to the development of physical dependence or addiction? Regular use at therapeutic doses can produce physical dependence. It may be that the emergence of withdrawal symptoms drives continued use. Patients may interpret symptoms experienced at the end of dosing intervals, with missed doses, or when their dose is decreased as proof that the medication is still needed. Although not all patients experience symptoms when discontinuing long-term benzodiazepine use, many people report anxiety, insomnia, restlessness, agitation, and irritability. Less frequently symptoms could include nausea, lethargy, blurred vision, aches and pains, and ataxia (Busto et al., 1986). Rarely serious symptoms are experienced such as seizures, psychosis, and tinnitus (Lader, 2011). The more serious symptoms, particularly withdrawal seizures, are more likely after abrupt discontinuation of high doses. Overall, it is recommended that benzodiazepines should not be abruptly discontinued, but tapered slowly, often over several months (Pottie et al., 2018). In practice, pharmacists should be continually evaluating long-term benzodiazepine use, communicating with patients and prescribers, balancing the risks and perceived benefits, and encouraging initiation of a taper. When managing a taper, it is important to let patients know what to expect, particularly that withdrawal symptoms are temporary.

Beyond physical dependence, some people develop an addiction to sedative-hypnotics. There are recreational drug users that use high doses of these drugs. They are often used by individuals who use other substances (Busto et al., 1996). For example, those with a past history of alcohol dependence are also more likely to become dependent on benzodiazepines. They are also one of the most common drugs to test positive in urine drug screens of patients on opioid agonist therapy (Heikman et al., 2016). They may be part of a polysubstance use pattern, or used when drugs of choice are not available. There are no pharmacotherapy options for the treatment of sedative-hypnotic addiction. Tapering strategies are used to manage withdrawal symptoms, and nonpharmacological therapies are the mainstay. In cases of multiple substance use, tapering may be initiated in inpatient medically assisted withdrawal settings; however, longer-term tapering may still be required. Pharmacists have a role in the development, implementation, and monitoring of tapering regimens, especially in a multidisciplinary environment.

Alcohol

Worldwide, almost one in five of the adult population engage in heavy episodic alcohol drinking (Peacock et al., 2018). In general, countries that have greater economic wealth have more people consuming alcohol and fewer abstainers. Approximately 5% of the global burden of disease and injury have been attributed to alcohol consumption (Global Burden of Disease Collaborators, 2018). All levels of government have instituted policies to help reduce the harmful use of alcohol.

In clinical practice, pharmacists have the opportunity to respond to several common clinical presentations of alcohol dependence. These presentations include patients experiencing alcohol withdrawal symptoms, those seeking help to reduce or stop drinking alcohol, and those experiencing medical complications due to alcohol use.

Alcohol withdrawal symptoms are common among those drinking more than 40 standard drinks per week on a regular basis (Butt et al., 2011). Although not needed for all patients, the goals of pharmacotherapy for alcohol withdrawal are to prevent the life-threatening symptoms (seizures, delirium tremens), reduce other symptoms such as autonomic hyperactivity, anxiety, and nausea/vomiting. Benzodiazepines are very effective in treating withdrawal symptoms due to cross tolerance with alcohol (Amato et al., 2010). Protocols where benzodiazepines are administered using a "symptom" triggered approach, particularly with an initial dosing load that matches the patient's level of tolerance have been shown to be effective (Devenyi and Harrison, 1985; Soravia et al., 2018). The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) is a validated, commonly used scale to guide medication needs (Sullivan et al., 1989). In addition, routine administration of thiamine helps to prevent Wernicke's encephalopathy, the symptoms of which could be missed during withdrawal (Chandrakumar et al., 2018).

For those seeking help to maintain abstinence and prevent relapse, acamprosate and naltrexone are options for adjunctive treatment that are thought to work by helping with cravings and reducing rewarding effects. They have very different mechanisms of action and unique features that help guide decision-making with patients. Disulfiram is an older medication that produces an aversive reaction when alcohol is consumed. The efficacy of this medication has not been well established in clinical trials; however, it may be helpful for some patients. Pharmacists can make two key contributions in the treatment of alcohol dependence. One is to advocate for the use of these medications when appropriate—they are not as widely used as they may be indicated, particularly in primary care settings. The other is to work with patients to promote adherence. Nonadherence is common and has been linked to poorer outcomes. Regular interactions and exploring ambivalence using techniques such as motivational interviewing may be helpful. Psychosocial interventions are key in the treatment of alcohol dependence. Approaches such as cognitive-behavioral

therapy focus on dysfunctional beliefs toward alcohol use and help to modify this. Options include individual or group therapy, family therapy (in outpatient or residential settings), and self-help groups (Ray et al., 2018).

Patients also seek health care for the medical complications of alcohol use, whether or not the attribution to alcohol has been made or acknowledged. These complications can be quite varied and include, but are not limited to, liver disease (fatty liver, hepatitis, and cirrhosis), esophageal varices, Wernicke's encephalopathy, Korsakoff's dementia, peripheral neuropathy, sleep disorders, hemorrhagic stroke, cardiomyopathy, arrhythmias, and impotence (Butt et al., 2011). Clinical assessments for these conditions must include a determination of the contribution of alcohol consumption to the clinical picture.

Many countries have instituted low-risk drinking guidelines. These are comprised of daily, weekly, and/or per episode recommended consumption limits, generally in the range of 2–3 drinks per day for men, and 1-2 drinks per day for women, with drink sizes ranging from 8 to 14 g of alcohol (Butt et al., 2011). A clinically useful definition of problem drinking includes regularly drinking above the guidelines and developing a social or physical problem as a result, without meeting the threshold for a diagnosis of alcohol dependence. In practice, people may not recognize their alcohol consumption is risky, if the patterns appear normal based on their peer group, for example. Reframing this within the context of what is "normal" or less risky may be helpful. The four-item screening test for alcohol problems (the CAGE) is a simple, validated clinical tool (King, 1986). The questions are Have you ever felt you ought to ***C***ut down on your drinking?; Have people ***A***nnoyed you by criticizing your drinking?; Have you ever felt bad or ***G***uilty about your drinking?; Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (***E***ye opener)? A "yes" response to two or more of these questions is suggestive of alcohol problems requiring further evaluation.

Routine screening and brief interventions (SBIs) in primary care or emergency department settings have a good evidence base for reducing alcohol-related harms (Wamsley et al., 2018). Research from several countries in pharmacy settings indicate that patients across the spectrum of alcohol use support involvement of pharmacists in reducing alcohol use and endorse the appropriateness of pharmacists to serve in this public health role (Dhital, 2010, Sheridan, 2012, Hattingh, 2016, Mackridge 2016, Fitzgerald 2015). Pharmacists are also express willingness to take on this further scope of practice, with some evidence for effectiveness (Fitzgerald, 2009, Horsfield, 2012, Khan, 2013). SBI in pharmacy settings often included used of the AUDIT C and a recent drinking history, followed by provision of feedback and advice. The service may also include providing referrals for further assessment and treatment (also known as SBIRT). People identified with higher risk are referred to their general practitioner or to specialized alcohol services. Factors influencing the success of the brief intervention approach include pharmacist attitudes (e.g., perception that alcohol is a sensitive topic) and lack of confidence and training in brief motivational discussions (Horsfield, 2012, Brown, 2014). It has been shown that pharmacists can be trained to deliver the service and those with more a positive attitude provide more brief interventions (Dhital, 2013).

Smoking Cessation

It has been estimated that approximately 15% of the adult population smoke tobacco daily (Peacock et al., 2018). Tobacco smoking has the highest burden of disease among substances (Peacock et al., 2018). The many health risks for people who smoke include cardiovascular diseases, several types of cancer, respiratory diseases, erectile dysfunction in men, and menstrual and pregnancy problems for women such as premature delivery and low birth weight babies. Successful interventions exist, both pharmacological and nonpharmacological, with combinations recommended. Nicotine replacement therapy (NRT), bupropion, and varenicline are the three first-line pharmacotherapy options recommended, with varenicline having the largest effect (Cahill et al., 2013). The choice of agent is based on patient preference and the clinical situation.

Nicotine replacement therapy is generally a safe choice since a regular smoker is already exposed to nicotine; however, the pharmacological nicotine products eliminate the risk of exposure to the harmful constituents in tobacco. Therefore, it is a better way to deliver nicotine to manage nicotine withdrawal symptoms. The nicotine patch in particular helps provide a more even exposure to nicotine with gradual reduction, avoiding the extreme peak and trough nicotine levels associated with smoking cigarettes. Combining nicotine patch treatment with other forms of NRT is reasonable with titrating the nicotine dose early in therapy, to provide options for faster onset products to help at times of severe craving, or based on patient preference to provide flexibility in choosing different products for different situations. Sometimes NRT can be used to help reduce smoking as a harm reduction approach. Earlier concerns regarding cardiovascular adverse events from smoking while on NRT have been dismissed. NRT, varenicline, and bupropion are all considered safe treatment options in patients with cardiovascular disease. (Benowitz et al., 2018) There has also been concern over neuropsychiatric adverse effects such as suicidality and aggression, but it is unlikely to occur, particularly in those without psychiatric disorders. For those with psychiatric disorders, it is less clear and they may have a small increased risk requiring close monitoring (Anthenelli et al., 2016). All three first-line agents are efficacious in patients with psychiatric disorders. This is important because this population has a higher rate of smoking than the general population (Lawrence et al., 2009). Other clinical factors can be considered in recommending an agent, for example, if the patient is at increased risk for seizures, then bupropion is not a good option. Likewise, varenicline may be less desirable in someone with poor renal function. Other comorbidities and concomitant medications must also be considered.

Although successful interventions exist, there is a need for more health-care practitioners to provide smoking cessation interventions. When surveyed, pharmacists see themselves as having a role in providing cessation support to their patients (Ashley et al., 2007). Pharmacists are generally very accessible health professionals and often a primary source of contact for smokers seeking advice on quitting smoking. In addition, community pharmacists are able to simultaneously provide both smoking cessation

interventions and NRT to smokers who want to quit. In some jurisdictions, pharmacists can initiate varenicline and bupropion. Increasing the utilization of pharmacists in smoking cessation activities may have a positive impact on reducing smoking rates at the population level.

All health-care providers, including pharmacists, should document the smoking status of patients and clearly advise those that smoke to quit. Patients should also be assessed for their interest in stopping smoking. A readiness to quit assessment can be as simple as asking the patient to indicate both their desire and confidence in quitting on a 10-point scale. Those willing to begin treatment should be offered assistance. Although any level of intervention can be helpful, the more intensive the intervention the patient receives (i.e., session length, number of sessions) the more it is effective (Stead et al., 2015). Patients can be offered a variety of supports, for example, self-help print or Internet-based resources, and individual or group sessions, in combination with pharmacotherapy. Motivational interviewing approaches to guide and encourage patients can be effective (Lindson-Hawley et al., 2015). Patients should have regular follow-up and support as needed.

When pharmacists are working with patients to initiate pharmacotherapy, there are several key additional considerations to take into account, in addition to usual factors weighed when making recommendations to prescribers (e.g., drug interactions, renal function, past responses), particularly when independently initiating varenicline or bupropion. When assuming responsibility for treatment with these agents, it is important to consider how well-known the patient is in order to be confident that it will be possible to provide adequate monitoring and follow-up, or that there is confidence that the patient will be in contact if an adverse effect develops. A risk evaluation is part of the clinical decision-making process. A comprehensive history and good clinical documentation is essential.

Evaluations of pharmacist-led smoking cessation services have included interventions ranging from providing minimal education to pharmacy personnel to providing comprehensive three- to four-month structured pharmacist-led programs. These programs have taken place in community pharmacies and, hospital settings, in person or by telephone, with prescriptive authority or not, and in groups or individual sessions. In general, these studies provide support for pharmacists delivering effective smoking cessation interventions in a variety of settings (Mdege, 2014, Dobrinas et al., 2014).

Harm Reduction

Harm reduction is often described as health or social initiatives aimed to reduce negative consequences of alcohol or drug use, without requiring individuals reduce or abstain from drug use (Thomas, 2005). Harm reduction does not equal approval of drug use. Instead, it is pragmatic and accepts that drug consumption does occur within a society and that individuals act autonomously in making decisions about drug use (Thomas, 2005).

Social initiatives aimed to reduce drug-related harms may include decriminalization or legalization of substance possession or consumption such that individuals who use drugs are less likely to receive a criminal record, and therefore, the downstream negative consequences that carries (Thomas, 2005). Alternatively, opioid-related mortality can decrease with relatively smaller changes in legislation. This includes improving access to take-home naloxone kits by delisting it as a prescription drug, or by offering protection for individuals who require or seek emergency help during an overdose to reduce fear of police and to encourage activation of emergency first responders (Health Canada, 2018).

With respect to reduction of other health-related harms, there is a vast amount of literature highlighting the cost-effectiveness of connecting individuals using substances to biopsychosocial support and treatment, as opposed to the criminal justice system.

To apply harm reduction principles, pharmacists must first ascertain whether or not their patient uses alcohol and/or other substances. While this may initially be a challenging question to ask given the shame that society frequently casts on individuals with drug use, pharmacists who incorporate this within their standard assessment simultaneously collect richer information about the patient and destigmatize drug and substance use. As much as possible, this information should be collected in a private area and kept confidential. Considering the profound impact of words, pharmacists should be mindful of what they say and how they say it. Using patronizing language such as "I don't think you use drugs, but I have to ask, are you using anything else other than alcohol?" is presumptive and closes the door to a more meaningful conversation about substance use. Instead, open the dialogue by stating "Many people use drugs or substances. These may impact their health or some of the medications they're on" to provide context for the question, and to build trust and engagement. This can be followed by, "Are you using anything other than alcohol?."

While abstinence is the only way to prevent negative consequences associated with drug use, for individuals who cannot or do not wish to abstain from substance use, pharmacists can apply recommendations from guidelines that promote lower-risk substance use. For example, in the context of alcohol use, while total abstinence is preferred, avoiding alcohol use in certain situations such as prior to, or during driving, can significantly reduce rates of motor vehicle accidents. By avoiding binge drinking and keeping alcohol use to a maximum of a few drinks per day, and having alcohol-free days during a week, patients can significantly reduce acute and long-term complications of alcohol use including cirrhosis, and a whole host of cancers (Global Burden of Disease Collaborators, 2018). To reduce the psychoactive effects of cannabis, pharmacists may advise individuals who wish to continue using cannabis to use strains of lower delta-9-tetrahydrocannabinol (THC) potency. Individuals may also reduce their exposure to carcinogenic chemicals by vaping, instead of smoking. Similar to alcohol use, individuals who use cannabis should be advised to avoid driving for several hours after cannabis use and to avoid using it with other central nervous system depressants (Fischer et al., 2017).

In the context of injection drug use, evidence-based harm reduction strategies decrease rates of blood-borne illnesses by making drug consumption supplies readily and freely available (e.g., needles and sterile water for injection) and by taking back used supplies. Other initiatives include improved access to legally sanctioned supervised drug consumption sites where individuals use drugs with the supervision of health-care providers who can respond quickly to any medical or psychiatric complications from drug consumption and connect individuals with harm reduction supplies or substance use disorder treatment. In particular, supervised injection sites have demonstrated lower rates of overdose mortality for people living within its vicinity, as well as reduced rates of ambulance calls to treat overdoses, reduced rates of cutaneous injection-related infections, and reduced rates of Human Immunodeficiency Virus (HIV) infection. Importantly, the presence of supervised injection sites has not been demonstrated to increase drug use or trafficking in nearby areas (Potier et al., 2014).

Given the relative ease of access to pharmacies, and therefore pharmacists, public, and preventative health initiatives promoting harm reduction could integrate well within pharmacy practice. One frequently cited example in the literature is pharmacists' involvement in reducing the harms associated with injection drug use, namely, transmission of HIV and Hepatitis C Virus (HCV). In some jurisdictions, pharmacists may be informally, and perhaps unconsciously, involved in reducing harms of injection drug use through selling needles to decrease transmission of blood-borne illnesses. However, legal restrictions may impede a pharmacist's ability to support these initiatives. For example, some jurisdictions prohibit pharmacists from distributing or selling sterile needles without a prescription and/or confirmation that the patient has a qualifying illness such as insulin-dependent diabetes. Other barriers to implementing harm reduction strategies may include lack of remuneration for services and/or supplies and insufficient education and training about substance use and harm reduction (Watson and Hughes, 2012). Simultaneously, pharmacists may consciously or unconsciously hold stigmatizing views on individuals who use drugs, which may present as fear of attracting the "wrong clientele" to their practice setting, or overlook the applicability of harm reduction to their current patients (Watson and Hughes, 2012).

As a key point of contact, pharmacists also play an important role in referring patients, and their caregivers, to other health-care provider and community resources. Pharmacists should be aware of local public health centers that provide harm reduction supplies, addiction treatment centers and supervised injection sites, where available.

Conclusion

The health burden of substance misuse and addiction are major causes of disability and premature loss of life globally. Pharmacists play a key role in optimizing pharmacotherapy in the management of alcohol, nicotine, and opioid use disorders. Pharmacists also have an important role in the prevention, monitoring, detection, and treatment of medication use disorders that arise during the therapeutic use of pharmaceutical products, for example, opioids, benzodiazepines, and medical cannabinoids. In addition, some pharmacists have been involved in screening and brief intervention activities and providing harm reduction services. There are barriers to pharmacists fully engaging in practice in the area of addictions, including the presence of pervasive stigma and a lack of robust education on the scientific basis of addiction and clinical management. Progress has been made in overcoming these hurdles. The prevalence of use of substances is extremely high; therefore, pharmacists can expect to be presented with opportunities to help people prevent or manage substance use disorders as part of everyday practice. With unique knowledge, skills, and responsibilities, the profession of pharmacy needs to take a lead role and actively engage in being part of the solution to the clinical problem of substance misuse and addiction.

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Self-Care/Over-the-Counter Drugs/Minor Ailments in Pharmacy Practice

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Introduction

This chapter introduces the concept of self-care and explores its universal value to healthcare.

The current self-care marketplace, including legislative and regulatory influences, and characteristics common to today's self-care consumers, are described. The expanding role of pharmacists in encouraging safe and effective self-care practices is reviewed, with consideration given to variation between countries. An introduction to the Pharmacists' Patient Care Process, as well as its application to self-care encounters is discussed. Interviewing frameworks and documentation considerations pertaining to self-care are also explored. Other tools to aid pharmacists in self-care recommendations are presented, including those to facilitate the provision of culturally competent care. Throughout this chapter, the term nonprescription replaces over-the-counter (OTC), reflecting formal usage in pharmacy practice—however, in other publications and common parlance, these designations are often used interchangeably. This chapter concludes with a discussion of thoughts on the future of self-care, as it relates to pharmacy.

Self-Care

The History and Evolving Definition

Self-care has been common practice among centuries of human history. There is no single definition of self-care that is universally accepted in the literature, as definitions vary depending on the setting in which the term is used and stakeholders' perspectives (Ausili et al., 2014; Godfrey et al., 2011; Health Canada, 2002; Soller and Mann, 2014). The World Self-Medication Industry (WSMI) defines self-care as "a life-long habit and culture. It is the action individuals take for themselves and their families to stay healthy and take care of minor and long term conditions, based on their knowledge and the information available, and working in collaboration with health and social care professionals where necessary" (WSMI, 2017).

All health-related activity can be described as a continuum (Self Care Forum), with purely self-initiated activities (e.g., preventative healthy lifestyle choices) on one end to fully managed care (e.g., major trauma) on the other (Self Care Forum). Treatment of minor ailments and self-management of long-term conditions are found towards the middle of this scale. Patient and caregiver engagement, understanding and support is essential across the continuum, as Dzau et al. (2017, pp.5) suggest it is associated with patient "health and wellbeing, as well as system efficiency, quality, and overall performance."

In summary, self-care is characterized by individuals who take proactive roles for themselves, on behalf of and with others in order to develop, protect, maintain, and improve their physical and psychological health (Self Care Forum) and involves three core elements: self-care maintenance, self-care monitoring, and self-care management (Riegel et al., 2017; WSMI, 2017).

The Seven Pillars of Self-Care

The International Self-Care Foundation (ISF) holistically illustrates the entire range of self-care activities and many possible entry points for self-care in their seven pillars framework (Fig. 1). It is known that unhealthy behaviors—smoking, excessive alcohol consumption, poor diet and insufficient exercise—tend to 'cluster' together in individuals and particular parts of a population (Nakhla, 2018). Interestingly, healthy behaviors in the seven pillars also cluster together. This implies that if a person is motivated towards one self-care aspect (e.g., smoking cessation), they may also be more strongly disposed towards undertaking other healthy behaviors (e.g., losing weight) (ISF, 2017). Clinicians can use this approach to better understand patients' self-care practices and to tailor specific interventions aimed at improving one or more of the domains (Nakhla, 2018).

It should be emphasized that while the seven pillars framework is designed to describe the entire range of self-care activities, individual circumstances, and country conditions mean that self-care practices vary considerably around the world. Self-care practices in resource-poor countries are inevitably somewhat different to those of richer countries, for example.

Minor Ailments

Minor ailments (also known as common ailments, common conditions, minor illnesses, self-limiting conditions, self-treatable conditions, and ambulatory conditions) are defined as "common or self-limiting or uncomplicated conditions which can be diagnosed and managed without medical intervention" (Paudyal et al., 2013). These conditions represent an important aspect of self-care, given that the public is more apt to self-treat such ailments (Nakhla, 2018). The most prevalent problems cited in the literature can be categorized into four therapeutic areas: pain disorders (e.g., headaches, musculoskeletal), respiratory issues (e.g., coughs, colds), skin conditions (e.g., acne) and gastrointestinal disturbances (e.g., indigestion) (Fielding et al., 2015; Rutter, 2015; Self Care Forum, 2018; Taylor and Joubert, 2016).

When people feel ill, a complex process is initiated to determine how best to return to health. This includes an assessment of symptom severity and the impact on day-to-day life, all within the context of their present health, social circumstances, finances, and other forces (Nakhla, 2018) Several paths could be followed: do nothing (wait-and-see approach), use a nondrug measure, take medication, or seek professional medical care (Taylor, 2013). In the United States (US), a recent survey found that 93% of adults prefer to treat minor ailments with nonprescription medications before seeking professional care (Consumer Healthcare Products Association, 2010). In the United Kingdom (UK), 87% of people report self-treating minor ailments often, with 42% saying they do

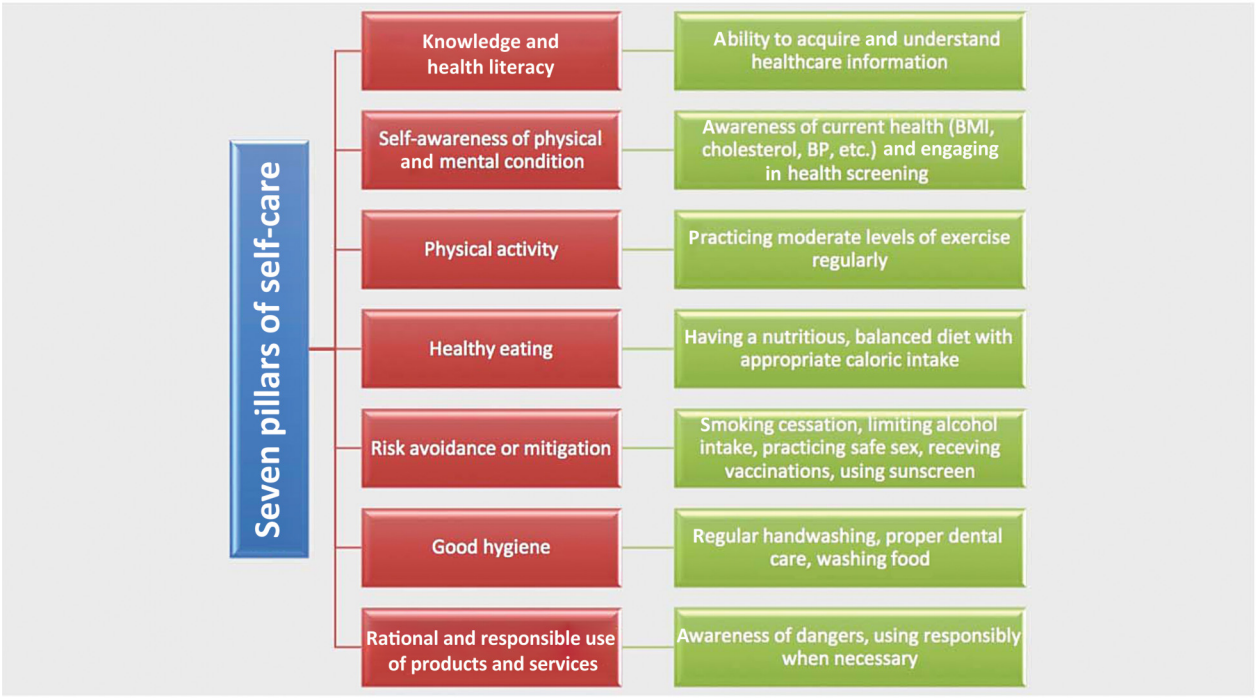

Figure 1 The seven pillars of self-care. *Source: Adapted from ISF, 2017. The seven pillars of self-care. International Self-Care Foundation (ISF). Available from: http://isfglobal.org/practise-self-care/the-seven-pillars-of-self-care/; Webber, D., Guo, Z., Mann, S., 2013. Self-Care in Health: We can define it, but should we also measure it? SelfCare, 4, 101–206.*

it all the time (Department of Health (UK), 2005). Despite this, minor ailments consultations in general practice cost an alarming £2 billion annually (Paudyal et al., 2013) and take up, on average, an hour a day for every general practitioner (GP) (Self Care Forum). As such, minor ailment consultations still present a major burden on higher cost healthcare settings; uncertainty about the services and treatments available from pharmacies exists with patients and HCPs, therefore, effective strategies are required to raise awareness regarding conditions that can be effectively managed by pharmacists and to assist patients in changing these health-seeking behaviors (Fielding et al., 2015).

It is imperative to note that although discussions of self-care and minor illness often go hand in hand, they are not the same. As alluded to above, self-care refers to the broad approach taken for the specific ailment, be it minor or otherwise (Taylor, 2013). For example, a person who rests and drinks warm fluids when they have a cold is engaging in self-care for a minor ailment, whereas a person who elevates their feet to alleviate swelling in heart failure is practicing self-care for a more serious, chronic condition (Taylor, 2013). A minor ailment, on the other hand, is the target illness itself when considered common, self-limiting or uncomplicated (Paudyal et al., 2013). Recognition is growing that promotion of self-care is considered a crucial factor for chronically ill patients' care (Ausili et al., 2014).

Understanding Today's Self-Care Landscape

Consumers today are increasingly driven and empowered to manage their health using self-care. According to a 2014 survey by the National Council on Patient Information and Education (NCPIE) and Pfizer Consumer Healthcare, most individuals agree that nonprescription products are an important tool to better manage one's health and to address health issues quickly (NCPIE, 2014). Furthermore, a 2013 survey showed that almost 98% of primary care physicians, nurse practitioners, and pharmacists recommend nonprescription medicines to their patients, with 84% of consumers saying they trust their HCP's recommendations (CHPA, 2013).

Self-Medication

Self-medication is a key component of self-care and is defined as the selection and use of medications – legally classified as drugs specifically designed and labeled for use without medical supervision and approved as safe and effective if used as directed for such use—by individuals to treat self-recognized illnesses or symptoms (Brown et al., 2013; Rutter, 2015; WSMI, 2017). Self-care medications are often called 'nonprescription' or 'OTC' and are available without a prescription. In some countries, nonprescription products are also available in other retail outlets (e.g., supermarkets, gas stations) and are commonly self-selected

by the public. Three general categories of products are available for self-medication: (1) Nonprescription medications, (2) dietary supplements, and (3) complementary and alternative medicines (CAMs). This chapter will focus on nonprescription medications.

While the common practice of self-medication has been around long before pills came into existence, there has been steep growth in self-medication practices globally as both HCPs and consumers recognize the value and cost savings that nonprescription products offer. US data show that 81% of US adults use nonprescription products as a first response to minor ailments, and off-the-shelf availability of these medicines provides symptomatic relief for an estimated sixty million people who otherwise would not seek treatment (CHPA, 2017b). However, choosing nonprescription products continues to be overwhelming for many consumers given the multitude of choices available, not only within each therapeutic class, but between brand, generic and private labels (Sclar et al., 1996).

Facilitated Self-Medication

"Facilitated self-medication" occurs when consumers seek assistance at the point of product purchase. In community pharmacies, pharmacy students/interns or pharmacists are often responsible for this facilitation. Limited research has revealed that recommendations provided by pharmacy staff influence consumer-purchasing decisions (Rutter, 2015). For example, in studies by Nichol et al. (1992) and Sclar et al. (1996), 25.4% and 42.6% of consumers, respectively, altered their nonprescription purchasing decision when proactively approached by pharmacy students. In the study by Sclar et al. (1996, pp.180), these changes reduced product expenditures by an average of US $1.53 per customer (attributable to movement from brand to lower-priced generic or private label equivalents). A notable number of consumers, 13.4% (Nichol et al., 1992) and 8% (Sclar et al., 1996), made no purchase after consultation, which resulted in cost savings and avoidance of errors in self-medication. Furthermore, 1.3% (Nichol et al., 1992) and 4.3% (Sclar et al., 1996) of consumers were referred to a physician after features warranting further medical assessment were identified. This emphasizes the role of pharmacists and pharmacy staff in self-care and highlights an opportunity for ensuring safe and effective self-medication practices. It also accentuates the consumer need for pharmacy consultation and additional product information in order to "optimize both the therapeutic appropriateness of, and pharmaceutical expenditures for, nonprescription medication" (Sclar et al., 1996).

Self-Care Market

Nonprescription medicines are a trusted first line of treatment to alleviate symptoms, with more than two-thirds of consumers preferring to use a nonprescription medication instead of a prescription agent when available (CHPA, 2013). Studies show that certain populations may be more inclined to use nonprescription products—90% of pregnant women, for example, have been reported to use them (Smedberg et al., 2016). Approximately 50% of Polish patients use nonprescription medications for the first time without consulting a pharmacist or physician (Piecuch et al., 2017).

In the US, retail sales of OTC medications and dietary supplements exceeded US$34 billion in 2016, representing a 10-fold increase since 1974 (CHPA, 2017a). In Canada, domestic retail sales of consumer health products have also increased rapidly over the last decade, valuing CAD$5.6 billion in 2014 (CHP Canada, 2017). The global self-care marketplace continues to expand, with well over 100,000 nonprescription products available in the US alone.

Impetus for Continued Growth

Two main trends that have contributed greatly to the expanding self-care market are (1) growing consumerism, and (2) increased healthcare costs and demands.

Various social and health trends have also altered individuals' outlook on health and the way in which they perceive their own health status. Increased access to almost instantaneous, limitless health information via the Internet and mobile, coupled with improved educational levels and subsequent health literacy, has caused a shift towards informed, empowered consumers wishing to become more active in their healthcare. Self-care products provide individuals with the opportunity to take more responsibility for, and become more involved in, their health. The spike in digital health technology has also engaged patients by supporting more personalized and tailored health care (Dzau et al., 2017). For example, mobile phone applications that monitor daily habits, weight fluctuations, steps taken, and calories burned (e.g., MyFitnessPal) are trending (Sarasohn-Kahn, 2013).

Changing demographics worldwide, including a greater number of older adults living longer and with more complex chronic conditions and medication regimens, the provision of medical care is becoming increasingly expensive. In some countries, wait-times, and access to family physicians are concerning. The increasing incidence of noncommunicable diseases, including potentially preventable conditions (e.g., heart disease, diabetes), is also associated with significant disease burden and costs. These rising healthcare costs have led to global healthcare reform, which has included encouraging the public to use effective and cost-efficient self-care. In many countries, self-care has been integrated into public health policy, with the main impetus to divert people from the formal healthcare systems to save resources. These efforts have successfully increased the self-management of conditions by patients, with approximately 80% of all care in the UK now being self-care (Self Care Forum), resulting in a self-care market with immense revenue potential. Also fueling this growth is prescription-to-nonprescription switches (Porteous et al., 2006) (see section, 'Regulatory and Legal Considerations').

The Benefits of Self-Care and Self-Medication

Self-care products play an increasingly important role in the healthcare of millions as they offer symptom relief and disease prevention while providing convenience and affordability to patients. As documented by Brown et al. (2013, pp.113) and several other researchers, "the added convenience of OTC medicines is the primary reason why consumers prefer these products to prescription medicines for the treatment of common health conditions, such as headache, heartburn, and allergies." This accessibility eliminates the stress and inconvenience of GP visits, saving time and money, and reducing lost work productivity. For example, a 2004 European Union study estimated over 16 billion in annual savings from shifting 5% of professional care to self-medication (AESGP, 2012). In the US, every dollar spent on nonprescription medicines saves the healthcare system US $6–7 in avoided costs.

Utilizing self-care can enhance patients' self-care confidence by improving their skill set and empowering them to care for certain conditions on their own, such that GPs are only visited when necessary (Bell et al., 2016). This gives the public greater control over their own health and encourages healthy behaviors that help prevent future illnesses. With other HCPs, namely pharmacists, guiding patients in the self-management of ailments, GPs are able to focus on caring for higher risk patients and managing long-term conditions (Self Care Forum). Canadian industry data shows that if only 16% of Canadians who see the doctor for mild symptoms practiced self-care instead, an additional 500,000 Canadians could have access to a family doctor (Willemsen and Harrington, 2012).

Furthermore, increased personal responsibility around healthcare has been shown to improve people's health and wellbeing (Self Care Forum). In particular, self-care management has been shown to enhance disease-state control, reduce overall health distress, and improve mental health when incorporated into therapy (Marks et al., 2005). For example, Ausili et al. (2017) showed that diabetics engaging in self-care have improved metabolic control, reduced cardiovascular risk, fewer disease-related complications, and enhanced quality of life. Other self-care initiatives with demonstrated success include, but are not limited to, the prevention of cardiovascular disease with lifestyle modifications (e.g., diet and exercise), the use of nicotine replacement therapy for smoking cessation, and the treatment of lice infestations with nonprescription medications.

In summary, empowering people to manage their health conditions through self-care, such that a physician is only consulted when needed, may improve wellness, increase life expectancy, reduce costs and demands on the healthcare system, allowing for scarce resources to be redeployed in priority areas. Note however, that while available literature on self-care is encouraging, significant correlations between self-care practices and outcome measures (e.g., general health status, quality of life, healthcare costs) have been underreported and additional studies are needed (Ausili et al., 2014).

The Pharmacist's Role in Self-Care and Minor Ailments

Pharmacists have a crucial role to play in self-care and minor ailment management as they are one of the most accessible HCPs worldwide (Nichol et al., 1992) and are among the best trained to advise patients on the selection and manner of use of nonprescription medications (Schimmelfing et al., 2017). In fact, supporting self-care is recognized as being a core activity of the profession in many countries (European Commission, 2013). Based on their knowledge, assessment skills, experience, location, and availability, pharmacists are ideally placed to assist a patient in their self-care journey to ensure safe and effective therapies are recommended to optimize health outcomes.

Pharmacists provide valuable information to ensure patients receive treatments that are appropriate for a given condition. Education specifically designed for the patient's level of understating is central to self-care monitoring (Wilde and Garvin, 2007). After the initial diagnosis of a condition, the pharmacist is responsible for educating the patient on identifying signs and symptoms of recurrence and ways to effectively self-treat these recurrences, as well as identifying circumstances when it would be more appropriate to consult a physician or emergency medical care (e.g., if symptom severity increases or alarm features develop). When patients understand the symptoms that correspond with their disease, they can learn to recognize these symptoms early on and can more effectively self-manage their disease and prevent complications (Wilde and Garvin, 2007).

Based on these functions and findings, the World Health Organization (WHO) describes pharmacists as being communicators, drug suppliers, collaborators, and health promoters in self-care and self-medication (WHO Consultative Group on the Role of the Pharmacist and World Health Organization, 1998). As communicators, pharmacists initiate dialogue with patients, formulate questions to gather pertinent information, and provide objective education on therapies using a variety of modalities based on patient-specific factors. As drug suppliers, pharmacists provide access to nonprescription medications and ensure products are from reputable sources and are of good quality. As collaborators, pharmacists establish relationships with patients, other HCPs, and various stakeholder groups to facilitate continuity of care, ensure resources and expertise are used to their full potential, and improve outcomes through shared decision-making and interdisciplinary care. Finally, as health promoters, pharmacists screen patients in the community to identify those at risk of health problems, advise patients on disease prevention and other health-related practices, and participate in campaigns to raise awareness of public health issues. Additional roles for pharmacists in self-care and self-medication include managing minor ailments and ensuring safe and appropriate self-medication practices, as described below.

Managing Minor Ailments in the Community

Estimates out of the UK suggest that 15%–40% of emergency department (ED) visits and 20% of GP consultations, respectively, are for minor ailments that could be managed in community pharmacies—a reportedly underutilized resource (Richardson et al., 2018). Results from a cohort study by Watson et al. (2015) suggest that patients with minor ailments presenting in community pharmacies have similar health outcomes to those in GP and EDs, but costs are substantially lower for pharmacy-managed consultations. The authors concluded that "the substantially lower costs associated with pharmacy management of these ailments, combined with similar health outcomes across settings, suggest there is an urgent need to identify effective interventions to promote the use of community pharmacies for the management of minor ailments. These interventions should be evidence-based and underpinned by behavior change theory to maximize their effectiveness and reproducibility" (2015, pp.13).

Thus, shifting care for certain conditions from physicians to other HCPs can help to alleviate the increasing burden on the healthcare system by reducing costs and resource utilization (Bell et al., 2016). Therefore, pharmacists play a vital role in helping consumers manage minor ailments without costly and time-consuming physician visits.

Facilitating Safe and Appropriate Self-Care and Self-Medication

Inappropriate use of nonprescription products can increase morbidity, mortality and related healthcare costs. One reason for this is that these medications have the potential to interact with prescription products, causing adverse events, especially in vulnerable patient populations (e.g., older adults, immunocompromised individuals). The increased risk of adverse outcomes secondary to self-medication in these groups may be related to the presence of multiple disease states, higher prescription drug use, and/or impairments in activities of daily living. Other vulnerable patient populations include infants, children, and women who are pregnant or lactating. Pharmacists should ensure patients understand that self-care products are not without safety concerns and emphasize the importance of using these products as directed (Nakhla, 2018).

The abuse and addiction potential of some nonprescription medications is also a growing concern (Cooper, 2013) and will be discussed further in Regulatory and Legal Considerations. Pharmacists can play a pivotal role in deterring misuse and abuse by informing related policy regulations, and interventions. However, essential to this is the need for additional research to more fully "quantify the scale of abuse, evaluate interventions and capture individual experiences" (Cooper, 2013, pp. 103–104).

Other inappropriate self-medication practices can be harmful from a public health perspective and require prompt action (Annadurai et al., 2017). For example, an increasing incidence of self-medication with antimicrobials has contributed to one of the greatest global health threats ever—antimicrobial resistance (Alhomoud et al., 2017; Annadurai et al., 2017; Ayalew, 2017; Wang et al., 2016; Zoorob et al., 2016). Pharmacists have a responsibility to advocate for appropriate self-care and raise awareness of the potential negative consequences of inappropriate practices. This may include participating in community antimicrobial stewardship efforts or other public health initiatives.

Another important role for pharmacists in self-care and self-medication is ensuring symptoms perceived to be minor are not the result of an undetected, more serious condition (European Commission, 2013). This requires that pharmacists exercise enhanced clinical judgment, with particular attention to the presence of alarm features, previous treatment attempts, and behaviors suggesting avoidance of care. Accurately identifying the need for further medical assessment is crucial for avoiding delays in the treatment of more serious ailments.Last but not least, collaboration with other HCPs is a key step in implementing system-wide improvements to facilitate the delivery of safe and effective self-care and to reduce healthcare costs.

Pharmacists' Patient Care Process in Self-Care

Advising patients on self-care activities is an important component of pharmaceutical care and carries great professional responsibility (Nakhla, 2016). A contemporary, consistent and comprehensive model, the Pharmacists' Patient Care Process (PPCP) was developed by the Joint Commission of Pharmacy Practitioners (JCPP) (JCPP, 2014). The PPCP was built on previous approaches to care and was designed to achieve the JCPP Vision for Pharmacists' Practice (JCPP, 2013), which states "patients achieve optimal health and medication outcomes with pharmacists as essential and accountable providers within patient-centered, team-based healthcare."

The PCPP provides a systematic five-step approach for the delivery of pharmacists' patient care services in any setting, however, the intensity of each step may vary depending on the service provided in that particular setting. By using principles of evidence-based practice to *Collect*, *Assess*, *Plan*, *Implement*, and *Follow-Up*, in addition to continual collaboration, documentation, and communication, this standardized process helps pharmacists provide consistent services to patients. The following section will provide a comprehensive overview of the PPCP, outlining each step within the process, the multiple components of each step, and ways of implementing the steps with a focus on self-care encounters.

PPCP: The Core

As shown in Fig. 2, the PPCP features a patient-centered core.

The patient-centered care approach depends first and foremost on the pharmacist having an established relationship with the patient—one that supports engagement and effective interactions throughout the process (JCPP, 2014). Several strategies can be

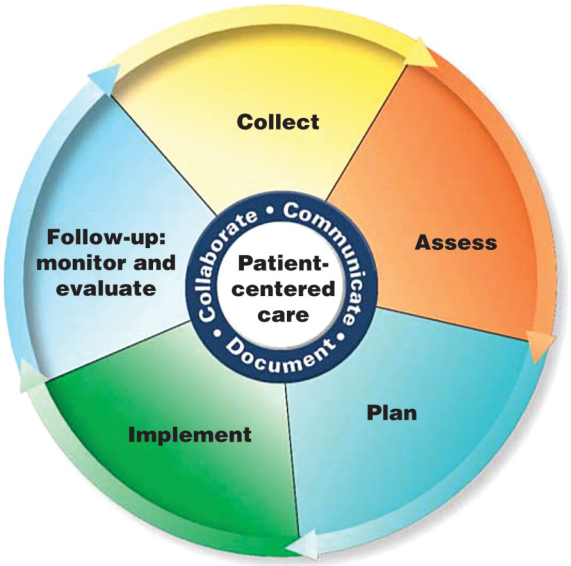

Figure 2 PPCP components. *Source: JCPP, 2014. The pharmacists' patient care process. Joint Commission of Pharmacy Practitioners. Available from: https://jcpp.net/patient-care-process/.*

used to encourage patient-centered self-care encounters including, but not limited to, active listening, empathy, ensuring patients are well-informed, and involving patients in their care.

Collaboration and communication occur most often with patients and/or caregivers in the context of self-care encounters, although other HCPs may be contacted for referral. An informed or shared decision-making model, based on information exchange and mutual expression of preferences between a professional (e.g., pharmacist) and a patient, is desirable when selecting nonprescription medication in a pharmacy, as such a model respects patient empowerment in self-medication and results from patient-centered care (Murray et al., 2006; Piecuch et al., 2017).

It is essential that self-care encounters be documented, as it demonstrates the pharmacist's "contributions to care, ensures continuity of care, provides legal evidence for professional liability, and contributes to billing and reimbursement needs" (Divine and McIntosh, 2018). Documentation can be completed on paper or in a computer system, so long as it is timely and legible. Documentation by pharmacists may include, but is not limited to, medication action plans, notes on interventions or referrals, and follow-up information. Some pharmacists may choose to use an established method of documenting, such as a *SOAP* note, which organizes information into *s*ubjective and *o*bjective data gathered, the pharmacist's *a*ssessment, and the recommended care *p*lan. Such an approach may help to ensure documentation is complete, organized and presented in a manner that is familiar to other HCPs.

PPCP: The Five Steps

Self-care encounters in pharmacies typically occur via two paths. In one, a patient or caregiver will initiate the interaction by contacting or approaching the pharmacist with their concern. In the second path, the pharmacist or pharmacy staff initiate the interaction and offer assistance after observing the patient or caregiver in the nonprescription aisle (Lauster and Srivastava, 2014; Nichol et al., 1992). Reports from various countries indicate that when advice is received, the process is initiated almost exclusively by patients (Sclar et al., 1996). Regardless of the path, the pharmacist must build rapport with the patient in order to establish engagement and effective communication, and complete the five PPCP steps to determine the most appropriate recommendation(s).

Collect

> "The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient" JCPP (2014).

Collecting appropriate information is key to understanding the patient's health status. This may include:

- *Medication history*: (current and past medications)
  - Prescription
  - Nonprescription
  - Dietary supplements
  - CAM

- *Relevant health data*:
  - Medical history
  - Health and wellness information
  - Biometric test results
  - Physical assessment findings
- *Patient-centered factors:*
  - Lifestyle habits
  - Preferences and beliefs
  - Health and functional goals
  - Socioeconomic factors

Professional clinical judgment should be exercised when determining which factors are pertinent to collect in each specific self-care situation. For these encounters, most information collected will be in the form of subjective data gathered from the patient or caregiver during the patient interview. There may or may not be a need to collect objective information—unbiased data that can be collected through direct observation and measurement—from medical and pharmacy records, diagnostic studies and laboratory tests, and physical assessment (Herrier et al., 2015). It may be appropriate to perform physical assessment for certain consults but not for others as some patients may not be able to explain what their condition looks like, but may be able to show it. For self-care interactions, it is important to determine why the patient is seeking help or looking for a nonprescription product and then ask the patient to explain the condition, symptom, or problem she/he wishes to treat. Throughout the interview, the pharmacist must use open-ended questions and carefully listen to and consider the patient's response, needs, wants, habits, preferences and beliefs to ensure the process remains patient-centered.

Assess

> "The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care" JCPP (2014).

This step includes:

- *Medication assessment*:
  - Appropriateness; effectiveness; safety; adherence
- *Patient history and risk assessment:*
  - Health and functional status; risk factors; health data; cultural factors; health literacy; access to medications or other aspects of care
- *Preventive care assessment:*
  - Immunization status; Preventive care needs; Other services, where appropriate

For self-care encounters, this step may or may not encompass all components listed above, and involves differentiating the patient's signs/symptoms to correctly identify the problem(s), its severity, urgency and most probable cause.

Medication assessment

In contrast to a comprehensive medication review involving the analysis of each medication the patient is currently taking (JCPP, 2014), a self-care encounter generally includes a more targeted medication review (Divine and McIntosh, 2018). For example, a focused medication review in self-care may include assessing the cause of a patient's chief complaint as potentially medication-related (e.g., was a patient presenting with vulvovaginal candidiasis recently started on a medication known to increase the risk of this type of infection, such as canagliflozin?). The pharmacist's role in these situations is to identify and prioritize medication-related problems and make subsequent modifications to the patient's care plan. While all are possible, the most likely medication-related problem in a self-care encounter is "needs additional drug therapy," as patients are presenting with the intent to purchase a product to treat a disorder and may require a nonprescription medication for resolution (Divine and McIntosh, 2018). It is also essential to consider the risks and potential benefits associated with each medication, including an assessment of whether current self-care therapies are working for the patient in the way they were intended to.

Patient history and risk assessment

Analyzing key information (e.g., health and functional status) in this category may alter a pharmacist's assessment and plan. For example, if it is determined that a patient seeking self-care for recurrent aphthous ulcers has human immunodeficiency virus, the assessment would be an exclusion for self-treatment as the patient requires further medical evaluation and treatment beyond self-care.

Preventive care assessment

For self-care encounters, the pharmacist often focuses the preventive care assessment on the presenting chief complaint. For example, if a patient presents with diaper dermatitis, the pharmacist may assess the need for future diaper dermatitis prevention and recommend a preventive plan that includes a barrier product.

Appropriateness for self-treatment assessment

For self-care encounters, patient-specific data should also be assessed to identify exclusions for self-treatment. To establish that the patient is an appropriate self-care candidate, ask if the patient (1) has any severe symptoms, (2) has any symptoms that persist or return repeatedly, or (3) is self-treating to avoid medical care. A patient meeting any of these three criteria is not an appropriate self-care candidate and should be referred to primary care providers for nonurgent issues or to emergency services for urgent issues (Buring et al., 2007), since most conditions that can be safely self-treated are characterized as having no severe symptoms and no symptoms that are persistent, or repeatedly return without an identifiable cause. Additionally, patients should not self-treat in an attempt to avoid evaluation and treatment by a HCP. Divine and McIntosh (2018) list additional exclusions for self-treatment, including:

- Patient-specific factors that preclude treatment with nonprescription medications
- Health status or history that precludes self-treatment, even if a nonprescription medication is indicated for the disorder
- Nonprescription medications are not indicated for the disorder
- Previous treatment with nonprescription medications was ineffective after an adequate trial

It is the responsibility of the pharmacist to be knowledgeable in exclusion criteria for self-treatment for presenting disorders or symptoms as well as gathering appropriate information that may result in this assessment (Divine and McIntosh, 2018).

Plan

> "The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective" JCPP (2014).

In a self-care encounter, information that has been gathered, assessed, and analyzed thus far will culminate in one of four general recommendations:

- Refer to another HCP (for treatment and/or further evaluation)
- Recommend self-care until another HCP can be consulted
- Recommend self-care
- Do nothing/watch-and-wait approach

If self-care is deemed appropriate, the pharmacist can provide the patient with a suitable plan. This plan may not include any pharmacologic recommendations but rather nonpharmacologic measures. If referring and recommending self-care measures, it is imperative to emphasize that the referral is the primary recommendation and explicitly states the repercussions of ignoring this advice.

This plan should be developed in collaboration with other HCPs and the patient or caregiver, and should be individualized, evidence-based, safe, cost-effective, and patient-centered. Four key areas that should be addressed within the created care plan include:

Medication-related problems

For self-care encounters, this usually results in the pharmacist recommending a safe and cost-effective self-care product to resolve the "needs additional drug therapy" problem (Divine and McIntosh, 2018).

To ensure patient-centrality and an individualized approach, it is crucial to involve the patient in the decision-making process for product selection or discontinuation and tailor therapy to meet the patient's preferences and beliefs. For example, provide the patient with a choice of products, dosage forms and regimens, costs, and flavors if possible, and consider their past medication experiences.

Goals of therapy

Goals of therapy serve as endpoints to measure outcomes and should contain three components: (1) clinical parameters (signs and symptoms) and/or laboratory values which are observable, measurable, and realistic; (2) a desired value or observable change in the parameter; and (3) a specific time frame in which the goal is to be met. For self-care encounters, the clinical parameter is likely to focus on resolution of the presenting sign or symptom, such as "alleviate the discomfort associated with primary dysmenorrhea" when an NSAID is recommended. Alternatively, the clinical parameter may be a preventive measure, such as suggesting oral rehydration solution to prevent progression of dehydration from mild to severe.

Establishing the patient's goals of therapy and formulating realistic timelines for achieving clinical outcomes in the context of their overall health goals and access to care is imperative (JCPP, 2014) and establishes clear expectations. For example, "curing" a cold is not possible but symptomatic relief is.

Patient engagement

Known as a "blockbuster drug of the century" (Chen et al., 2016), patient engagement in healthcare has the potential to achieve the "triple aim" of improved health outcomes, better patient care and lower costs (Chen et al., 2016). Every self-care encounter requires the pharmacist to engage the patient through education, empowerment, and self-management (JCPP, 2014). Education should encompass the presenting illness, pharmacologic and nonpharmacologic options, as well as when to seek medical attention. Empowerment results from engaging the patient in goal setting and aligning expectations.

Care continuity

The plan should include the continuity of care, involving follow-up, referral, and transitions of care to another HCP, if necessary.

Implement

> "The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver" JCPP (2014).

Included in this step is execution of the developed plan, in which the pharmacist:

- Addresses *medication- and health-related problems*
  - Engages in preventive care strategies, including vaccine administration
- *Initiates, modifies, discontinues, or administers medication therapy* (as authorized)
- *Provides education and self-management training* to the patient or caregiver
- *Contributes to coordination of care*, including referral or transition of patient to another HCP
- *Schedules follow-up care* as needed to achieve goals of therapy

The pharmacist should share the goals of therapy that were established and the subsequent self-care strategies. It is important to explain what the therapies are, how they will help, and what the patient should do as follow-up. The pharmacist should then educate on how to take the medication and the duration of therapy; addressing common adverse effects and ways of managing them is also important. Clear articulation, in patient-friendly language, of what the patient should expect from treatment, as well as an understanding of follow-up and monitoring parameters (including signs that the condition might be worsening and when to seek the advice of a physician) are imperative. Where applicable, the education should also include lifestyle modifications, nonpharmacologic therapies, as well as future prevention measures. In some instances, no medications will be indicated, and only wellness and preventative measures will be suggested.

Follow-Up: Monitor and Evaluate

> "The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed" JCPP (2014).

The final step of the PPCP is ongoing monitoring and evaluation of:

- *Medication appropriateness, effectiveness, safety, and patient adherence* (through available health data, biometric test results, and patient feedback)
- *Clinical endpoints* contributing to the patient's overall health
- *Outcomes of care*, including progress toward or the achievement of goals of therapy

It is imperative to evaluate the self-care plan outcomes and adjust when results are not optimal. From a patient safety perspective, this step should include the documentation and reporting of any adverse drug events to appropriate personnel, followed by appropriate adjustments to therapy to avoid additional adverse outcomes. Changes to care plans should also be documented and communicated to the patient's entire healthcare team to ensure patient safety, effective follow-up, and continuity of care.

Patients should be provided with an appropriate follow-up plan, including timing and triggers, which would warrant a pharmacist or physician visit. Encourage patients to call or return if symptoms fail to resolve. While follow-up may not be possible in some self-care encounters due to the patient being unfamiliar to the pharmacy or workload/time restrictions, there are times when follow-up is vital to ensure patient safety. Pharmacists should use professional judgment in determining which cases require follow-up.

Tools and Mnemonics for PPCP Efficiency

A systematic approach to determining patients' self-care needs results in consistent and comprehensive patient assessment, optimizing therapeutic outcomes. Several tools have been developed (Bates et al., 2002; Buring et al., 2007; Margolis et al., 2016; Maguire, 2015; McCallian and Cheigh, 2002) to assist pharmacists in standardizing their approach to information gathering, patient assessment and triage. It is important to note that these tools and mnemonics are NOT meant to replace the

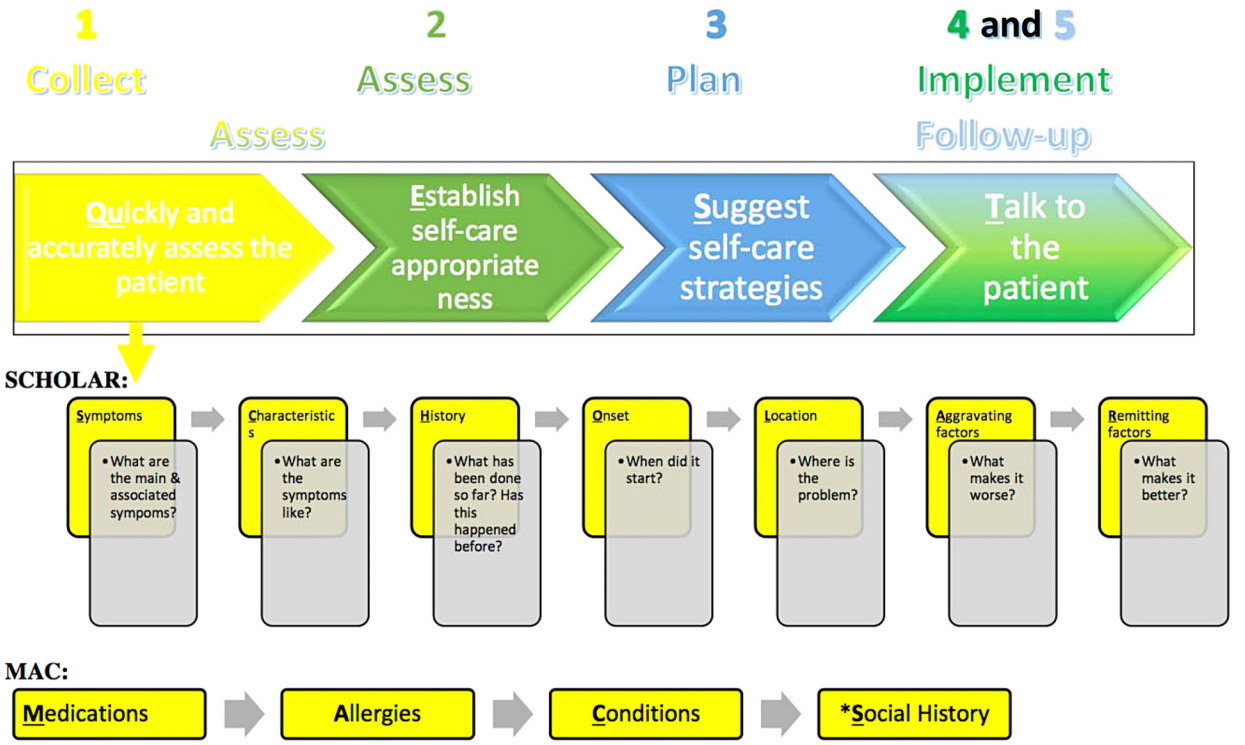

Figure 3 Tools and mnemonics for PPCP efficiency. *S for social history is not part of the original published algorithm, but was added by the author to ensure pharmacists also consider lifestyle factors such as physical activity, diet, smoking, alcohol intake, caffeine consumption, etc. *Source: Adapted from JCPP, 2014. The pharmacists' patient care process. Joint Commission of Pharmacy Practitioners. Available from: https://jcpp.net/patient-care-process/; Divine, H., McIntosh, T., 2018. Pharmacists' Patient Care Process in Self-Care. In: Krinsky, D. L., Ferreri, S. P., Hemstreet, B. A., Hume, A. L., Newton, G. D., Rollins, C. J., Tietze, K. J. (eds.). Handbook of Nonprescription Drugs, nineteenth ed. American Pharmacists Association, Washington, DC.)*

PPCP in self-care encounters, but rather to assist in streamlining the process by highlighting the key areas most relevant for self-care, improving efficiency.

One useful tool, QuEST, was designed specifically for self-care encounters (Leibowitz and Ginsburg, 2002). Each letter in the acronym QuEST represents an ordered step in the pharmacists' problem-solving process:

1. *Qu*ickly and accurately assess the patient (using SCHOLAR-MAC).
2. *E*stablish that the patient is an appropriate self-care candidate.
3. *S*uggest appropriate self-care strategies.
4. *T*alk with the patient about various aspects of those strategies.

Note: each letter in SCHOLAR represents subjective information about the patient's current chief complaint. MAC was added to QuEST/SCHOLAR to capture information on an individual's medications, allergies, and medical conditions (Fig. 3).

Evidence shows that the use of a structured interviewing framework, along with adequate training, improves user confidence, ensures elicitation of a comprehensive patient history and assessment, and results in appropriate recommendations for management of self-care concerns (Buring et al., 2007; Curley et al., 2016).

Developing Cultural Competency for Self-Care

With increasing globalization, countries have become more culturally diverse. HCPs including pharmacists have an obligation to provide care that is equitable for all patients, irrespective of culture. This requires that HCPs recognize their own cultural beliefs and biases, and continually pursue efforts to become more culturally competent. A failure to do so may have negative implications on patient satisfaction and health outcomes. Cultural competency, as it relates to self-care, will be explored here, including strategies pharmacists can employ to facilitate the delivery of culturally sensitive care.

Rationale for Improving Cultural Competency in Healthcare

Countries have become more culturally diverse over time. A major reason for this has been the rapid growth in international migration—since 2000, the number of international migrants worldwide has increased by an average of 2.3% annually, reaching a

total of US$244 million in 2015 (United Nations, 2016). Populations have also become more diverse in terms of gender expression, socioeconomic status, sexual orientation, and religious affiliation (Sias and Jacobson, 2018). As such, HCPs, including pharmacists, are encountering increasingly heterogeneous patient populations.

Health disparities exist in culturally diverse populations and may be attributed to differences in determinants of health, such as education, living conditions, and access to health services (CDC, 2015). The prevalence of diabetes, for example, is higher among Hispanics and those with lower education levels, than non-Hispanic Whites and those with higher education levels (Sias and Jacobson, 2018). To successfully care for a diverse patient population and resolve existing disparities, HCPs must be culturally competent. This idea is supported by several studies that demonstrate cultural competency in healthcare care not only enhances patient satisfaction (Govere and Govere, 2016), but may improve health outcomes as well (Truong et al., 2014).

Important Considerations for Working Across Cultures

An essential component of cultural competency is recognizing patients' unique experiences and understanding how those experiences influence interactions with the healthcare system. A patient's language abilities and health literacy are also important considerations for pharmacists providing crosscultural care.

Beliefs of Different Population Groups

To provide care recommendations that are culturally respectful and acceptable, a basic understanding of cultural values, beliefs, and practices is necessary. For example, in African and Asian cultures, CAMs are often preferred approaches to self-care, and being aware of this will help pharmacists to make recommendations that are more acceptable to patients (Sias and Jacobson, 2018). A comprehensive review of cultural values, beliefs, and practices in the context of healthcare is beyond the scope of this discussion, and culture-specific resources should be consulted for more detail.

Communication

Establishing effective communication may be one of the greatest challenges in providing crosscultural care. Language barriers may hinder pharmacists' ability to accurately assess a patient and provide recommendations that are easily understandable. Furthermore, when language barriers exist, nonprescription drug labels are inadequate for ensuring safe and effective use of these products. Nonverbal communication may also cause difficulties, as specific body language and gestures have different meanings across cultures. Low health literacy is also common in minority groups—pharmacists should never assume that patients fully comprehend recommendations, even when potential language barriers are overcome (Sias and Jacobson, 2018). Strategies for mitigating communication barriers and low health literacy are described in "Providing Culturally Competent Care" below.

Providing Culturally Competent Care

Recognizing Personal Beliefs and Biases

An important step in providing culturally competent care is recognizing personal cultural beliefs and biases. During each encounter, pharmacists should treat patients as unique individuals and avoid stereotyping. In doing so, pharmacists recognize that each patient has distinct values and beliefs, and acknowledge that not all persons within a group behave in the same manner. Pharmacists should also be cautious when making generalizations, however, knowledge of typical health-related practices may facilitate more successful crosscultural encounters (Sias and Jacobson, 2018).

Several cultural competency models have been developed (Campinha-Bacote, 2002; Cross, 1988; Purnell, 2002) and can aid pharmacists in identifying where on the continuum they fall and what to strive for. The Cultural Competence Continuum model has been summarized in **Fig. 4**, however, an in-depth review of this model, and others, is beyond the scope of this discussion.

Strategies for Gathering and Assessing Patient Information

The following strategies may be employed by pharmacists during crosscultural encounters to assist in information gathering and assessment (Sias and Jacobson, 2018):

- Open-ended questioning to encourage disclosure
- Patient mirroring and inclusive language to build trust and rapport
- Models such as LEARN to facilitate cross-cultural communication (**Fig. 5**)
- Kleinman's patient explanatory model to elicit beliefs about illness (**Fig. 6**)
- Language assistance tools to overcome language barriers, including interpreters and translation apps for smartphones

Note: using family members as interpreters should be avoided where possible, as patients may feel uncomfortable disclosing information and such practices may place undue burden on family members (Sias and Jacobson, 2018). Unrelated interpreters—preferably ones with training in medical language translation—should be used to uphold patient privacy and reduce the risk of misinterpretations (Sias and Jacobson, 2018).

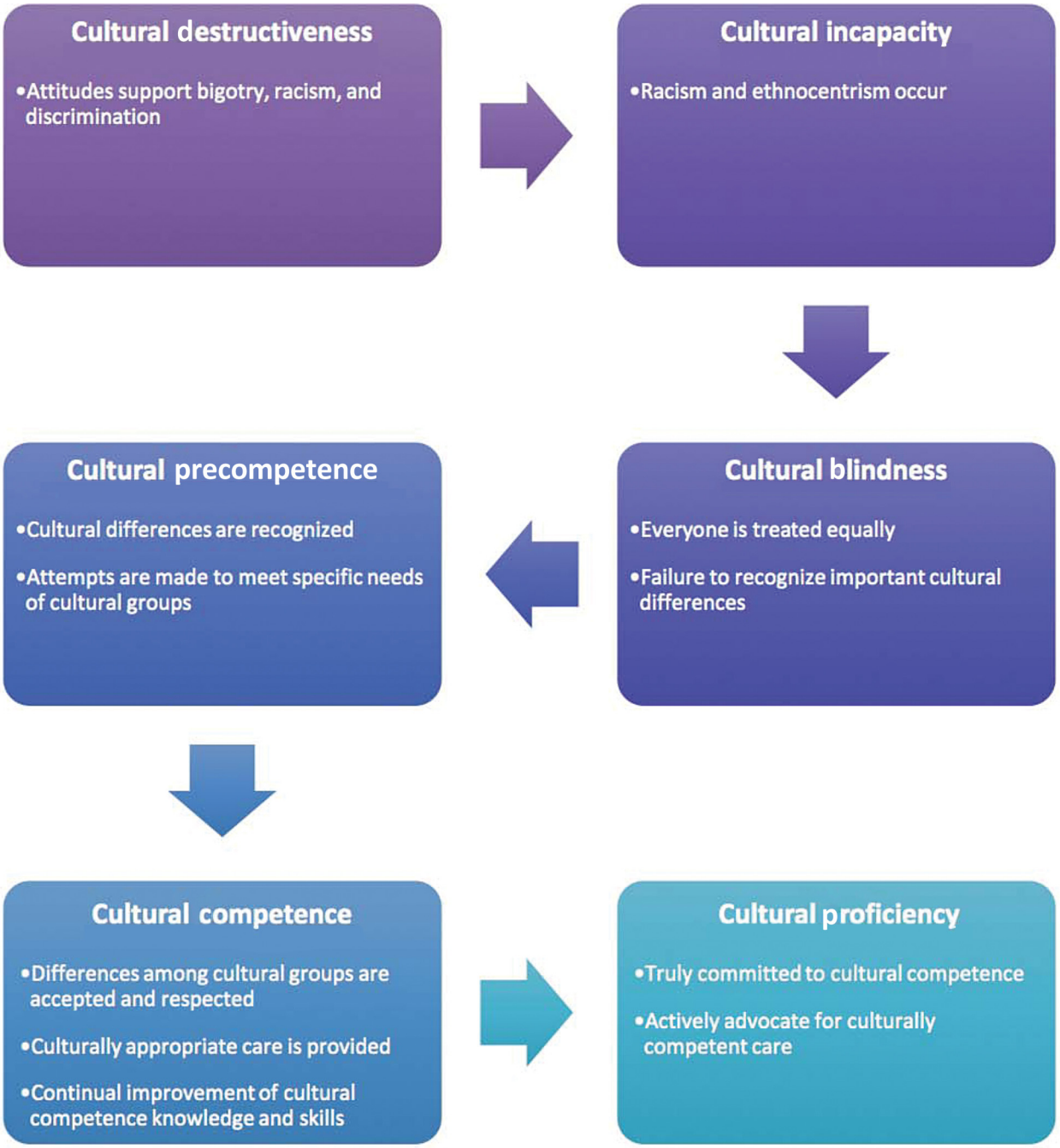

Figure 4 Summary of cross' cultural competence continuum model. *Source: Cross, T., 1988. Cultural competence continuum. Focal Point: The Bulletin of The Research and Training Centre on Family Support and Children's Mental Health. Portland State University, Portland.; Sias, J. J., Jacobson, A. N., 2018. Exploring Cultural Aspects of Self-Care. In: Krinsky, D. L., Ferreri, S. P., Hemstreet, B. A., Hume, A. L., Newton, G. D., Rollins, C. J., Tietze, K. J. (eds.) Handbook of Nonprescription Drugs, nineteenth ed. American Pharmacists Association, Washington, DC.*

Developing and Articulating a Self-Care Plan

In developing a care plan, it is essential that pharmacists consider patient values and beliefs to increase the likelihood their recommendation will be followed. No matter how clinically sound a pharmacist's care plan is, if the patient does not follow the recommendation, it has failed (Nakhla, 2018).

Ethical dilemmas may arise when patient values and beliefs do not align with the safest and most effective care plan. In an ideal situation, the pharmacist and patient will be able to negotiate a care plan that is mutually acceptable to both parties. In some situations, pharmacists may have to accept the use of safe, but less effective treatment modalities out of respect for patient autonomy. If a pharmacist does not feel comfortable or competent in providing such care, patients should be referred elsewhere.

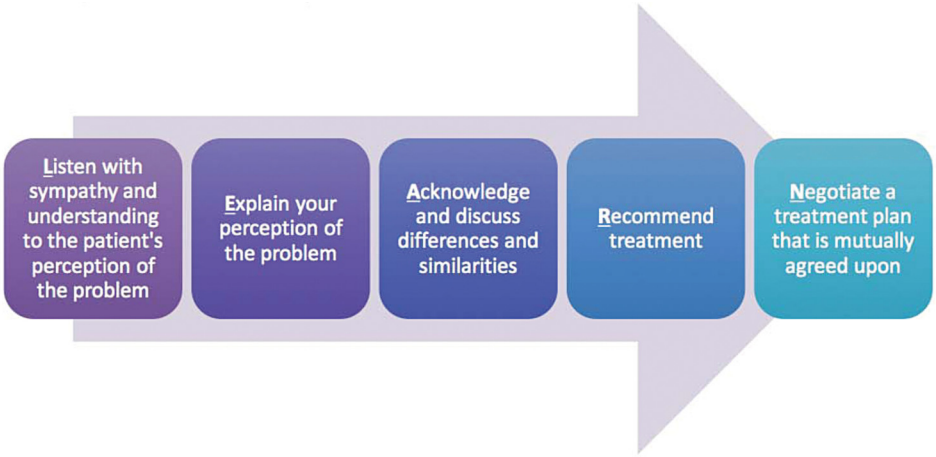

Figure 5 The LEARN model for cross-cultural communication. *Source: Sias, J. J., Jacobson, A. N., 2018. Exploring Cultural Aspects of Self-Care. In: Krinsky, D. L., Ferreri, S. P., Hemstreet, B. A., Hume, A. L., Newton, G. D., Rollins, C. J., Tietze, K. J. (eds.) Handbook of Nonprescription Drugs, nineteenth ed. American Pharmacists Association, Washington, DC.*

Figure 6 Example questions from Kleinman's Patient Explanatory model. *Source: Kleinman, A., 1989. The Illness Narratives: Suffering, Healing, and The Human Condition. Basic Books, New York.*

When discussing care plans, it is important to ensure information is communicated effectively. This may include using interpreters or translation services, and providing educational materials in a patient's native language or as pictograms. The teach-back method—where patients repeat back, in their own words, information provided—is an effective means of ensuring clarity and understanding (Sias and Jacobson, 2018).

Regulatory and Legal Considerations

The definition of self-care is highly dynamic and reflects ever-changing legislative and regulatory activities worldwide. Legislation and regulations surrounding nonprescription drugs vary from country to country and consequently, the availability and accessibility of these products also varies. However, there are some global commonalities in the self-care framework—trends in nonprescription drug regulation, approval, safety, and liability will be discussed here. Key differences in the regulation of nonprescription products will also be considered, however, country-specific resources should be consulted for more detail. Although beyond the scope of this discussion, it should be noted that natural products, dietary supplements, homeopathic products, and point-of-care testing devices also play an important role in shaping self-care, with varying regulatory practices worldwide.

Regulatory Considerations for Nonprescription Drugs

The regulation of nonprescription products is complex—excessive regulation may restrict access and a patient's ability to engage in self-care, whereas insufficient regulation may compromise drug quality and patient safety. Historically, countries have struggled to differentiate between prescription and nonprescription products from a regulatory standpoint. However, more recent initiatives reflect key differences between drug classes. These differences and their resulting impact on regulations have been described by the World Self-Medication Industry (WSMI, 2007), and include:

1. Nonprescription products commonly have a longer history of international experience than prescription products. As such, nonprescription products may not be subjected to the same degree of regulation at the time of market authorization or with ongoing use.
2. Nonprescription products are not often protected by intellectual property patents on the basic molecule, like with prescription products. Therefore, several countries offer data protection or market exclusivity for new indications on existing self-care products.
3. Nonprescription products can be obtained without direct intervention by a HCP. As such, most countries have specific regulations surrounding the labeling and advertising of nonprescription products to facilitate appropriate selection and use by consumers.
4. In several countries, there is pricing freedom for nonprescription products, but not prescription products. Consequently, regulations surrounding nonprescription drug pricing controls have been eliminated, reducing the administrative burden for regulators in these countries.

In many countries, including New Zealand and Singapore, nonprescription drugs are further classified as over-the-counter (OTC) or behind-the-counter (BTC) products—the latter requiring intervention by a pharmacy staff member, typically a pharmacist, for sale (Field, 2005). In Poland, the majority of nonprescription products are available BTC (Piecuch and Kozlowska-Wojciechowska, 2013). Unsurprisingly, BTC products are subjected to greater regulatory control than over-the-counter products, but are less heavily regulated than prescription products. Classifying drugs as BTC has potentially significant implications on product surveillance and cost. As such, countries like the US have opted to continue using a two-tiered system, with drugs being classified as prescription or nonprescription only. The UK and Canada, however, use a three- and four-tiered system, respectively. In the UK, classification categories include prescription only medicine (POM), pharmacy (P), or general sales list (GSL; available in any retail outlet), with P and GSL products being available without a prescription (Paudyal et al., 2013). In Canada, drug products are classified as Schedule I (prescription-only), II (BTC), III (OTC), or U (unscheduled; available in any retail outlet), with II, III, and U products being available without a prescription.

Although specific regulations for nonprescription drugs differ between countries, the underlying goals are same—ensure the quality, safety and efficacy of products, improve public health, and encourage competition in the nonprescription sector. With appropriate regulation of nonprescription products, patients can be empowered to engage in self-care without potential compromises in safety.

Approval of Nonprescription Drugs

In most countries, there is a formal means of approving nonprescription products. In the US and India, these activities are governed by the Food and Drug Administration (FDA) and Central Drugs Standard Control Organization, respectively (Mulaje et al., 2011). Products generally obtain nonprescription status by one of two ways: (1) they are classified as nonprescription with initial market authorization, or (2) they become nonprescription after initial approval as a prescription product. Note that in many countries, drug scheduling decisions are made following recommendations of an independent committee, such as the Advisory Committee on Medicines Scheduling in Australia (Therapeutic Goods Administration, 2011a).

Regardless of the route to nonprescription status, approval requires that the safety, efficacy, pharmacokinetics, pharmacodynamics, and indications of a drug be well established and documented (WHO, 2000). For novel drugs, initial evidence of safety and efficacy is primarily from animal studies. To be given nonprescription status with initial authorization, many countries require that clinical trials reflect the self-care paradigm and that postmarketing surveillance be undertaken to monitor long-term safety and efficacy in humans (WHO, 2000). Several countries have adopted an accelerated approval process for prescription drugs seeking nonprescription status, as safety and efficacy were established with initial authorization (WSMI, 2007). In the case of prior market authorization, approval decisions focus more on evaluating a drug's suitability for self-care, rather than reassessing safety and efficacy data.

In assessing the appropriateness of a drug for self-care, regulatory and/or advisory bodies commonly review the product's approved indications, efficacy, side effects, dosage form, and route of administration. Additionally, the feasibility of implementing potential safeguards, such as restricting package size or improving labeling, is often evaluated. An analysis of the pros and cons of granting nonprescription status is also commonly performed. Characteristics that suggest a drug may be suitable for self-care are outlined in **Table 1**.

Despite assessing similar information, countries have drawn varying conclusions regarding the appropriateness of specific drugs for self-care. The Ingredients Directory (AESGP, 2016), published by the Association of European Self-Medication Industry, lists drugs that have nonprescription status somewhere in the world and highlights differences in classification among 39 countries. This

Table 1 Characteristics of drugs suitable for self-care

Clinical:

- Used for conditions or symptoms that are readily recognizable and/or self-limiting
- Provides reliable relief of symptoms
- Has a wide safety margin, even if used incorrectly
- Low potential for dependence and abuse
- Adverse effects are minimal and/or well-characterized
- Low risk of masking a serious underlying disease
- Pharmacokinetic properties unlikely to be affected by other common drugs or food

Administration:

- Oral or topical preparation
- Technical expertise is not required for administration

Safety:

- Appropriate treatment duration has been defined
- Package size reflects recommended treatment duration and reduces risk of misuse
- Available in child-resistant packaging

Source: WHO, 2000. Guidelines for the regulatory assessment of medicinal products for use in self-medication. World Health Organization, Geneva. Available from: http://www.who.int/iris/handle/10665/66154.

publication underlines that, even for well-established drugs, nonprescription status is not universal, contributing to an inconsistent self-care environment worldwide (AESGP, 2016).

A Note on Prescription-to-Nonprescription Switches

Prescription-to-nonprescription switches are currently the most common means by which products obtain nonprescription status. These switches are thought to be motivated by three factors: (1) the desire to extend product viability by pharmaceutical companies, (2) attempts to contain costs by healthcare payers; and (3) an increasing interest in self-care from the public (Cohen et al., 2005). Examples of prescription drugs that have transitioned to nonprescription status in the US, the UK, France, or the Netherlands are provided in **Table 2**. The UK has led the way in prescription-to-nonprescription transitions, with 22 switches between 2000 and 2013 (Cohen et al., 2013). Fewer switches have been approved in the US, perhaps owing to the lack of a BTC regulatory class and the consequential struggle to mitigate safety concerns (Cohen et al., 2005).

Prescription-to-nonprescription switches will continue to play a significant role in expanding the global nonprescription market, with an increasing focus on drugs for health promotion and disease prevention (Cohen et al., 2005). With this brings cost savings for public and private payers and patients through lower drug costs, reduced physician visits, and increased productivity. However, public and private payers have shown a tendency to remove switched drugs from their formularies and increase copayments for prescription drugs in the same class, increasing out-of-pocket expenses for patients (Cohen et al., 2005). Thus, while prescription-to-nonprescription switches have been argued to increase accessibility, the shift of financial burden to other HCPs (particularly pharmacists) and consumers may create a new barrier to care for some patients.

Another consideration for an expanding nonprescription market is the role of pharmacists. Pharmacists will be increasingly responsible for helping inform patients' self-diagnosis of ailments, selection of products, and monitoring of therapy. For example, it

Table 2 Examples of prescription-to-nonprescription switches and year switch occurred

	United States	*United Kingdom*	*France*	*Netherlands*
Azithromycin		2008		
Fluticasone		2002		
Ipratropium bromide				2009
Levonorgestrel	2006	2001		2005
Loratadine	2002		2006	
Omeprazole	2003	2004	2010	2008
Simvastatin		2004		
Sumatriptan		2006		
Tamsulosin		2009		
Terbinafine		2001	2002	

Source: Cohen, J., Millier, A., Karray, S., Toumi, M., 2013. Assessing the economic impact of Rxto-OTC switches: systematic review and guidelines for future development. J. Med. Econ., 16, 835–44.

will be mandatory for pharmacists to assess a patient's erectile dysfunction symptoms, comorbid conditions, and other medications prior to dispensing Sildenafil without a prescription in the UK—a recent prescription-to-nonprescription switch (Medicines and Healthcare Products Regulatory Agency (MHRA), 2017).

Ensuring Nonprescription Drug Safety

At the center of regulatory controls for nonprescription drugs is patient safety, irrespective of the country. Not only is this reflected in formal approval processes for market authorization, as described previously, it is also reflected in regulations for the labeling, packaging, advertising, and postmarketing surveillance of approved nonprescription products.

Labeling, Packaging, and Advertising

Although labeling, packaging and advertising regulations vary by country, overarching themes exist. For example, most, if not all, countries require that information necessary for the correct and unsupervised use of nonprescription drugs be included on the product label or package insert (WSMI, 2007). This generally includes the product name, intended use, active and nonmedicinal ingredients, directions for use, common side effects and drug interactions, contraindications, storage requirements, lot number and expiry date, and the name and location of the manufacturer or distributor (WSMI, 2007). Furthermore, regulations require that information be provided in easily understandable and patient-friendly language (WHO, 2000). Additional labeling requirements are country-specific—for example, the FDA in the US has regulations pertaining to the placement of information included and font size (Rumore, 2018).

For packaging, regulations are typically aimed at reducing the risk of accidental drug exposure by children, facilitating recognition of product tampering, and deterring the misuse of nonprescription drugs (WHO, 2000). In Australia, for example, the Therapeutic Goods Administration requires that nonprescription products be sold in child-resistant packaging if the quantity marketed is likely to cause significant harm in a child weighing 11 kg (Therapeutic Goods Administration, 2008). Similar mandates for child-resistant packaging are found in the UK, Canada, and the US.

Regulations pertaining to drug advertising ensure information communicated to consumers is truthful and not misleading (WSMI, 2007). This is important, as misinformation regarding the use of nonprescription products can have significant implications on patient safety and wellbeing. In the Netherlands, Australia, and the UK drug advertising is monitored by a self-regulatory body that acts on behalf of the government (WSMI, 2007). In Argentina, Mexico, and Japan drug advertising is overseen by both government and self-regulatory bodies (WSMI, 2007).

Adverse Drug Reaction Reporting

Several countries have systems in place for reporting adverse reactions related to nonprescription drug use, allowing for ongoing monitoring of drug safety. In most countries, reporting can be completed by anyone, including healthcare professionals, consumers, and manufacturers. In the US and Canada, it is mandatory to report serious adverse reactions (e.g., death, birth defects, etc.) related to nonprescription drug use. Reporting of nonserious adverse reactions is also encouraged, but may not be mandatory. Routine analysis of information reported may lead to product recalls, safety alerts, revision of contraindications, and advisory statements, with the intention being to maintain safe nonprescription drug use (Therapeutic Goods Administration, 2011b).

Safety Concerns Related to Nonprescription Drugs

Despite best regulatory efforts, ongoing safety concerns related to nonprescription drug use exist worldwide and will be discussed in this section.

Substandard and falsified products

A substandard product is one that fails to meet quality standards and/or specifications (WHO, 2017a). With falsified products, the identity, composition or source is deliberately misrepresented. These products may contain the wrong active ingredient (AI), no AI, or the wrong amount of the correct AI (WHO, 2017a). Additionally, substandard and falsified products commonly contain unknown impurities as they are often compounded in unsanitary conditions, by unqualified personnel.

The growing risk of substandard and falsified medications may be related to increased internet connectivity, as those responsible for manufacturing and distributing such products have gained access to a global market. Consequences related to the use of substandard and falsified medications can be far reaching, from the failure to prevent or cure disease to serious patient harm or death (WHO, 2017b). Furthermore, patients may lose faith in drug regulatory authorities, manufacturers, and the healthcare system when concerns of product safety and efficacy arise (WHO, 2017b).

In 2013, the WHO launched the Global Surveillance and Monitoring System (GSMS) to encourage reporting of substandard and falsified medications. As of 2017, over 1500 products had been reported. **Fig. 7** shows countries in which substandard and falsified medications have been discovered and reported, highlighting that this is a global problem.

Abuse of nonprescription medications

Nonprescription drug use and abuse includes using these products for reasons other than those intended, and exceeding recommended dosages (Conca and Worthen, 2012). Factors that may contribute to inappropriate nonprescription drug use include public perception that these medications are without safety concerns, and the ease of procurement (Conca and Worthen, 2012). Rates of

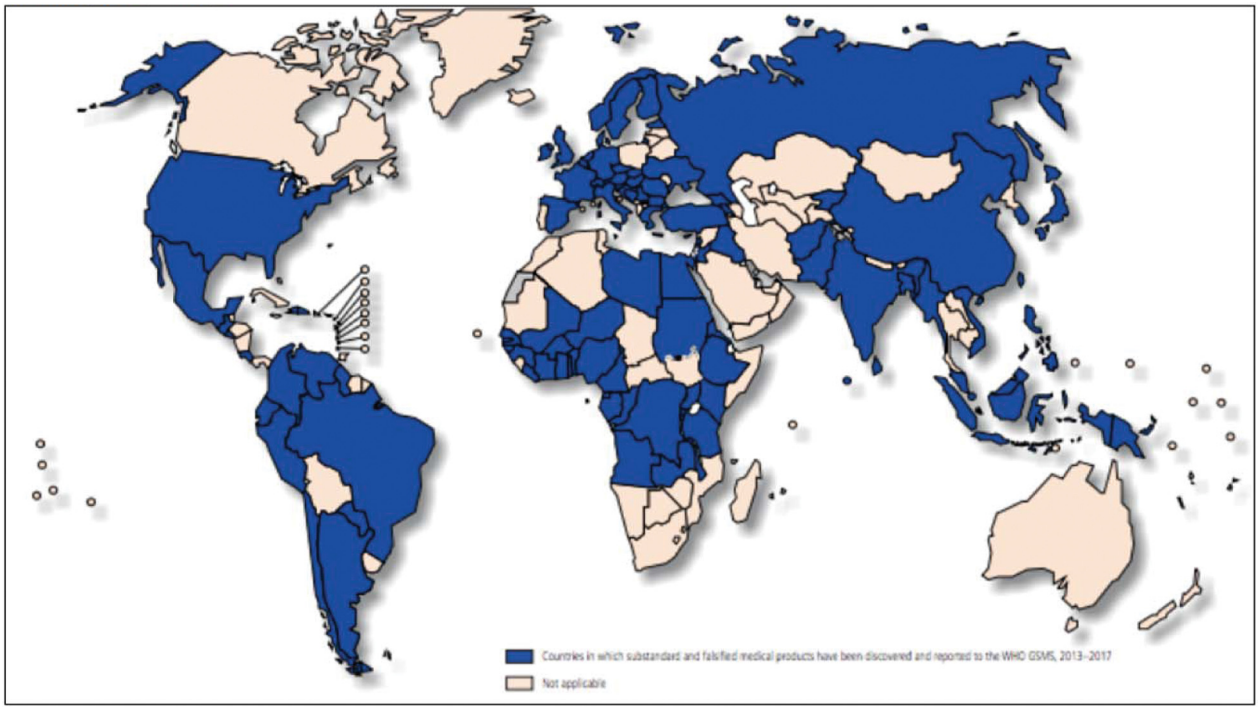

Figure 7 Countries in which substandard and falsified medical products have been discovered and reported to the GSMS, 2013–17. *Source: WHO, 2017a. Substandard and falsified medical products. World Health Organization, Geneva. Available from: http://www.who.int/mediacentre/factsheets/fs275/en/; WHO, 2017b. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. World Health Organization, Geneva.*

nonprescription drug abuse have increased over time. In the US, for example, dextromethorphan abuse increased 15-fold from 1999 to 2004 among adolescents aged 9–17 (Levine, 2007). Nonprescription drug abuse can occur in all patient population, however, those with mental health issues, pain disorders, and diseases of aging may be more susceptible (Conca and Worthen, 2012). Although abused products vary worldwide, a 2013 systematic review identified codeine products, laxatives, sedating antihistamines, cough products, and decongestants as the most commonly abused drug classes worldwide (Cooper, 2013). With an ever-expanding nonprescription drug market, initiatives to improve the detection of abuse will be paramount to ensure patient safety—pharmacists will have a prominent role in such initiatives.

Legal Considerations for Nonprescription Drugs

Liability in the context of nonprescription drug therapy varies greatly with jurisdiction, however, general commonalities exist. First, manufacturers are held liable for the *quality* and *safety* of drugs they produce and distribute. Historically, most legal proceedings related to nonprescription products have been against manufacturers due to defective drugs. However, an increasing number of pharmacists and pharmacies are finding themselves in litigation for advice provided on nonprescription products. Such cases are complex, as a pharmacist's duty to counsel patients on the safe use and risks of drugs available for self-selection is debated. In countries where certain nonprescription products are kept BTC, expectations for pharmacists are clearer—those who fail to provide appropriate intervention for such medications may be ruled negligent in legal proceedings. Pharmacists and pharmacies may also be found liable if harm occurs following the provision of inaccurate information on nonprescription drug use or the sale of expired or recalled products. With increasing responsibility in direct patient care, including prescribing authority in some jurisdictions, the liability of pharmacists is evolving. Pharmacists are encouraged to regularly consult legal resources to stay up-to-date on professional obligations in their jurisdiction.

Pharmacist-Led Minor Ailment Services (PMAS)

Pharmacists have a long history of helping patients manage minor ailments—traditionally, this has involved making nonprescription medication recommendations, facilitating lifestyle changes, and referring patients to other HCPs when needed. Canadian estimates show 10%–30% of physician consultations are for minor ailments (Taylor and Joubert, 2016). In recent years, several countries have introduced pharmacy-led minor ailment services (PMAS) in hopes of reducing the burden of minor ailments on these high-cost settings (e.g., GP offices, emergency departments) by transitioning minor ailment care to community pharmacies (Paudyal et al., 2013). PMAS grant pharmacists the option of selecting medications traditionally under control of prescribers for minor

ailment treatment. A 2013 report (Ontario Pharmacists Association, 2013) estimated that introducing a program involving nine minor ailments could save CAD$12.3 million over 5 years in Ontario, Canada alone. Realizing this cost-saving potential, several countries have implemented PMAS, with no reported compromises in patient safety or quality of care.

PMAS regulations differ from country to country and even from jurisdictions within the same country. For example, pharmacists in Saskatchewan, Canada are limited to selecting from a set formulary of medications for a specified condition and must follow a detailed protocol. Pharmacists with prescriptive authority in Alberta, Canada have more autonomy as they can prescribe most medications and are not limited to specific ailments. There is no overarching national initiative and government reimbursement of the service also varies by province (Taylor and Joubert, 2016). In the UK, PMAS allow pharmacists to supply any nonprescription agent (P drugs and GSL products) in addition to POM through locally agreed protocols or by supplementary and independent prescribing (Fielding et al., 2015).

A recent systematic review has supported PMAS as an effective and cost-effective strategy for managing patients (Watson et al., 2014). Furthermore, research shows GPs are generally in favor of diverting the care of minor ailments to other areas, including community pharmacies, to allow for a greater focus on complex cases (Paudyal et al., 2013) but some are concerned with the ethics behind pharmacists diagnosing then prescribing an agent (Taylor and Joubert, 2016). Mounting evidence shows the public response to PMAS has been positive, with patients seeking pharmacist help judiciously.

The success of PMAS has emphasized the value of pharmacists as care providers and encourages further expansion of pharmacists' scope of practice and pharmacy-based services. Such initiatives may further reduce strain on healthcare systems and facilitate sustainability.

The Future

With a growing and aging population and subsequent rising healthcare costs, stakeholders worldwide have been challenged to identify opportunities for cost-savings. Research shows that encouraging pharmacist-guided self-care is an effective means of reducing healthcare costs, without compromising quality of care (Nakhla, 2018). As such, many countries have implemented formal programs, including pharmacy-based minor ailment schemes (PMAS), to promote and facilitate community-based care. Essential to the success of these programs, is identifying opportunities for increasing public awareness of pharmacists' expertise in self-care, and improving patient engagement (van Eikenhorst et al., 2017). Strategies may include becoming more active in health promotion campaigns, such as those targeting drug safety, or displaying signs in nonprescription aisles to encourage consumers to seek pharmacists' advice prior to product purchase (Covington, 2002, pp.519).

As self-care becomes more prevalent, additional clinical tools will be required to ensure pharmacist-led care is not only evidence-based and outcomes-focused, but also efficient and consistent (Boyce, 2017). Curley et al. (2016) recently explored developing and utilizing guidelines/protocols for minor ailment management in community pharmacies. These tools facilitate the accurate assessment of patients, including identifying when referral to another healthcare professional (HCP) is warranted, and the urgency of this, and when patients can be safely treated in the pharmacy setting. Such community pharmacy triage services (CPTS) have already emerged in a number of countries (Curley et al., 2016). Tools to better identify potential drug interactions will also be needed, as current interaction surveillance systems are not often applied to self-medications (Indermitte et al., 2007). Lastly, improving pharmacy efficiency will be critical to ensuring pharmacists have sufficient time to respond to the growing demand for self-care consults.

Increasing awareness of the importance of health and wellness has motivated patients to play a greater role in their care. This, coupled with prescription-to-nonprescription switches and advances in technology, products and devices, has contributed to an expanding self-care market worldwide. Amid this ever-growing self-care movement has been the need for an accessible and knowledgeable HCP to facilitate safe and effective self-medication practices. Pharmacists, as community-based medication experts and gatekeepers, have taken on this role. Through thorough assessment, evidence-based recommendations, effective communication, and active collaboration with patients and other HCPs, pharmacists can empower patients to engage in self-care safely and effectively. Life-long learning to stay current is paramount, if pharmacists wish to remain preeminent self-care advisors and nonprescription drug therapy managers in a rapidly changing self-care environment (Covington, 2002).

Glossary

Culture the ideas, customs, attitudes, and behaviors of a particular nation, people, or social group (Oxford Dictionary, 2017)
Cultural competency in healthcare "the ability to provide care to patients with diverse values, beliefs and behaviors, including tailoring delivery to meet patients' social, cultural, and linguistic needs" (Betancourt et al., 2002)
Complementary and alternative medicines (CAMs) treatments that are usually less well-studied and are used in addition to (complementary) or instead of (alternative) standard treatments—examples include herbal preparations, acupuncture, magnetic therapy, and spiritual healing (NCI, 2015)
Generalizations documented or self-described behaviors or characteristics of groups or cultures that are often used as a starting point for understanding these populations (Sias and Jacobson, 2018)

Health literacy degree to which individuals have the capacity to obtain, process, and understand basic health information needed to make appropriate health decisions (US Department of Health and Human Services, 2000)
Medication-related problems the term replacing 'drug therapy problems' in the PPCP (JCPP, 2014) which includes unnecessary drug therapy; needs additional drug therapy; ineffective drug; dosage too low; adverse drug reaction; dosage too high; and adherence(Cipolle et al., 2012).
Minor ailment "common or self-limiting or uncomplicated condition which can be diagnosed and managed without medication intervention" (Paudyal et al., 2013)
Nonprescription medications (aka over-the-counter medicines) drugs which are available for sale without a medical prescription (Oxford Dictionary, 2017)
Patient-centered care providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions (Institute of Medicine (US), 2001).
Pharmaceutical care a philosophy of practice in which the patient is the primary beneficiary of the pharmacist's actions (Hepler and Strand, 1990).
Self-care confidence the ability to perform a specific self-care-related task and persist in performing that action or behavior, despite barriers or challenges (Riegel et al., 2012); "not an element of self-care but a factor that strongly influences self-care maintenance, self-care monitoring, and self-care management" (Ausili et al., 2017)
Self-care maintenance behaviors (e.g., making healthy lifestyle choices, engaging in physical activity) used to preserve health, maintain physical and emotional stability, improve well-being, or avoid disease and complications (Ausili et al., 2017; Riegel et al., 2012).
Self-care management autonomous or consultative process of responding with appropriate behaviors (e.g., responsible treatment implementation, adherence to medication therapies, implementing lifestyle modifications, collaborating with HCPs in shared decision-making) to health changes and problems to avoid an exacerbation (Ausili et al., 2017; Ausili et al., 2014)
Self-medication the selection and use of medications by individuals to treat self-recognized illness or symptoms (Rutter, 2015).
Self-care monitoring process of routine, vigilant body monitoring or surveillance, including symptom recognition and interpretation as well as self-surveillance of signs and symptoms for deterioration or improvement (Ausili et al., 2017); it serves as the link between self-care maintenance and self-care management(Riegel et al., 2012)
Stereotypes widely held, but fixed and oversimplified, images or ideas of particular types of people or things (Oxford Dictionary, 2017).

List of Relevant Web Pages

American Academy of Family Physicians: https://familydoctor.org/your-health-resources/drugs-procedures-and-devices/over-the-counter-products/
Agency for Healthcare Research and Quality- Pharmacy Health Literacy Center: https://www.ahrq.gov/professionals/quality-patient-safety/pharmhealthlit/index.html
American College of Lifestyle Medicine: https://lifestylemedicine.org
Association of the European Self-Medication Industry—Classification of OTC Ingredients by Country: http://www.aesgp.eu/facts-figures/otc-ingredients/
Consumer Healthcare Products Association: https://www.chpa.org and www.knowyourOTCs.org
Consumer Health Products Canada: https://www.chpcanada.ca and http://selfcare.ca
Ethnomed: https://ethnomed.org
European Lifestyle Medicine Organization: https://eulm.org
Institute for Safe Medication Practices: http://www.consumermedsafety.org/tools-and-resources/over-the-counter-medicines
International Self-Care Foundation: http://isfglobal.org/practise-self-care/
National Counsel on Patient Information and Education (NCPIE): http://www.bemedwise.org
Pharmaceutical Services Negotiating Committee: http://psnc.org.uk/services-commissioning/essential-facts-stats-and-quotes-relating-to-minor-ailments-services/
Proprietary Association of Great Britain (PAGB): https://www.pagb.co.uk
Self Care Forum: http://www.selfcareforum.org
SelfCare Journal: http://selfcarejournal.com
University of Saskatchewan and medSask Guidelines for Prescribing for Minor Ailments and Patient Self-Care: http://medsask.usask.ca/professional/guidelines/
World Self-Medication Industry: http://www.wsmi.org

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Extemporaneous Compounding in Pharmacy Practice

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Introduction

This chapter will familiarize the reader with basic principles involved in nonsterile compounding. As regulations pertaining to compounding, vary regionally, the emphasis will be on the basic pharmaceutics and practical scientific principles relating to compounding, rather than local policies regarding regulatory requirements. The reader is referred to seek their regional guidance for country-specific details regarding pharmacy setup and compounding requirements. Any recommendations or suggestions made in this chapter are intended to supplement, and not supersede or contravene these guidances. As regulations change, the compounder is always responsible for consulting the latest compounding guidances.

After reading this chapter, the learner will:

1. contextualize the importance of compounding and its applicability to patient care;
2. understand the roles and responsibilities within a pharmacy pertaining to compounding, including the pharmacy technician and compounding pharmacist;
3. garner a workflow for the general setup of a compounding pharmacy, in terms of layout, equipment, and record keeping;
4. have a basic framework for compounding common liquid, semisolid, and solid formulations; and
5. recognize that compounding is a high-risk process in pharmacy practice and it warrants special attention with respect to patient safety.

As sterile compounding carries an added risk of sepsis, stroke, and death, with regional-specific requirements for setup, monitoring, and testing, sterile compounding will not be discussed in this chapter. The learner is referred to their local pharmaceutical college and pharmacy regulatory authorities for training, recommendations, and guidance regarding sterile compounding.

Compounding in Community Pharmacy

In the pharmaceutical field, compounding refers to the creation of a medication through the addition, mixing, alteration, or removal of ingredients to provide customized medications to patients. It may involve the modification of an existing manufactured drug product or the preparation of a compound using raw ingredients (Feldschuh, 2008). The most common reason to compound medications is to mask unpleasant tastes, change the formulation of the medication and to provide patients with doses, not commercially available. All of these common barriers position compounding in community pharmacy to improve patient care by incorporating individual patient preference in the administration of medications. Compounding can also eliminate the administration of unnecessary ingredients, which is relevant with increasing intolerances and awareness of allergies. There is a growing patient population base that is allergic to preservatives, dyes, or binders that can be commonly found in manufactured medications. Compounding can also allow the patient to receive multiple medications in one formulation to increase compliance. Veterinary compounding can also allow for treatment of pets, farm animals, and even zoo animals (Bednarczyk et al., 2009; Connolly et al., 2018) (**Table 1**).

Table 1 Reason to compound medications

- Requirement of different dosage form (liquid instead of tablet, ointment instead of cream)
- Manufactured medication has been discontinued (reason not related to safety concern)
- Dose required not available as a manufactured product
- Alternate route of administration required
- Patient has allergy/intolerance/sensitivity to ingredient(s) in manufactured product
- Patient compliance will be improved with compounding (palatability for pediatric formulations, viscous suspension for palliative (or any) patients who have trouble in swallowing tablet formulations)

Source: Feldschuh, M., 2008. Compounding in community pharmacy. Aust. Prescr., 31 (2), 30–31.

Nonsterile Compounding

Compounding in the retail pharmacy setting is usually nonsterile compounding. Nonsterile compounding involves creating a medication in a clean environment but does not require the environment to be completely free from all microorganisms. This type of compounding is used for medications that will be taken orally, such as capsules, liquids, oral disintegrating tablets (ODTs), lozenges, or lollipops to name a few. It is also used for medications that are to be administered topically, such as creams, ointments, gels, toothpastes, sprays, and deodorants. Compared to medications that are injected into the body or put into the eyes, oral, and topical preparations have a much lower risk of causing infections (Connolly et al., 2018).

Before starting any compound, the USP 795 Guidance Document provides helpful guidance on the following questions that need to be answered (Okeke, 2014; USP, 2007):

1. Are the active ingredients already available in a manufactured product of the same formulation and dose?
2. Is a referenced formula available?
3. Is the beyond-use date (BUD) and relevant stability data available?
4. Does pharmacy staff have the dedicated space for compounding and is this space clean and free from clutter?
5. Are the appropriate equipments, ingredients, and materials readily available to make the compound in question?
6. Are the pharmacy personnel trained and competent to perform compounding for the preparation?
7. Can pharmacy personnel compound the preparation uninterrupted?
8. Should the compounded preparation be referred to another pharmacy with appropriate facilities, equipment and expertise?

Overcoming Errors in Compounding Pharmacy

Although dispensing errors in community pharmacies are generally low, ranging from 0.26% to 1.6% (Ashcroft et al., 2005; Boyle et al., 2011; Flynn et al., 2003), as the volume of compounded prescriptions increases, there are common dispensing errors that pharmacy staff should be mindful of. The following table depicts the multiple categories of possible dispensing errors to consider (**Table 2**).

In order to overcome these potential errors while compounding, the pharmacy staff must have designated roles, responsibilities, training, and procedures in place. In general, the following should be considered in pharmacy practice with respect to nonsterile compounding prescription preparation (Christ et al., 2017):

- Design labeling and packaging of compounding ingredients or chemicals in order to minimize the risk of identification and/or selection confusion.
- Adopt or apply a unique identification number or identifier for each ingredient in compounding formulas.
- Incorporate automated identification of compounding ingredients or chemicals (e.g., barcode scanning).
- Verify each ingredient and its measured amount of a compounded prescription through an independent double check process.
- Have written policies and procedures, or checklists for the preparation of compounded products that are based on professional standards of practice and guidelines for training and orientation of pharmacy staff.

Table 2 Categories of dispensing errors in compounding pharmacy

• Medication dispensed to the incorrect patient
• Incorrect medication is dispensed to the patient
• Dispensing the incorrect strength or concentration of the medication
• Dispensing the incorrect dose or frequency of the medication
• The wrong quantity is dispensed
• Incorrect dosage form or formulation dispensed
• Medication is dispensed with an incorrect route of administration
• Medication is dispensed with an incorrect duration of treatment
• Medication is expired or will expire during the regimen length
• Failure to dispense
• Dispensing an incorrectly compounded medication
• Dispensing a compounded prescription with omitted medication or dose
• Labeling error on dispensed medication (incorrect patient name, drug name, drug strength, quantity, instructions, dosage form, expiry date, omission of warnings, incorrect pharmacy information, etc.)
• Errors during compounding (wrong ingredients, wrong weights incorporated, inappropriate compounding techniques used, using expired products)
• Contamination during compounding (utensils, active pharmaceutical ingredient, surface contaminants)
• Improper storage of ingredients or compounded preparations prior to dispensing
• Errors during third-party billing of compounded prescriptions

Source: Cheung, K., Bouvyl, M., De Smet, P., 2009. Medication errors: the importance of safe dispensing. Br. J. Clin. Pharm., 67 (6), 676–680; Gudeman, J., Jozwiakowski, M., Chollet, J., Randell, M., 2013. Potential risks of pharmacy compounding. Drugs R&D, 13 (1), 1–8; Ho, C., Hung, P., Lee, G., Kadija, M., 2010. Community pharmacy incident reporting: a new tool for community pharmacies in Canada. Healthc. Quarter., 13 (Special Issue), 16–24.

Nonsterile Basic Pharmacy

Although roles and responsibilities can vary from pharmacy to pharmacy, in a typical compounding pharmacy, the owner or manager assigns a designated compounding lead that is responsible for developing, organizing, and supervising all activities related to nonsterile pharmacy compounding. The compounding lead can share the responsibilities or assign them to a pharmacist or pharmacy technician. Just like regular pharmacy dispensing, compounding requires a strict standard of operations. Personnel need additional training, as common compounded preparation errors include calculation, unit of measure, calibration, and mixing errors. Appropriate measures need to be taken to ensure the safety of personnel during the preparation of each compounded prescription. Typically, the pharmacy manager or compounding lead is responsible for developing the policies and procedures, regularly reviewing them to ensure they are updated. The current recommendations are to review procedural documents every 2–3 years to ensure that they reflect any regulatory changes (National Association of Pharmacy Regulatory Authorities, 2016).

As a part of the initial compounding pharmacy setup, the facilities and the equipments used to compound must meet requirements and need to be calibrated or certified according to manufacturers' specifications or standards (whichever is more stringent) (National Association of Pharmacy Regulatory Authorities, 2016).

The compounding lead should also ensure that the available resources reflect recognized scientific literature to determine stability and to establish beyond use dates (BUD) for each non-sterile preparation. Any master formulation records that are developed are regularly reviewed and updated. The formulas utilized in compounding should either be gathered from reputable compounding or evidence-based drug information resources, or can be formulated by the compounding pharmacist or pharmacy technician. Stability data needs to be readily available to make educated considerations when designing a compound. If any formula is designed or formulated in-house, the compounded preparation should be sent for testing to a contract laboratory for stability analysis. The act of preparations, weighing, measuring, and formulations can be delegated if the pharmacy technician or assistant has received the appropriate training on compounding techniques and procedures (National Association of Pharmacy Regulatory Authorities, 2016).

Since compounding is considered as one of the high-risk processes in community pharmacy practice (Boucher et al., 2018), all steps in the process should be independently double-checked by pharmacy professionals to ensure errors are prevented and processes are maintained (Bednarczyk et al., 2009; Gudeman et al., 2013). The significance of independent double checks and strict compliance to standardized procedures to confirm accuracy and quality of compounded preparations can be illustrated by the incident below (Kawano and Ho, 2012).

> *A pharmacist intended to compound an oral suspension of clonidine (using clonidine powder) for a 15-year-old male. The pharmacist incorrectly compounded the clonidine suspension (due to mixing up during calculations/conversions among grams, milligrams, and micrograms) resulting in a preparation 1,000 times more concentrated than prescribed. Before the error was discovered, the patient was admitted to hospital multiple times.*
>
> Evans et al. (2011)

A miscalculation could lead to dispensing a preparation 1000 times more concentrated than the intended prescription, resulting in harm to patients. On the other hand, an incorrect conversion could also result in a compounded preparation, many times less concentrated than prescribed, rendering a suboptimal therapy to patients.

Physical Layout

General

Pharmacy compounding must be performed in a designated space that allows room for equipment and materials in a fashion that will prevent errors among ingredients, containers, or in the processing of the compounded prescription (National Association of Pharmacy Regulatory Authorities, 2016).

Layout

The design should prevent the opportunity for cross contamination between products. The active ingredients should be stored in a way that would prevent recognition error or confusion between sound-alike and look-alike ingredients. Some techniques could include storing ingredients based on typical formulations in which they would be compounded, ultimately separating oral, topical, and other formulation ingredients (e.g., Diclofenac, Baclofen, Gabapentin, Lidocaine, and similar active pharmaceutical ingredients (APIs) being stored in a cabinet of items used in topical pain preparations along with vehicles). This type of structure would prevent the inadvertent use of a topical API in an oral formulation. A haunting incident occurred in Toronto, Canada in 2016 leading to the death of an 8-year-old patient who was dispensed a compounded suspension of baclofen 150 mg/mL instead of a tryptophan suspension of equal concentrations. This incident resulted in pharmacy practice changes throughout the country (Christ et al., 2017). The compounding pharmacy layout must be easily cleanable including any fixtures that collect dust. The areas utilized for nonsterile compounding must be maintained in clean, orderly, and sanitary conditions.

Lighting

The lighting must be optimized, with fixtures located in such a way as to provide a well-lit area to facilitate the compounding process and to allow verification at all stages of compounding. Personnel need to be cognizant of light labile ingredients and store them appropriately.

Heating, Ventilation, and Air Conditioning System

Measures need to be in place to ensure that heating, ventilation, and air conditioning are controlled. Appropriate temperature and humidity is required to be maintained as chemicals, components, and compounds are subject to degradation. Proper ventilation is required to prevent contamination of products during compounding, ensuring the quality and purity of stored products. Heating, ventilation, and air conditioning systems need to be in place to ensure staff safety and comfort during compounding as well. For items requiring refrigeration, a separate refrigerator in the compounding room is recommended.

Water Supply

Potable water is required for hand and equipment washing. The compounding lab should have a reasonable stainless steel sink and faucet that is ideally accessible to all compounding areas. Distilled water is required for use in compounding nonsterile drug preparations when formulations indicate the inclusion of water. The facility plumbing system is required to be free of any defects that could contribute to possible contamination in compounded preparations.

Work Surfaces

Furniture and work surfaces need to be constructed of smooth, nonporous material that is impermeable and easy to clean. This material must be resilient to repeated cleaning and disinfecting and must be resistant to damage from cleaning or disinfecting products.

Furniture, Walls, and Flooring

All furniture, floor, and wall surfaces must be designed and placed to facilitate cleaning and disinfecting.

Basic Equipment

The equipment chosen must be appropriate to the type of preparations that are to be compounded. The designated apparatus or instruments should only be used for compounding activities. The equipment must be comprised of material that can be easily cleaned and disinfected and will not react with any of the ingredients used in compounding. Table 3 is not exhaustive of all compounding lab equipment but may serve as a list to consider when a compounding pharmacy is to be set up.

Introduction to Common Extemporaneous Formulation Types

This section will introduce the reader to the basic-building blocks of pharmaceutical compounding.

Compounded nonsterile preparations include, but are not limited to the following types of medications:

- Oral liquids (solutions, suspensions, and emulsions)
- Ointments and creams
- Other topical products (lotions, powders, emulsions, and gels)
- Suppositories
- Lillipops, troches, lip balms, mouthwashes
- Sachets and oral powders
- Capsules and tablets

Liquids

Oral liquids are useful in delivering medication to specific patient demographics. Pediatric patients (5 years and younger) are typically unable to swallow solid-fixed dosage forms like tablets, caplets, or capsules. Another issue that arises in the pediatric population is the frequent inability to use fixed doses, as weight or surface area based dosing is the gold standard. Thus, compounded

Table 3 Basic compounding equipment

Glassware	*Beakers flasks graduated cylinders watch glass*
Hot plate and accessories	Hot plate, beaker holder, extension clamp, thermometers, stir bars, stirring rods
Mortar and pestles	Various sizes, porcelain or flint glass
Ointment slab and paper	Ointment paper, glass or marble slab
pH products	pH paper, pH meter
Scoops, spoons, and spatulas	Measuring spoons, mini metal spatulas, mixing spatulas, stainless steel spatulas
Digital scale and accessories	Electronic scale, weighing paper, weighing boats, calibration weights
Dispensing containers	Glass bottles, plastic bottles, drop containers, plastic or glass droppers, spray bottles, ointment jars of various sizes, lotion pump dispensers, sealable tubes, Topi-CLICKS(R)
Molds	Lozenges/troches, lollipops, suppositories, triturate (oral disintegrating tablet [ODT])
Personal protective equipment	Latex or nitrile gloves, N95 masks, gowns, safety glasses (eye protection)
	Lab coat
	Hair cover
	Other protective wear (as appropriate)

liquid preparations are particularly useful in the pediatric population to ensure appropriate dosing ranges are maintained, as the dose can be varied by the volume of compound administered.

Suspensions

Typically, community pharmacies compound using available fixed dose medications, pulverize them, and then suspend the drug in a palatable, flavored vehicle to promote administration and compliance. Carboxymethylcellulose or methylcellulose suspensions and simple syrup are commonly used vehicles for suspending medications (Nahata and Allen, 2008).

Best practices recommend utilizing the pure, raw API when compounding liquid medications. Manufactured oral medications in the tablet form contain excipients that may not be soluble when suspended. These ingredients include disintegrants, diluents, coatings, glidants, lubricants, and colorants (Troy and Beringer, 2005). Although the drug may be soluble in the vehicle, the excipients may not be, ultimately yielding an unappealing, unusable product.

When compounding liquid formulations using tablet or capsule manufactured drugs, it is important to avoid using controlled release formulations (slow-release, controlled-release, delayed-release) or enteric-coated formulations. If coated is the only option, the coating may need to be dissolved or very finely ground to unbind the active ingredient. See section, *Product Example Formulations and Calculations*, for example: sample formula for Baclofen 5 mg/mL Oral Suspension (60 mL) (Sick Kids Pharmacy, 2007).

Emulsions

An emulsion is a two-phase system where one liquid is dispersed in the form of small globules throughout other liquid. The dispersed liquid is known as the internal phase and the dispersion material is known as the internal or continuous phase. A typical emulsion is an oil-in-water emulsion where oil is the dispersed phase in an aqueous solution as the continuous phase. These mixtures require emulsifying agents to promote homogeneous mixing.

Emulsions serve a couple of purposes in compounding for oral use. The absorption and penetration of some medications are easily controlled if they are incorporated into an emulsion formulation. Emulsions are widely used in compounding pharmacy when certain medicinal ingredients have an unpleasant taste. Emulsions can create a more palatable product to be administered orally as is commonly used when masking oil-in-water administration of drugs. The aqueous phase can be formulated to contain appropriate sweetening and flavorant to mask the oil and drug mixture. For example, in an oil-in-water emulsion, the API may be readily soluble in the oil phase. After administration, the oil droplet that contains the medication will be absorbed using normal absorption mechanisms of oils. Typical emulsifying agents in oral mixtures include acacia, gelatin, and lecithin. The ideal emulsifying agent is stable, compatible with the other ingredients, colorless, odorless, tasteless, nontoxic, and will not interfere with the delivery of the API (**Tables 4 and 5**).

Emulsions have been used ubiquitously in the formulation of dermatological products like creams and lotions. External emulsions like lotions and creams serve to provide an external medication delivery vehicle of a drug that has low aqueous solubility.

A compounding pharmacist may rely on hand homogenizers and electric mixtures when preparing emulsions.

Table 4 Natural emulsifying agents

Class	*Example*	*Emulsion type; route of administration*
Finely divided solid	Bentonite	o/w and w/o; topical
	Aluminum hydroxide	o/w; oral
Phospholipid	Purified lecithin	o/w; oral
Polysaccharide	Acacia	o/w; oral
	Methylcellulose	o/w; oral

Source: Troy, D., Beringer, P., 2005. Remington: The Science and Practice of Pharmacy, twenty-first ed., Lippincott Williams & Wilkins, Baltimore, MD, Philadelphia.

Table 5 Density factors for selected agents in cocoa butter

Aspirin	1.3
Barbital	1.2
Cocaine HCl	1.3
Menthol	0.7
Morphine HCl	1.6
Opium	1.4
Phenobarbital	1.2
Procaine	1.2
Quinine HCl	1.2
Sulfathiazole	1.6
Zinc Oxide	4.0
Zinc Sulfate	2.8

Source: Allen, L., 2014. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, tenth ed., Lippincott Williams & Wilkins.

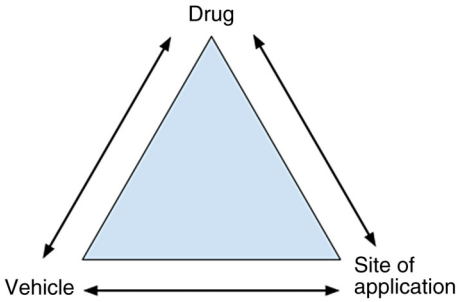

Figure 1 With topical the drug, base, and application sites affect each other, which can affect release of the drug from the base, and ultimately the potency of the formulation.

Ointments

Semisolid-dosage forms are intended to be applied on the skin or other topical surfaces of the body (e.g., eyes, fingernails, and lesions), for the purpose of:

1. providing lubrication (emollients);
2. bringing into contact with the drugs for skin, that are required in healing skin disorders;
3. acting as protective coverings to prevent contact of the skin surface with chemicals, solutions, and organic solvents.

The preparations include primarily ointments/creams (salves), cerates, jellies, pastes, plasters, and poultices. Ointments are of such a consistency that they may be readily applied to the skin by spreading. The viscosity of an ointment should allow it to soften, but not necessarily melt when applied to the body. Creams and jellies generally have a lower viscosity than ointments whereas cerates, pastes, plaster, and poultices generally have a higher viscosity (Dubins et al., 2017).

When semisolid preparations are applied to local areas of the skin, the vehicle often has a more pronounced initial effect than the APIs. The effect produced is often due to a synergistic effect between the APIs (e.g., antibiotic agent, keratolytic agent, antipyretic agent, antiseptic) and the base itself. The base usually has a more general action on the skin, providing occlusion to water loss from the skin, emollient and lubricating action, or a drying action. In turn, the base also will affect the properties of the tissue on which it is directly applied, which can also affect absorption of the API. The relationship between vehicle, API, and site of application is extremely contextually dependent. Drug absorption through thicker skin (e.g., knees and elbows) will be slower and more susceptible to mechanical removal by rubbing against clothing than drug absorption through intertriginous areas (e.g., armpits and groin). Fig. 1 illustrates the interrelationships between API, vehicle, and properties of the skin. For instance, an occlusive vehicle can hydrate the skin, making it more porous and therefore, more permeable to the API. These interrelationships are not always predictable, and are sometimes not completely understood until clinical testing.

Ointments in the pharmaceutical sense are one phase—having one component (e.g., oily ointment or hydrophilic ointment). This can give ointments a translucent appearance (e.g., Petrolatum USP), although depending on the identity of the ointment and the API incorporated, an ointment need not be translucent (e.g., Hydrophilic Ointment USP is opaque white).

Preparation by Fusion

If any components of an ointment are solid, fusion is required to compound the ointment. Ointment preparation is easily accomplished by fusion, provided the vehicle melts easily and is thermostable within bench-top heating temperatures (<200°C), and the API is reasonably thermally resistant to degradation at the temperatures and duration they are exposed to heat during compounding. The principle of fusion is simple. It involves melting all of the intended excipients in a ceramic dish, over a hot plate (and preferably a water bath to control the temperature and protect the excipients from burning). The excipients can be added to the ceramic dish in reverse order of melting point, in order to minimize exposure of each excipient to high-temperatures. A thermometer may be used to monitor the temperature to ensure that the mixture is above the melting point of the highest excipient, but in general, most excipients melt quite readily and are qualitatively homogeneous liquids when melted properly. It is important not to overheat the melted mass, or the excipients may burn, degrade, or separate. The mixture should be continually stirred with a glass rod while melting.

Once the mixture is melted, the API is added at this point, again to minimize exposure of the API to heat unnecessarily. The API can be added directly as a powder, or tituated through a wire mesh screen to reduce the particle size. Once incorporated, the mixture should be removed from heat and stirred continuously while congealing to ensure the API is evenly distributed throughout the vehicle. Some API powders will disperse and not dissolve in the ointment; this can result in separation or caking of the API powder in the vehicle, which precludes an elegant, homogenous ointment. After the mixture congeals, it can be removed and packed into an ointment jar.

Fusion may also be used to prepare solid formulations (e.g., suppositories, lip balms, etc.), and the same method is followed (Fig. 2).

Preparation by Mechanical Incorporation

Mechanical incorporation is often used on the pharmacy bench if a ready-made ointment is purchased through a compounding retailer, and especially if an API is heat-sensitive. Mechanical incorporation involves directly mixing the API into the vehicle in a

Figure 2 A steam bath is set up to limit direct exposure to heat from the hot plate. A ceramic dish is set on top of the steam bath to melt components of the formulation.

controlled way, ensuring even distribution of the API. If the API is a course or lumpy powder, it can be pulverized or passed through a handheld sieve using a spatula to reduce the particle size. Two common techniques for mechanically incorporating an API into a base are first *levigation* and then *geometric dilution*.

Levigation

Whether or not a drug is compatible with a vehicle (e.g., a hydrophobic drug is to be incorporated into a hydrophobic base), most APIs are available as white or off-white dry powders. It is difficult to disperse a dry powder evenly throughout a semisolid vehicle. Air can entrap between powder particles, and ointments by nature have very high-surface tensions, making wetting the surface of the particles a lengthy task. In order to facilitate the drug being dispersed into the vehicle, a minimal amount of liquid *compatible in hydrophilicity* with the vehicle may be mixed with the powder, in order to wet the powder granules, and reduce particle size. This process is known as *levigating* the powder. The following procedure is used for levigation:

1. The API powder is weighed, and transferred to the middle of a glass slab or wax paper compounding pad using a spatula.
2. A levigating agent is selected that is compatible with the ointment vehicle. For a hydrophobic ointment, mineral oil (heavy) USP may be used in many cases. For a hydrophilic ointment, Glycerine USP may be used. If the vehicle is not very viscous, then the vehicle itself can be used to levigate the API.
3. The levigating agent is added drop by drop to the powder and carefully mixed, until a homogenous, toothpaste-like consistency is obtained. Mixing should be controlled and contained so that the API remains in a small mound at the center of the glass slab or pad. A thin, diffuse layer of API will dry out quickly, and will be difficult to recover in its entirety. The total volume of levigating agent added should be quantitatively minor compared to the overall batch weight of the ointment (**Figs. 3 and 4**).

Geometric dilution

Once the API is levigated and at the center of the glass tile or wax pad, the next task is mixing the API with the intended amount of vehicle, to produce the correct overall concentration in the ointment. Many topical ointments are highly potent (e.g., progesterone or hydrocortisone), and the challenge is incorporating a small amount of API evenly in a large amount of vehicle. For example, a 0.1% Hydrocortisone Ointment, batch size 30 g would only require 30 mg of drug. If drug and vehicle are mixed together all at once, the API can "get lost" in the vehicle, resulting in uneven ointment potency. A more efficient way of mixing a small amount of API in a comparatively large amount of vehicle is by *geometric dilution*. The principle of geometric dilution is that it is more efficient to mix equal parts of mixtures (half/half). The following procedure is used for geometric dilution:

1. The total amount of vehicle required for the formulation is prepared and weighed.
2. The API powder required for the formulation is added to the center of a marble or glass tile.

Figure 3 A few drops of a levigating agent is added to the component to be dispersed in the ointment vehicle.

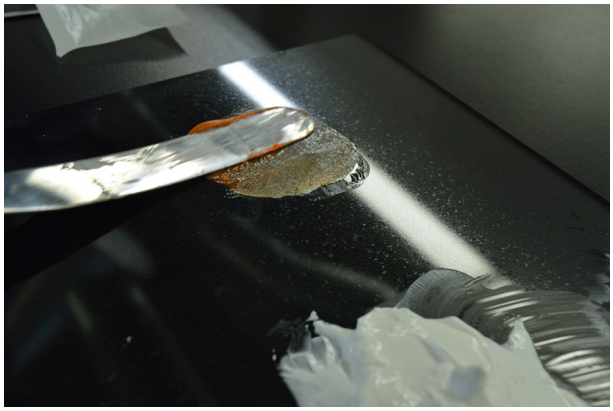

Figure 4 Using a spatula, the powder is reduced to a fine paste by mixing with the levigating agent.

3. The API powder is levigated with a levigating agent (if required), or reduced in particle size mechanically with a handheld sieve (if required).
4. An amount of vehicle approximately equal to the amount of API powder on the compounding pad is added to the pad, directly beside the API.
5. A spatula (hard rubber, plastic, or stainless steel) is used to evenly mix the equal amounts of API powder and vehicle. Mixing is performed in a controlled but thorough way, in order to prevent the ointment mixture from spreading out on the compounding pad. Continue mixing until the mixture is uniform.
6. Once the moieties are mixed, steps (4) to (5) are repeated (this time adding an amount of vehicle approximately equal to the amount of mixed API powder + vehicle, then mixing until uniform), until the entire amount of vehicle has been incorporated into the mixture.

The ointment is then ready to be recovered, packed, and labeled, using an ointment jar appropriate for the volume of ointment prepared (Fig. 5).

Ointment Jar/Container Selection

Since ointments tend to be very viscous, it can be difficult to pack a thick ointment into an ointment jar. The first consideration for packing an ointment is to choose an appropriate ointment jar size (one where the ointment jar is full, allowing for a bit of space at the top). As with other formulation packaging, jar size is important for various reasons:

- a patient shouldn't have to reach deeply into the jar to recover the ointment;
- an ointment jar that appears to be less than half full has the perception of being empty or underfilled;
- the amount of air in the ointment jar should be minimized;
- if the jar is overfilled, it will stick to the lid and appear pharmaceutically inelegant.

An ointment tube may also be considered, if the compounding pharmacy has a tube end-sealer (Fig. 6).

Figure 5 The vehicle is mixed in equal proportions sequentially to the levigated powder, to ensure even mixing.

Figure 6 From left to right: lip balm tube, ointment jar, foam dispenser, pump dispenser, armpit applicator.

Ointment Jar Packing

Once a jar size is selected, the compounded ointment is transferred to the ointment jar using a spatula, by adding a small amount of vehicle to the tip of the spatula, and plunging the spatula directly downwards into the mouth of the ointment jar. Then, the ointment is scraped onto the inside ridge of the ointment jar by removing it at a 45-degree angle while gently pressing down. This action reduces the amount of air entrapped at the bottom of the ointment jar. The jar is rotated slightly each time a new amount of ointment is transferred from the compounding pad (Fig. 7).

Figure 7 The ointment is packed by scraping it off the spatula on the inside of the ointment jar lid, while pressing downward. The ointment jar is rotated slightly for each new transfer of ointment.

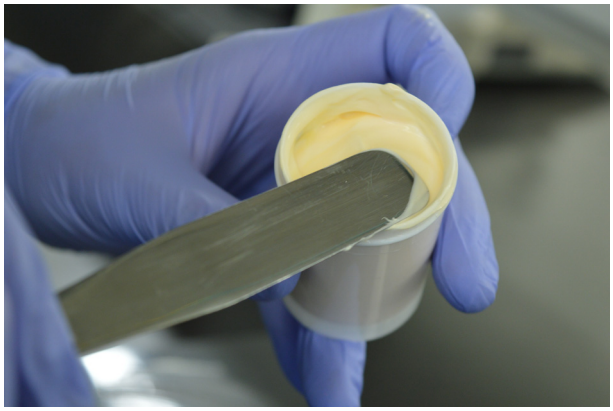

Figure 8 The ointment jar is rotated as a spatula is used to smooth out the surface of the ointment.

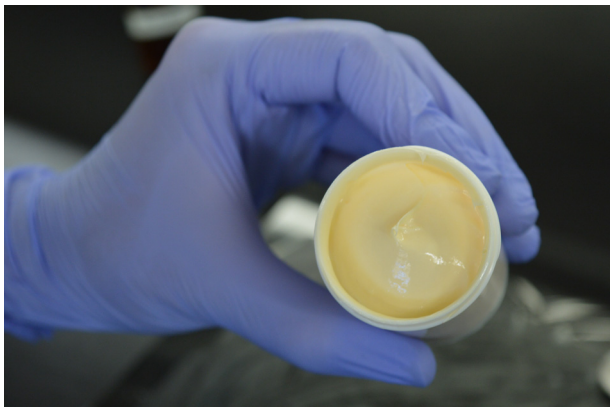

Figure 9 The ointment is finished with a clean looking cone-shaped spiral.

If the ointment jar becomes too full before all of the ointment is transferred, consider the following actions:

- Plunging the spatula up and down quickly, but gently in the middle of the ointment jar. This will work any entrapped air pockets upwards, freeing up more room for ointment.
- Selecting a larger ointment jar.

In the past, ointment jars were typically made of glass. Generations of pharmacists were taught not to bang the ointment jar body against the counter in concern of cracking the glass. Although modern ointment jars are hard white plastic, plunging the ointment is preferred to banging the jar body against the counter, as it is a more effective measure of mechanically removing entrapped air.

After the entire compounded vehicle is transferred to the ointment jar, the top of the ointment should be smoothed out with a spatula into a single spiral peak, providing a pharmaceutically elegant looking product. This is obtained by carefully placing the tip of the spatula on the surface of the ointment, angled upward, toward the middle of the jar, then rotating the base of the jar (**Figs. 8 and 9**).

Finally, the sides of the ointment jar should be wiped clean of any ointment, and the lid should be capped tightly. The packed full ointment jar should not result in any ointment sticking to the lid. The jar is then appropriately labeled. See section, Product Example Formulations and Calculations, for a hydrocarbon ointment example: White Ointment USP XXII: (hydrocarbon ointment) (Troy and Beringer, 2005).

Creams: O/W, W/O

A cream is a mixture of two otherwise immiscible phases: a hydrophobic phase and a hydrophilic phase, and usually a surfactant or emulsifying agent to keep the cream from separating. For this reason, since one phase is dispersed in the other, the refractive index between the continuous and dispersed phases imparts a milky, opaque color to creams, scattering light as it travels through.

The method of preparing creams by the fusion process is slightly more complicated. In this case, both the aqueous phase and the oil phase are heated separately, to somewhere between 60–80°C. As a general rule, the oil phase should be heated to at least 5°C above the melting point of the highest melting waxy ingredient. The water phase is heated to 5°C *above* the temperature of the oil phase to prevent premature solidification prior to mixing and emulsification. Melting points can be obtained through literature values, or the compounder can simply observe when the last solid disappears during the melting process, and heat the mixture an

additional 5°C. Water-soluble excipients are dissolved in the heated aqueous phase with stirring, while nonvolatile oil-soluble ingredients are dissolved in the heated oil phase. Generally, the internal (dispersed) phase is gradually added to the external (continuous) phase and vigorously mixed. An electric hand blender may be used to facilitate mixing. Multiple excellent creams have been produced by combining the reverse order, and the method of preparation may vary from one formula to the other.

If the hydrophilic phase of a cream contains water, then a preservative should be considered. The following formulation is an example of a common O/W emulsion (discrete oil-based phase suspended in a water-based continuous phase). An O/W emulsion will be less oily, and more washable than a W/O emulsion (Dubins et al., 2017). See section, Product Example Formulations and Calculations for O/W cream example: Hydrophilic Ointment USP (USP, 2007), and a W/O cream example: adapted from Cold Cream USP XVIII (Singh, 2010).

Poloxamer Gel Cream

Gels can offer a unique vehicle for topical (especially ocular), or systemic delivery. Gel properties can be custom tailored to the formulation. Compatibility may be an issue, as the biochemical properties of the API can alter the integrity of the gel. Temperature is also a very important control, particularly in the vicinity of the gel-sol transition temperature of the vehicle. Preparation of a gel vehicle is therefore extremely formulation dependent, since some gelling agents undergo this transition backwards, gelling with increasing temperature. One such gel cream is poloxamer/lecithin isopropyl palmitate vehicle (also called PLO/LIPS cream). Poloxamer creams are extremely versatile. The poloxamer moiety, purchasable at different concentrations under the name "pluronic gel", constitutes the aqueous component of the cream. Interestingly, this gel sets at and above room temperature, into a stiff jelly-like consistency. The gel also "rings" when tapped, reverberating the vibrations against the walls of its container. When chilled, the gel reverts back to a free-flowing solution (an interesting phenomenon called reverse thermal gelling). Poloxamer gels have wide-ranging applications from teeth-bleaching to artificial skin. Pluronic gel may be purchased, or compounded at the desired concentration using the protocol provided in section, Product Example Formulations and Calculations (Poloxamer 20%/LIPS gel cream [Dubins et al., 2017]).

Carbomer and Cellulose-Based Gels

Carbomers (also called Carbopols) are one of the most common thickening agents for water phases. Their properties in aqueous solutions depend both on temperature and pH. At low pH, the gel is more liquid, so adjustment to neutral pH may be required depending on the formulation (Sultana et al., 2006). The pH of the vehicle may be adjusted with sodium or potassium hydroxide for aqueous solutions. If alcohol gels are required, triethanolamine can be used to adjust pH to neutrality (https://pharmlabs.unc.edu/labs/gels/agents.htm). At lower concentrations, these same agents can be used as suspending agents, which are more free-flowing than their gelled form. Carbopol can also be combined with methylcellulose to form stiffer gels. Working with gelling agents can be difficult, as they can be difficult to solubilize, and readily clump together when added to water in a single pour, floating on the surface. One way to accomplish this task (the "hot" method) is by heating one third of the required vehicle just below boiling (80–90°C), then slowly adding the gelling agent while stirring vigorously with a large magnetic stir bar or glass rod. Once the powder is dispersed, the remainder of required vehicle is added as cold water, and then the mixture is refrigerated overnight. See section, Product Example Formulations and Calculations for an example: 2% Methylcellulose Gel (Dubins et al., 2017).

Another method (the "cold" method) is performed, by adding the powder to the required amount of vehicle in a large beaker, and then using an electric-hand blender to disperse and solubilize the particles. As with any aqueous solution, a preservative should be added to prevent bacterial growth. See section, Product Example Formulations and Calculations for an example: 1% Carbomer Gel (cold method).

Preparations Using Molds (Solids)

The compounding pharmacist or pharmacy technician has unique opportunities to help design and prepare custom formulations by shape and type, in order to best meet the needs of patients. Using a mold, whether by pouring in a vehicle that solidifies, or compressing a powder, offers the ultimate flexibility. Mold preparations have found their way into pediatrics (lollipops, suppositories, gummy bears), adult medicines (rectal rockets, troches, vaginal suppositories, and lip balms, rapid-dissolving tablets), and veterinary medicines as well.

Whereas, most pharmaceutical preparations are prepared by weight (% w/w), preparations involving mold filling are performed by volume. This results in the need to either calibrate the mold in order to plan for the correct dose, or formulate in such a way that the *volume* of the APIs in the formulation is taken into account. Molds offer the ultimate flexibility in creating a useful and potentially innovative shape and appearance. This can help with administering the drug (e.g., the shape of a suppository is tapered to facilitate insertion), or can improve the organoleptic properties of the drug (e.g., adding colorants and flavorants to a lollipop formulation). See section, Product Example Formulations and Calculations, for calculations pertaining to formulations using molds.

Suppositories

A suppository is a plug of medication that is intended to be inserted in an orifice other than the mouth (e.g., rectum, vagina, urethra) that melts or dissolves at body temperature. They can be formulated for local or systemic drug delivery. Table 6 lists some common uses for suppository formulations, intended for local and systemic drug delivery.

The ideal suppository vehicle should be compatible with the drug intended for delivery (i.e., not degrade or interact with the drug), have a melting temperature in the vicinity of body temperature (or dissolve in body fluids), and not interfere with drug release

Table 6 Suppository formulation examples for local and systemic drug delivery

Local delivery	*Rectal:* • Constipation (glycerin, bisacodyl) • Antipruritic (lactic acid) • Vasoconstrictor (phenylephrine) • Local anesthetic (lidocaine) • Steroid (hydrocortisone) *Vaginal:* • Antifungal (clotrimazole) • Antibiotic (metronidazole) • Fertility agent (progesterone) *Urethral:* • Erectile dysfunction (alprostadil)
Systemic delivery	*Rectal:* • NSAIDs (diclofenac, indomethacin) • Antipyretic (acetaminophen) • Antiemetic (prochlorperazine, chlorpromazine, dimenhydrinate, ondansetron) • Opioid analgesia (oxymorphone HCl)

or absorption. Generally speaking, absorption occurs across a topical surface, but because the vehicle melts or dissolves, the thermodynamic activity of the drug in the vehicle helps drive diffusion. Consequently if systemic absorption of the drug is intended, a vehicle should be selected that is *opposite* in hydrophilicity to the drug. In other words, a hydrophilic vehicle should be selected for a hydrophobic drug, and conversely, a hydrophobic vehicle should be selected for a hydrophilic drug. Table 7 illustrates examples of the major types of suppository vehicles: oleaginous, hydrophilic, and water-dispersible.

Suppository compounding equipment

Although in an industrial context, suppositories are made by compressing the vehicle/drug mixture into a mold, in a compounding context, fusion molding is required (melting the required ingredients, mixing, pouring into the mold, and cooling to solidify). Various mold types are available. The first suppositories were cocoa butter, and were formed by hand-rolling, a practice no longer used (Allen, 2014). Subsequently, large aluminum molds were used, consisting of plates that could be separated to expose the formed suppositories lengthwise. This facilitated removal of the dosage form from the mold. Lubrication of the mold (e.g., with mineral oil) was required, particularly with hydrophilic vehicles, in order to recover the suppositories without breaking them.

Table 7 Common suppository vehicles

Base type	*Advantages*	*Disadvantages*	*Examples*
Oleaginous	• Easy to prepare • Self-preserving • Better for inflammation/irritation (emollient) • Most common • Self-lubricating (facilitates insertion)	• May leak out of orifice upon melting • Poor systemic absorption of hydrophobic drugs • Unfavorable polymorphs of cocoa butter may form with overheating or rapid cooling	• Cocoa butter • Hydrogenated vegetable oils (e.g., Theobroma oil) • Synthetic triglycerides (Witepsol H-15)
Hydrophilic	• Melts at 37°C • Melts more slowly than oleaginous vehicles • Well-suited to rectal/vaginal/prolonged release • Chemically stable, nonirritating • Miscible with water/mucous secretions	• Not self-preserving (will require a preservative if formulation contains water) • Hygroscopic (may cause pain in orifice) • Not self-lubricating (wet before insertion) • Poor/sensitive mechanical properties (brittle) • Glycerinated gelatin requires mold lubrication prior to casting	• Glycerinated gelatin • Hydrogels (polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid, polyethylene) • Polyethylene Glycol (macrogols)—high-molecular weight, or mixtures
Water dispersible	• Can make an oleaginous base more hydrophilic	• Surfactants can irritate the orifice lining (e.g., the anal mucosa) • This can result in expulsion of the dosage form, and/or have a laxative effect	• W/O emulsions • Polyoxyl 40 stearate (surfactant) • Oleaginous vehicles with surfactant

Source: Allen, L., 2014. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, tenth ed. Lippincott Williams & Wilkins; Baltimore, MD; Aulton, M.E., Taylor, K.M.G., 2013. The Design and Manufacture of Medicines, fourth ed. Aulton's Pharmaceutics, Churchill Livingstone, London.

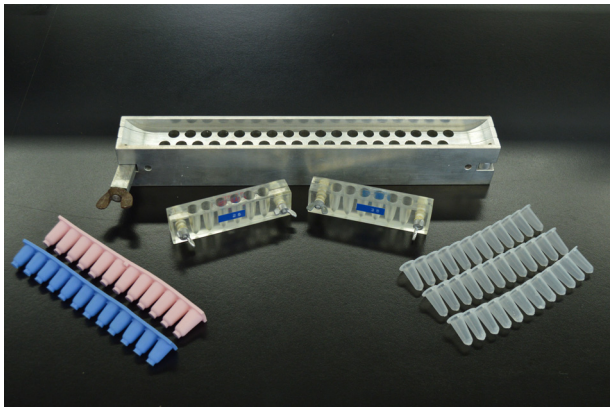

Figure 10 Various suppository molds. Left: silicone molds, center: aluminum and acrylic molds, right: plastic shells.

Contemporary compounding sees less of this style mold in favor of disposable rubber, plastic, or silicon suppository strips. Heat-shrink suppository shells can be purchased that also function as the dispensing package, leaving removal of the suppository as a task for the patient.

At the very minimum, the compounding pharmacist or pharmacy technician would require the following equipment for making suppositories:

- hot plate
- pyrex beaker (for a steam bath)
- large ceramic dish
- stirring rod
- suppository mold (Fig. 10)
- suppository mold stand, or suitable bracket to keep the mold from tipping over (Fig. 10)
- metal spatula or microspatula
- Personal protective equipment: laboratory glasses, lab coat, and oven mitts.

See section, Product Example Formulations and Calculations, for a suppository vehicle example: Polyethylene Glycol Suppository Vehicle

Rectal Rockets

As their interesting name suggests, rectal rockets have a unique rocket-like shape, allowing them to be partially inserted before bedtime, to apply medication topically overnight on both sides of the anal sphincter. This is particularly useful in treating anal fissures and prolapsed hemorrhoids. A radial slit runs longitudinally down the rectal rocket body, to allow for the passage of gas without the concern of ejecting the dosage form. See section, Product Example Formulations and Calculations, for a training formulation (Rectal Rocket Vehicle Example) from the University of Toronto, which could be used as a vehicle for rectal rockets, although any suppository vehicle may be considered in conjunction with the physicochemical properties of the drug, and the intended delivery (local or systemic).

Lollipops

Pediatrics offers a particular challenge for drug delivery, as poor organoleptic or aesthetic qualities of the formulation will likely result in poor patient adherence. Lollipops are a preferred pediatric formulation, particularly when local drug delivery is required to the oral mucosa, teeth, gums, or throat. Depending on the vehicle selected, the drug requires a high resistance to thermal degradation. Temperature monitoring is important, particularly with sucrose-based vehicles.

Lollipops can be formulated with many classes of drugs, including those intended for systemic effects. Table 8 lists some common uses for lollipop formulations.

See section, Product Example Formulations and Calculations, for an example training formula at the University of Toronto, which uses silica gel as a stiffener (optional), to accelerate solidification. The formulation requires ample mixing while incorporating ingredients and while pouring. The flavorant should be selected with the preferences of the patient in mind (Dubins et al., 2017).

Troches

Troches (pronounced tr-oh-keys) are another interesting term for oral lozenges. The shape of the troche will depend on the mold. Two major types of vehicles for troches are gelatin based, and higher molecular weight polythene glycols. In fact, the lollipop vehicle above could also be used to formulate troches. However, a gelatin-based training formulation from the University of Toronto is provided here as another example. Selection of vehicle may depend on the physicochemical properties of the drugs, and potential drug-excipient interactions. Troches are appropriate for pediatric (but not infant) or adult formulations, and share the same

Table 8 Common uses for lollipop formulations

Local delivery	Dental/buccal pain (lidocaine, tetracaine, benzocaine)
	Excessive bleeding (tranexamic acid)
	Oral thrush (ketoconazole)
Systemic delivery	Systemic pain (fentanyl)
	Cough suppressant (dextromethorphan)
	Antipyretic/analgesic (acetaminophen)
	Conscious sedation (ketamine)

advantages and indications. Troche molds can be smaller than lollipops, and thus a higher number of doses can be administered in a troche case compared with a lollipop. An example troche mold is provided in Fig. 17. See section, Product Example Formulations and Calculations, for an example training formula.

Lip Balms

Lip balms or lip salves are fantastic for delivering medication locally to the topical surface of the lips, and can also be applied to other areas of the body (e.g., lesions, hives, sores, insect bites, or even as sunscreen). Anesthetics (e.g., lidocaine, prilocaine) or steroids (e.g., hydrocortisone) can be incorporated to relieve pain or inflammation. A hydrophobic formulation would be occlusive, and thus hydrating to the lips. Almond or orange oil could be substituted for lemon oil, depending on the fragrance preference of the patient. See section, Product Example Formulations and Calculations, for a training formula at the University of Toronto, an example lip balm vehicle (Petrolatum/Beeswax).

Capsules

Capsule sizes run counter-intuitively backwards, with larger numbers having smaller internal volumes. Table 9 presents the most common capsule sizes for humans. Veterinary capsules can be much larger, depending on the animal, and strength required. One of the parameters used to perform capsule filling calculations is the capsule fill weight. The fill weight of an excipient or API is the mass that would occupy a capsule of a given size if it were completely filled with that ingredient alone. Capsule fill weight tables are available for common pharmaceutical excipients (Allen, 2014), and also by powder density (Troy and Beringer, 2005). However, these values are easily calculated if the tapped powder density of the excipient(s) and API(s) are known (or determined). If the fill weight of an excipient or API is not known, it may be determined by completely filling 5 capsules with that excipient or API alone, weighing, and then calculating the average filled weight (not including the weight of the empty capsule bodies).

Having the flexibility to compound capsules allows a pharmacist or pharmacy technician to produce a non-standard dose of a drug, or compound an oral drug in the event of a shortage. Capsules are filled by volume, and consequently the calculations are normalized by the fill volumes of the capsule, which vary depending on capsule size and powder density. The overall assumption

Table 9 Capsule size volumes, and tapped powder densities of common pharmaceutical powders

Capsule size	*Capsule volume*[a] *(mL)*	*Tapped powder densities of selected common pharmaceutical powders (g/mL)*
000	1.40	Acetaminophen: 0.343[b] (bulk)
00	0.95	Aspirin: 0.743[a]
0	0.68	Avicel PH-101: 0.338[c]
1	0.50	Avicel PH-102: 0.350[c]
2	0.37	Avicel PH-105: 0.46[d]
3	0.30	Corn starch: 0.441[c]
4	0.21	Dibasic calcium phosphate anhydrous: 1.43[d]
5	0.13	Ibuprofen 110: 0.453[b] (bulk)
		Lactose: 0.713[c]
		PEG 4000: 0.571[c]
		Povidone K-30: 0.434[c]
		Quinine sulfate: 0.464[a]
		Sodium bicarbonate: 1.021[a]
		Sodium carboxymethylcellulose: 0.489[c]
		Sorbitol: 0.73[d]
		Stearic Acid:0.59[d] (bulk)

[a]Troy and Beringer (2005)
[b]Jallo et al. (2012)
[c]Rahman et al. (2017)
[d]Hancock et al. (2003)

made is that powder volumes are indeed additive despite excipients having different densities. See section, Product Example Formulations and Calculations, for example capsule filling calculations.

Hand Filling

Once the capsule blend is compounded, hand filling the capsule may be performed for small batch sizes (e.g., 10 or less capsules). This technique is slower and more manual, but does not require any specialized equipment. In order to facilitate hand-filling, compressible powders like Avicels and cornstarch are useful as diluents, since they will compress well into the capsule body without falling out. Hand filling may be accomplished using the following protocol.

1. Scale up the batch to allow for extra powder (e.g., by a factor of five).
2. Mix the powder formulation and mix by inverting repeatedly in a closed bag (e.g., 2 min of continuous inversions).
3. Add the mixed powder contents to the center of a marble or glass slab.
4. Smooth the surface of the powder so that it is a thick even layer in height, equivalent to approximately half the length of the capsule body.
5. Remove the cap from the capsule body.
6. Gently push and rotate the capsule body down into the powder bed. Perform this motion repeatedly until the capsule body is filled.
7. Replace the capsule cap by firmly pressing it onto the capsule body until it snaps shut.
8. Dust and weigh the final capsules, and weigh each capsule.
9. Weigh five empty capsules, and calculate the average empty capsule weight.
10. Each capsule should be within 90%–110% of the theoretical mass per capsule + average empty capsule weight. Capsules can be opened and adjusted (powder blend added or removed with a microspatula) if they are outside these limits.

Capsule Machine Filling

Capsule filling machines enable the compounder to make large batches of capsules without having to individually fill them. Various commercial products are available, each with specific instructions. Some machines have the capacity to remove capsule lids with one single motion, and replace the lids after they are filled. The batch weight is calculated as the total mass per capsule multiplied by the number of capsules to be compounded. A card is used to move and press the powder down into the capsule bodies, and a tamper is used to compress the powder so that the entire batch can be loaded. No losses are anticipated provided the capsule machine is used correctly.

Oral Disintegrating Tablets (Molds and Baked Versions)

An ODT is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongues or in the buccal cavity) without water within a minute or less. These tablets are distinguished from conventional sublingual tablets, lozenges, and buccal tablets which require more than 1 min to dissolve in the mouth. ODT can be used to administer a medication to a patient that has difficulty swallowing other oral formulations (elderly, palliative, bedridden, stroke patients). This formulation is also an option for patients that refuse to swallow medications such as pediatric, geriatric, and psychiatric patients. It is the choice of formulation for patients that have a high risk of choking from oral drugs (Nagar et al., 2011). It may also be useful for vomiting patients since absorption occurs through the oral mucosa, and one example that is widely used is ondansetron wafer for vomiting pediatric patients, avoiding the need for i.v. therapy.

In general, when an ODT medication is administered, water must quickly enter the tablet to facilitate rapid disintegration and dissolution. When deciding if this formulation is appropriate based on patient characteristics it is important to consider other characteristics. The API must not be bitter and have a small to moderate molecular weight. It must be readily soluble in water and saliva and have the ability to penetrate the oral mucosal tissue (Nagar et al., 2011). ODT formulations are hygroscopic and must be handled very carefully. Specific packaging is required prior to dispensing ODT tablets. Drugs, which are usually formulated as ODT include antiepileptics, antibacterials, PDE-5 inhibitors used in erectile dysfunction, analgesics, sedatives, and anxiolytics.

Typical excipients used in ODT formulations include at least one disintegrant, a diluent, a lubricant, sweeteners, and flavorant. Table 10 details common excipients and their role in ODT compounds.

This custom formulation types can be created in the compounding lab but an oven is usually required for basic ODT compounds. Tablet triturate molds are recommended to facilitate easy compounding. Compounding distributors generally formulate rapid-dissolving tablet bases that can be mixed with the active ingredient. Trituration is not done in these cases as temperatures of 105–110°C for 10–15 min establish bonding, ultimately resulting in a homogenous solid disintegrating tablet. The heat enables tablet shrinking and ease of removal from the mould. This type of formulation is beyond the scope of this introductory chapter but was included to provide background for consideration.

Flavorants

Flavorants are a critical component of oral, buccal, and sublingual formulations, as they play an important role in masking unpleasant flavors of drugs, excipients, and their combination. Surfactants, preservatives, and certain vehicles can impart bitter or sour tastes to oral preparations. To make matters more complicated, taste can be very subjective. The perceived flavor of a formulation can vary greatly based on the patient's preferences, and importantly, the patient's expectations. Particularly in pediatrics,

Table 10 Excipients for oral disintegrating tablets

Excipient type	*Example*	*Function*
Binders	Hydroxypropylcellulose	Maintain the integrity of the dosage form prior to administration
Colors	Amaranth	Enhances the appearance and organoleptic properties
	Red iron oxide	
Fillers	Mannitol	Maintains the bulk of the dosage form
	Sorbitol	
	Xylitol	
	Calcium carbonate	
Flavors	Flavoring oils as per patient preference, fruit essences	Improve palatability, enhance patient adherence
Lubricants	Stearic acid	Reduce friction and wear between the mechanical moving parts of the punching machine and tablet parts
	Talc	
	Polyethylene glycol	
	Colloidal silicon dioxide	
Superdisintegrants	Microcrystalline cellulose	Increase rate of disintegration
	Sodium starch glycolate	
	Carboxymethylcellulose	
Surface active agents	Sodium doecylsulfate	Reduce interfacial tension and enhance solubilization
	Sodium lauryl sulfate	
	Fatty acid esters (Tweens)	
	Sorbitan fatty acid esters (Spans)	
	Polyoxyethylene stearates	
Sweeteners	Aspartame	Taste masking properties and improve patient adherence
	Dextrose	
	Fructose	
	Mannitol	
	Sorbitol	
	Xylitol	

Source: Nagar, P., Singh, K., Chauhan, I., Verma, M., Yasir, M., Khan, A., Sharma, R., Gupta, N., 2011. Orally disintegrating tablets: formulation, preparation techniques and evaluation. J. Appl. Pharm. Sci., 1 (04), 35–45.

the success of administering an oral formulation can hinge on its appearance and flavor. Color, consistency, smell, and mouthfeel all play a part in the intricate organoleptic experience that is lumped under "taste." The perceived sensory experience of a taking a drug can also have direct consequences on its efficacy, which formulators can manipulate to an extent (Sharma and Sharma, 1988).

An ideal flavorants masks any unpleasant tastes or aftertastes of the preparation, is compatible/miscible with the preparation, does not affect the stability of the drug or excipients, is only required in small quantities, and is favorable to the patient. There is a cultural aspect of flavoring that should be taken into account by the formulator. For instance, bubble gum is a very popular North American flavorant for pediatric syrups, and yet has far less appeal in European and Asian countries. A colorant used with a flavorant can impact the patient's perception of the flavor, even if the coloring agent has no flavor on its own. In recent years, the use of coloring agents has become less popular for pediatrics due to parental concerns about food dyes. Patients may express other requirements, such as a formulation that is sugar-free, gluten-free, or casein-free. Thus, the decision to use a flavorant and colorant should be made in consultation with the patient (patient's parents, if applicable). A private taste test can also be arranged to ensure the optimal flavorants are selected, at the optimal concentrations.

The amount of flavorant used will vary depending on the API, the flavor selected, and the flavorant vehicle. As a very approximate guideline, water-based flavorants are typically used at 1–3% w/v of the formulation. However, at the upper end of this range, adding too much flavorant can affect the stiffness of solid formulations (e.g., PEG/Sorbitol lollipops). Water-based flavorants are best used in aqueous or anhydrous hydrophilic or amphiphilic vehicles. Oil-based flavorants tend to be more potent, and are used in concentrations an order of magnitude lower (0.1–0.3% w/v). They are best used in vehicles that are hydrophobic (e.g., wax-based preparations like lip balms). Mixing an oil-based flavorant into a hydrophilic vehicle (or vice versa) will result in poor mixing and phase separation of the flavorant.

Veterinary preparations have different flavor requirements than preparations for human use. Beef, chicken, tuna, cheese, and liver flavors are commonly used for dogs, cats, and other animals. Table 11 provides some suggestions regarding common drug classes and flavors to help mask the taste of some drug classes, and tastes. Table 12 provides recommendations regarding sweeteners.

Formulation Stability

Beyond Use Dates: A Guideline

A BUD is provided to inform the patient when to stop taking a compounded preparation. Over time, particularly in aqueous preparations, microorganisms will grow. In addition, even at room temperature, drugs and excipients are expected to degrade. Coming up with a reliable estimate for a BUD would depend not only on the APIs and excipients, but also the container, the label,

Table 11 Flavorant table: suggestions

Drug class	*Masking flavorant*
Antibiotics	Fruit flavors (cherry, pineapple, orange, banana–pineapple, strawberry–vanilla), coconut–custard
Antihistamines	Fruit flavors (apricot, cherry, grape, lime, peach–range, raspberry), honey, root beer, cinnamon
Barbiturates	Fruit flavors (banana–pineapple, orange, peach–orange, lime, grenadine–strawberry, banana–vanilla), root beer
Decongestants and expectorants	Fruit flavors (coconut–custard, custard–mint–strawberry, grenadine–peach, strawberry–lemon, orange, tangerine, pineapple, raspberry), coriander, maple, butterscotch
Electrolyte and geriatric solutions	Fruit flavors (cherry, grape, lemon–lime, raspberry, lime, strawberry), root beer
Masking general flavors	*Masking flavorant*
Salty	Cinnamon, raspberry, orange, maple, butterscotch, glycyrrhiza (licorice)
Sweet	Berry flavors, vanilla
Bitter	Chocolate–mint, glycyrrhiza (licorice), cherry, raspberry, walnut, tutti-frutti
Sour/acid	Fruit flavors, citrus, cherry
Oily	Wintergreen, peppermint oil, lemon, anise oil
Metallic	Mint, marshmallow

Source: Medisca, Suggested Flavoring Reference Chart: Suggested Flavorings to Mask Tastes & Drug Classes. Available from: https://www.medisca.com/Files/ReferenceCharts/Suggested%20Flavoring%20Reference%20Chart%20-%20MUS%20&%20MCA.pdf; Sharma, A.V., Sharma, P.V., 1988. Flavouring agents in pharmaceutical formulations. Ancient Sci. Life, 8 (1), 38

the storage conditions (temperature and humidity), exposure to sunlight, and a whole host of other factors that are not easily predicted. Even under perfect storage conditions, the patient repeatedly opens the drug-containing vessel, potentially introducing and promoting microbial growth. Stability testing is employed by pharmaceutical manufacturers in order to estimate a conservative expiry date to protect the patient. The compounding pharmacist or pharmacy technician does not have these capabilities or resources, and so guidelines for setting BUDs can be suggested, which are dependent on the regulatory body, and change from time to time. In the absence of specific drug formulation stability information, USP 795 and the National Association of Pharmacy Regulatory Authorities provide some recommendations, summarized in **Table 13**, for nonsterile compounded drug preparations. These recommendations are currently in review at the time of writing this chapter. The pharmacist and/or pharmacy technician is responsible for ensuring they have consulted and are following the most recently accepted guidance for estimating the BUD in their regulatory jurisdiction(s).

Preparations should be packaged in tight, light-resistant containers and stored at controlled room temperature or colder, depending on the nature of the formulation (Kawano and Ho, 2012). In addition, the BUD should be not later than the expiration data of any component (Connolly et al., 2018).

Preservatives

Particularly when compounds contain water, antimicrobial and antifungal preservatives are essential for protecting the formulation. Different strategies may be used, which depend on physicochemical properties of the drug and formulation. For instance, some preservatives only work above or below certain pH values. Benzoic acid, for instance, has little antimicrobial activity above pH 8

Table 12 Sweetener chart (approved sweeteners vary by country and local regulations)

Sweetener	*Relative sweetness (relative to 10% sucrose solution)*	*Class*
Acesulfame potassium	180–200	High-intensity sweetener
Aspartame	180–350	High-intensity sweetener
Neotame	7,000–13,000	High-intensity sweetener
Saccharin	300	High-intensity sweetener
Sucralose	600	High-intensity sweetener
Glucose	0.5	Monosaccharide
Fructose	1.5–1.8	Monosaccharide
Maltose	0.4	Disaccharide
Mannitol	0.5–0.72	Sugar alcohol
Sorbitol	0.6	Sugar alcohol
Xylitol	1	Sugar alcohol
Stevia	30	Stevia plant extract
Sucrose	1	Disaccharide

Source: Chattopadhyay, S., Raychaudhuri, U., Chakraborty, R., 2014. Artificial sweeteners—a review. J. Food Sci. Technol., 51 (4), 611–621; Aulton, M.E., Taylor, K.M.G., 2013. The Design and Manufacture of Medicines, fourth ed. Aulton's Pharmaceutics, Churchill Livingstone, London; Rowe, R.C., Sheskey, P.J., Quinn, M.E., 2009, Handbook of Pharmaceutical Excipients, sixth ed., Pharmaceutical Press, London.

Table 13 Beyond Use Dates (BUD guidelines vary by country and local regulations)

Non-sterile preparation	*Beyond-use date (BUD)*
Non-aqueous formulations (such as ointments, suppositories, fixed oils, waxes, and others *where no water is contained*). (USP 795 proposed revisions, March 30 2018: any preparation other than solid dosage forms that have a reduced water activity, Aw of ≤0.6.).	Not later than 25% of the time remaining until the product's expiration date or 6 months (180 days, with Day 1 as the day of compounding), whichever is earlier. Stored at controlled room temperature.
Solid dosage forms, where USP or NF substance is the source of the active ingredient.	Not later than 6 months (180 days, with Day 1 as the day of compounding). Stored at controlled room temperature.
Water-containing oral formulations (nonpreserved—USP795 proposed revisions, March 30, 2018).	Not later than 14 days (with Day 1 as the day of compounding) when stored at controlled cold temperatures (2–8°C, or 36–46°F).
Water-containing topical/dermal, mucosal liquid and semi-solid formulations (and preserved aqueous dosage forms—USP795 proposed revisions, March 30, 2018).	Not later than 30 days (with Day 1 as the day of compounding).

Source: Connolly, C., Acharya, A., Bertrand, G., Boulanger, A., Christ, H., Cooney, D., Mosher, J., Eriksen, J., Healey, M., Solven, S., Resnick, A., Sampson, S., Wyand, M., Mereniuk, T., Hardy, J. 2018. Guidance Document for Pharmacy Compounding of Non-Sterile Preparations: Companion to the Model Standards for Pharmacy Compounding of Non-Sterile Preparations. National Association of Pharmacy Regulatory Authorities (NAPRA), Ottawa, Ontario; USP, 2007. January 1, last update, Hydrophilic Ointment [Homepage of US Pharmacopeia].

(Rowe et al., 2009). Sometimes, multiple strategies may be used together. Occasionally, some excipients have antimicrobial activity at opportune concentrations in solutions (e.g., Glycerine at 20% or sucrose above 70%). Ultimately the patient should be considered, particularly in consultation with the parents in the event that the patient is a child or infant. Some preservatives have become less popular in pediatric populations, for example, parabens in pediatrics. Benzyl alcohol is not recommended for use with infants (Rowe et al., 2009). It is the responsibility of the pharmacist or pharmacy technician to research and select the appropriate preservative for the formulation, and if there is more than one phase (e.g., a cream) that the selected preservative not partition into the oil phase, leaving the aqueous phase vulnerable. Nonionic surfactants interfere with many preservatives (e.g., parabens) by enclosing them in micelles (micellization) and thus preventing their activities in solution.

Table 14 is a summary of some typical preservatives used in compounding preparations, and their working ranges.

Product Example Formulations and Calculations

This section focuses on how to prepare the common classes of liquid, semisolid, and solid preparations. An emphasis is made on proper technique. Formulas are provided as examples. It is up to the discretion of the formulator to select the most appropriate vehicle and formulation for a particular drug.

Sample formula for Baclofen 5 mg/mL oral suspension (60 mL) (Sick Kids Pharmacy, 2007)

Baclofen 20 mg tablet	15 tablets
Glycerin USP	2 mL
Simple syrup	q.s. to 60 mL

1. Crush tablets to a fine powder (ideally the powder is sifted to ensure finely ground).
2. Wet powder with glycerin and levigate to form a fine paste (can add some simple syrup as well).
3. Gradually add simple syrup in small amounts, levigating well after each addition until a liquid is formed.
4. Transfer to a graduated cylinder.
5. Use additional simple syrup to rinse the remaining drug from mortar and add to the graduated cylinder.
6. Continue up to the final volume stir well.
7. Transfer to glass amber bottle and label accordingly.

This suspension needs to be refrigerated, and shaken well prior to dose administration.

Hydrocarbon Ointment Example: White Ointment USP XXII: (Hydrocarbon Ointment) (Troy and Beringer, 2005)

White wax	5 g
White petrolatum	95 g
To make	100 g

Table 14 Common preservatives used in compounding nonsterile preparations

Antimicrobial agents	*Active against*	*Typical uses in nonsterile preparations*
Ethanol (10%–20% by volume)	Bacteria (not spores)	Oral, transdermal
Benzalkonium chloride 0.01%–0.02% (pH 4–10)	Bacteria, yeast, fungi	Topical, ophthalmic, nasal (not otic or oral)
Benzethonium chloride 0.01%–0.02% (pH 4–10)	Bacteria	Topical, ophthalmic, otic (not oral)
Benzoic acid 0.01%–0.5% (<0.15% for oral) (pH 2.5–4.5)	Bacteria (not spores), molds, yeasts, fungi	Oral, topical, vaginal
Benzyl alcohol 1%–3% (pH < 5)	Bacteria, fungi	Oral, topical, ophthalmic, aerosol sprays
Boric acid 0.03%–1% (also, sodium borate) some safety concerns in pediatrics/neonates	Bacteria, yeast	Ophthalmic, topical (not oral), cosmetics (also emulsifier)
Bronopol 0.01%–0.1% (pH 4–6, light sensitive)	Bacteria	Topicals, cosmetics. High affinity for polar solvents.
Butylene glycol 8% (antimicrobial) 17% (antifungal)	Bacteria, fungi	Topical creams, ointments, lotions, transdermal patches
Butylparaben 0.006%–0.05% (oral), 0.02%–0.4% (topical) (pH 4–8)	Yeast, mold, bacteria	Oral, topical, cosmetics
Certrimide 0.005% (pH > = 7)	Bacteria (not spores), fungi, some viruses	Oral, topical. Not for use with magnesium stearate.
Chlorhexidine 0.01%–0.05% (pH 5–7, light sensitive)	Bacteria, molds, yeasts, fungi	Ophthalmic (also antiseptic at higher concentrations)
Chlorobutanol 0.5% (pH 3.0–5.5)	Bacteria, fungi	Ophthalmic, nonaqueous liquids (incompatible with plastic vials)
Chlorocresol 0.05%–0.2%	Bacteria, spores, molds, yeasts	Ophthalmic, topical, emulsions, cosmetics (shampoos)
Chloroxylenol 0.1%–0.8% (broad pH) (higher: antiseptic, disinfectant)	Bacteria (not spores), fungi, yeast	Topicals (creams, ointments), cosmetics (not oral or ophthalmic)
Cresol 0.15%–0.3% (pH < 9)	Bacteria (not spores), yeasts and molds	Topical, wound disinfection
Edetic acid (EDTA) 0.01%–0.1% copreservative	Bacteria, yeasts, fungi	Topical solutions, oral, otic, rectal, cosmetics (also chelating agent, antioxidant)
Ehylparaben 0.1%–0.25% (pH 4–8)	Yeasts, molds bacteria	Oral, topical
Glycerin 20%–30% also a sweetener, plasticizer, humectant, emollient	Bacteria, molds	Oral, ophthalmic, topical, inhalations, nasal, suspensions, otic, rectal, vaginal, transdermal
Hexitidine (up to 0.1%)	Bacteria, fungi, yeasts	Solutions (e.g. mouthwash) (incompatible with strong acids and oxidizing agents)
Imidurea 0.03%–0.5% (pH 3–9), synergistic with parabens	Bacteria, fungi	Cosmetics, topicals
Methylparaben 0.015%–0.2% (pH 4–8)	Yeasts, molds, bacteria	Inhalation solutions, nasal, oral solutions and suspensions, rectal, topical, vaginal, cosmetics
Phenol 0.1%–0.5% (acidic pH, light sensitive)	Bacteria, fungi, viruses	Topical, cosmetics (not oral) (incompatible with gelatin)
Phenoxyethanol 0.5%–1.0% (copreservative, wide pH)	Bacteria	Topicals, cosmetics, vaccines, wound disinfection
Phenylethyl alcohol 0.25%–0.5% (pH <5, copreservative), 1% (topical)	Bacteria (not spores)	Nasal, ophthalmic, otic
Potassium benzoate 0.03%–0.1% (pH < 4.5)	Bacteria	Beverages, food products where low sodium desired
Potassium sorbate 0.05%–0.2% (pH < 6) (also: sorbic acid) • Used as a co-preservative • Incompatible with bases, oxidizing agents, reducing agents	Fungi, bacteria	Topicals, nasal sprays, oral capsules, solutions, suspensions, syrups • Compatible with nonionic surfactants
Propionic Acid (5%–10%) (also: sodium propionate—higher solubility)	Fungi, molds	Oral, topical
Propylene glycol (solutions and semisolids: 15%–30%, oral solutions: 10%–25%, topicals: 5%–80%)	Bacteria, molds	Topical, oral, dental, ophthalmic, otic, rectal, vaginal, aerosol solutions. Excellent general solvent/cosolvent, plasticizer, flavor vehicle, humectant.
Propylparaben 0.005%–0.02%, used together with methylparaben. Topicals: as high as 0.6%. (pH 4–8) (also: propylparaben sodium—higher solubility)	Yeasts, molds, bacteria, fungi	Oral solutions and suspensions, topical, nasal, inhaled solutions, rectal, vaginal, cosmetics (not ophthalmic).
Sodium benzoate 0.02%–0.5% (pH 2.5–4.5) avoid with neonates	Bacteria (not spores), molds yeasts	Oral capsules solutions and tablets, topicals, rectal, cosmetics
Sodium metabisulfite 0.01%–1.0% (neutral to acidic pH) (also: potassium metabisulfite) avoid sulfites with asthmatics	Bacteria	Oral, topical, inhalations, ophthalmic, rectal, topical, vaginal (also acts as antioxidant)—avoid sulfites with asthmatics
Sodium sulfite 0.1% avoid sulfites with asthmatics	Fungi	Topical creams and emulsions, oral syrups and suspensions, otic, inhalations, topicals, ophthalmic, cosmetics

Source: Rowe, R.C., Sheskey, P.J., Quinn, M.E., 2009, Handbook of Pharmaceutical Excipients, sixth ed., Pharmaceutical Press, London; Troy, D., Beringer, P., 2005. Remington: The Science and Practice of Pharmacy, twenty-first ed., Lippincott Williams & Wilkins, Baltimore, MD, Philadelphia.

1. Set up a steam bath by filling a 250 mL beaker approximately one-third full with water. Set the beaker on a hot plate. Set the hot plate on high.
2. Set a large ceramic dish on the beaker. Melt the white wax in the ceramic dish.
3. Add the white petrolatum, warming until liquefied.
4. Remove the ceramic dish from the steam bath.
5. Stir until the mixture congeals, and allow it to cool.

White petrolatum USP is a purified mixture of semi-solid hydrocarbons from petrolatum and is decolorized. It may contain a stabilizer. Synonyms: white soft paraffin, white petroleum jelly, Vaseline, White Ointment USP.

Yellow-soft paraffin is often used in eye ointments, as it is not bleached and probably does not contain a stabilizer. Hydrocarbon ointments are the most occlusive, meaning that they form a physical barrier on the skin that is somewhat impermeable to water. This prevents water leaving the surface of the skin, and therefore a hydrocarbon base has the strongest hydrating effect on the skin.

Hydrophilic Ointment Example: Polyethylene Glycol Ointment

Carbowax PEG 3350 (formerly polyethylene glycol 4000)	40 g
PEG 400 (also known as PEG-8)	60 g
To make	100 g

1. Set up a steam bath by filling a 250 mL beaker approximately one-third full with water. Set the beaker on a hot plate. Set the hot plate on high. Bring the water to a boil, and reduce heat to a rolling boil.
2. Set a large ceramic dish on the steam bath. Melt the PEG 3350 in the ceramic dish.
3. Add the PEG 400, and mix until uniform.
4. Remove the ceramic dish from the steam bath.
5. Stir until the mixture congeals, and allow it to cool.

O/W cream example: hydrophilic ointment USP (USP, 2007)

		Alternate formulas for a softer base	
Methylparaben (methyl *p*-hydroxy benzoate)	0.025 g	0.025 g	0.025 g
Propylparaben (*n*-Propyl *p*-hydroxy benzoate)	0.015 g	0.015 g	0.015 g
Sodium dodecyl sulfate	1 g	1 g	1 g
Propylene glycol	12 g	24 g	20 g
Stearyl alcohol	25 g	19 g	25 g
White petrolatum	25 g	19 g	17 g
Purified water	37 g	37 g	37 g
To make	100 g	100 g	100 g

1. Set up a steam bath by filling a 250 mL beaker approximately one-third full with water. Set the beaker on a hot plate. Set the hot plate on high. Bring the water to a boil, and reduce heat to a rolling boil.
2. Set a large ceramic dish on the steam bath. Melt the stearyl alcohol and white petrolatum together in the ceramic dish.
3. Dissolve the other ingredients in a second beaker, warmed to ~75°C.
4. Discontinue heating. Add the water to the melted oil phase with agitation.
5. Allow to cool, and stir until congealed.

Notes:

- The parabens are used as preservatives. Water-containing ointments should have a preservative.
- Stearyl alcohol functions as an adjuvant emulsifier and makes the cream smoother.
- Propylene glycol (a humectant) thickens the water phase (suspending agent) and lessens evaporation. It is typically also used in humidors for the same reason.

The following formulation is an example of a common W/O emulsion (an aqueous phase suspended in a continuous oil phase). An oily cream results in a hydrophobic drug partitioning into the continuous (oil) phase. Together with their occlusive action on the skin, oily creams tend to result in relatively higher transdermal delivery of a hydrophobic drug than their hydrophilic counterparts (O/W creams) (Dubins et al., 2017).

W/O Cream Example: Adapted from Cold Cream USP XVIII (Singh, 2010)

Cetyl esters wax (Spermaceti)	12.5 g
Beeswax or white wax (granulated)	12 g
Mineral oil (heavy)	56 g
Sodium tetraborate	0.5 g
Purified water	19 g
to make:	100 g

1. Set up a steam bath by filling a 250 mL beaker approximately one-third, full with water. Set the beaker on a hot plate. Set the hot plate on high. Bring the water to a boil, and reduce heat to a rolling boil.
2. Set a large ceramic dish on the steam bath. Melt the cetyl esters wax and white wax together in the ceramic dish.
3. Once the waxes are melted, add the mineral oil to the large ceramic dish.
4. Continue heating until the temperature of the mixture reaches 70°C; maintain at 70°C for 5 min.
5. In a separate beaker, dissolve the sodium tetraborate in the purified water, warmed to 70°C.
6. Slowly add the warmed aqueous phase to the melted oil mixture, while continuously mixing with a stirring rod.
7. Remove from heat. While the mixture is cooling, *use a hand blender* to emulsify the two phases. Run the hand blender on the lower speed until the mixture appears milky.
8. *Stir rapidly and continuously* until the mixture has congealed. Otherwise, the phases will separate (the emulsion will break).

Notes:

- The aqueous (internal) phase is preheated before it is combined with the oily (external) phase, so that it does not cause congealing.
- Nivea Cream and Pond's Cold Cream are commercial examples of W/O emulsions.
- Sodium tetraborate is a detergent, and acts as an emulsifier along with the cetyl esters wax. However, this vehicle requires a lot of mechanical agitation to produce a homogenous vehicle.

Poloxamer 20%/LIPS Gel Cream (Dubins et al., 2017)

Poloxamer 20% (PLO 20%)

Poloxamer 407 (Pluronic F127)	20 g
Potassium sorbate	0.3 g
Purified water (chilled)	q.s. to 100 mL

1. Transfer poloxamer 407 to an amber 220 mL graduated prescription bottle.
   a. Note: Pluronic F127 powder is a respiratory irritant. Wear an N95 mask when dealing with poloxamer 407 powder.
2. Weigh 0.3 g of potassium sorbate and place in the same bottle.
3. Cap the amber bottle and gently mix the pluronic F127 and potassium sorbate together so that it is adequately blended.
4. Open the cap, and while gently agitating, slowly add cold purified water (5–10°C) to approximately 100 mL (use the graduated markings on the amber bottle).
5. Gently agitate the mixture, label, and place in a refrigerator.
   a. The PLO will disperse and dissolve in the fridge in 1–2 days.
6. More water is added up to the designated volume.

Notes: pluronic F-127 is a nonionic surfactant, MW 12,500, which forms gels of tailorable strength and gelling temperature, depending on the concentration and excipients used.

The lecithin isopropyl palmitate (also called LIPS) is made up primarily of soy lecithin granules, which are yellow and sticky. The following protocol is for preparing LIPS vehicle, the second precursor for the poloxamer/lecithin isopropyl palmitate cream. Ready-made LIPS may also be purchased at the desired concentration (e.g., under brand names such as Lipmax).

Lecithin/Isopropyl Palmitate (LIPS)

Lecithin	22.7 g
Sorbic acid	0.45 g
Isopropyl palmitate	22.7 g (26.6 mL)

1. Transfer lecithin into a 100 mL amber prescription bottle.
2. Add sorbic acid to the bottle.
3. Add isopropyl palmitate to the bottle. Store at room temperature.
4. The lecithin beads will dissolve at room temperature over 1–2 days.

Once both precursors are sourced or prepared, the drug is dispersed in one of the components. Usually, a hydrophobic drug would be levigated with a suitable hydrophobic levigating agent, then dispersed in the LIPS solution, whereas a hydrophilic drug would be levigated with an appropriate hydrophilic levigating agent, then dispersed in the poloxamer solution. Then, at room temperature, the two are combined in a ratio of one-part LIPS to three-parts poloxamer gel, forming an O/W emulsion. Particle size may be reduced by vigorously triturating in a mortar with a pestle, or extrusion through the small bore opening of a syringe (without needle tip).

In the following example, a 2% salicylic acid cream is prepared in PLO/LIPS vehicle.

1. In a glass mortar, combine 0.8 g salicylic acid in an equal quantity (0.8 g) of 95% ethanol, and mix with a pestle until smooth.
2. Shake the LIPS solution prior to using.
3. Add 8.8 mL of the LIPS solution, and continue mixing until smooth.
4. Add 28.8 g of PLO 20% (about 29 mL), and triturate until a smooth gel/cream is made.

Gel formation happens as the mixture equilibrates to room temperature. The lecithin gives the mixture an opaque light beige color. The pestle should be able to stand upright in the mortar when the gel is finished.

2% Methylcellulose Gel (Hot Method) (Dubins et al., 2017)

Methylcellulose USP (1000 cps)	4.0 g
Propylparaben	0.02 g
Methylparaben	0.1 g
Purified water	196 mL

1. Add about 70 mL of purified water to a large beaker. Heat the water to just below boiling (~90°C).
2. Sprinkle in methylcellulose while vigorously stirring with a magnetic stir bar or glass rod.
3. Add parabens.
4. Remove beaker from heat. Carefully add the remainder of the purified water as chilled water, with stirring. Bring it up to 200 mL volume mark.
5. Refrigerate overnight.

Notes: at lower concentrations (e.g., 0.5%), methylcellulose solution is an excellent suspending agent, which thickens/imparts viscosity to a liquid formulation.

1% Carbomer Gel (Cold Method)

Carbomer 940	2.0 g
Propylparaben	0.02 g
Methylparaben	0.1 g
1N Sodium Hydroxide	(Required number of drops)
Purified Water	200 mL

1. Add the purified water to a large beaker.
2. Using a plastic dropper, adjust the pH of the water with 1N sodium hydroxide. Test with a digital pH meter or pH paper, until pH 7 is attained.
3. Add the propylparaben, and methylparaben.
4. Slowly sprinkle in the carbomer 940 while blending with a hand blender, until solubilized.

Notes: for a stiffer gel, increase the pH of the solution by titrating up with 1N sodium hydroxide (ANFCC Ltd., 2018).

Mold Preparation Calculations

The calculations involved in formulating each mold type share a common theme - filling by volume. There are different methods to accomplish this. Once the principles of mold filling are understood, they are inevitably applicable to new mold types. A good understanding of these principles will unleash the power of the pharmacist, together with the prescriber, to improve patient compliance and efficacy.

Mold Calibration

In order to formulate a product with the correct dose, the first step in formulating using a mold is to calibrate it with the intended vehicle. For a very approximate filling weight, the mold can be weighed empty, tarred, and then filled with water. This will provide an approximate figure for how much vehicle to prepare, for calibrating the mold with the intended vehicle. Some molds come "precalibrated" to a specific base. However, it is worthwhile calibrating the mold even given this information, since the provided value may have been performed using a different vehicle. When preparing the placebo vehicle for calibration, prepare more vehicles (e.g., double) than required by the number of units intended to compound, since most vehicles for molds are viscous, and will stick to the sides of the glassware when pouring.

In order to calibrate the mold, prepare the empty vehicle, filling all units in the mold completely. Cool the mold, recover the units, and calculate the average weight of one unit. This is the calibrated unit weight (m_{placebo}). We will begin our discussion on the various methods to determine the amount of vehicle required using suppositories as they are more common in compounding, although these methods are applicable to other mold preparations as well.

Density Factor/Displacement Factor Method

Once the mold is calibrated with the intended vehicle, the volume of the drug must be taken into account, in order to formulate the correct strength. A popular way of accounting for the volume of the drug is by using a published or calculated *displacement factor*, or *density factor* (DF) for the drug in the specific vehicle. The mass of vehicle required for the formulation will be *less* than the amount required for calibrating with empty vehicle, because we now have to make room for the drug. The following formula is used:

$$(1)\ m_{\text{vehicle}} = m_{\text{placebo}} - \left(m_{\text{drug}}/\text{DF}_{\text{drug}}\ \text{in vehicle}\right)$$

This formula can be used for a single unit (e.g., one suppository), but is more often used when planning the entire batch. This method requires an accurate estimate of the displacement factor and correct calculations, or compounding will result in an incorrect potency (Kalmár et al., 2014).

Example: a 100 mg suppository strength of a drug is required. A formulator calibrates a suppository mold with PEG vehicle, finding that the average unit weight is 1.203 g (=m_{placebo}). The drug is known to have a displacement factor of 1.1 in PEG vehicle. The formulator plans to compound 24 suppositories (scaling up to account for losses from glassware and breakage upon ejection). One suppository will have the following:

$$m_{\text{drug}} = \text{formulation strength} = 100\ \text{mg}$$

$$m_{\text{vehicle}} = m_{\text{placebo}} - \left(m_{\text{drug}}/\text{DF}\right) = 1.203\ \text{g} - (0.100\ \text{g}/1.1) = 1.203\ \text{g} - 0.091\ \text{g} = 1.112\ \text{g}$$

The formulator would then scale up the batch for a *planned* 24 units:

$$m_{\text{drug,batch}} = 100\ \text{mg} \times 24\ \text{units} = 2.400\ \text{g drug}$$

$$m_{\text{vehicle,batch}} = 1.112\ \text{g} \times 24\ \text{units} = 26.688\ \text{g vehicle}$$

Calibrated Batch Volume Method

This method involves remelting placebo units in a small vessel and marking the volume occupied. The medicated units are made in the same vessel and brought up to volume with melted vehicle, thus resulting in the correct concentration of drug in the vehicle.

1. First calibrate the mold with an excess amount of empty vehicle (no API).
2. Cast and recover each perfectly formed unit (let the number of recovered perfectly formed units be $n_{\text{recovered}}$).
3. Measure and record placebo weights, then calculate the average placebo weight for one unit (=m_{placebo}).
4. Remelt the perfectly formed units in a small beaker (Beaker A).
5. Mark the meniscus on the side of the beaker with a wax pencil or marker. This volume mark is precisely the batch volume required to compound $n_{\text{recovered}}$-medicated units.
6. Pour off about half the melted vehicle into a second beaker (Beaker B).
7. Add the total amount of API required for the number of units melted to Beaker A (=formulation strength $\times n_{\text{recovered}}$).
8. Mix the API in Beaker A until evenly dispersed or dissolved in the vehicle.
9. Bring up the volume of Beaker A to the marked line, using the poured-off melted vehicle from Beaker B.
10. Mix Beaker A, then pour the API-vehicle mixture from Beaker B into the mold.
11. Cool and recover the medicated units.
12. Weigh the medicated units and then calculate the final average medicated weight (=$m_{\text{medicated}}$).

This method does not require using a density factor. However, once performed, the density factor of the API in the vehicle may be calculated using the following formula, and used for subsequent compounding: (Allen, 2014)

$$(2)\ \text{DF} = \text{Dose}/\left(m_{\text{placebo}} - m_{\text{medicated}} + \text{Dose}\right)$$

where Dose is the mass of active ingredient in one unit, $m_{placebo}$ is the mass of one placebo unit, and $m_{medicated}$ is the mass of one medicated unit. Note that if the dose is quantitatively minor compared to $m_{placebo}$ and $m_{vehicle}$, this formula will give erratic estimates for DF, and the displacement factor method need not be used (e.g., if the drug occupies less than 1% of the formulation by weight). The calibrated beaker can be retained to make future batches of the same formulation, or the calculated displacement factor method may be used if the strength or batch size changes.

There are a few limitations to using the Calibrated Batch Volume method. Since the vehicle is melted twice, excipients sensitive to degradation may be less resilient and more prone to degradation. In addition, the liquid/solid transition upon cooling must be reversible. This is not the case for all vehicles, as some formulations require the evaporation of water, and remelting the solidified vehicle could result in burning (e.g., a hard candy lollipop base). Alternately, the following modified step can rectify this problem:

6. Pour out and discard the entire melted vehicle from Beaker 1. Prepare an excess of fresh vehicle in a second beaker (Beaker 2).

When the total unit weight is quantitatively small, it may also be imprecise to find a small enough container to calibrate by volume, making this method impractical for physically small units, or when only a few units are required.

Double-Casting Method

The double-casting method is another clever way of accounting for the volume contribution of the API without using displacement factors. It is similar to the Calibrated Batch Volume method:

1. A portion of melted base *less than required* for a placebo batch is mixed with the correct amount of drug for the batch, thus underfilling the mold cavities with a mixture of API and vehicle.
2. Empty vehicle is then used to "top up" each cavity.
3. The units are recovered, cooled, and remelted for proper mixing.
4. A second round of casting is performed with the remelted mixture, so that the medicated units are uniform in terms of potency.
5. The medicated units are cooled and recovered.

The vehicle and drug are exposed to heat twice when this method is used, which may be a concern for thermo-sensitive APIs. As with the Calibrated Batch Volume method, solidification of the vehicle must be thermoreversible, which may not be practical with some formulations. This method precludes the calculation of a displacement factor, or estimation of the placebo unit weight ($m_{placebo}$), since placebo units are never formulated and weighed.

Disregarding the Volume Contribution of a Drug or Excipient

As mentioned above, if the drug occupies a negligible proportion of the formulation, then subtracting off a density-factor corrected mass from $m_{vehicle}$ will not result in a meaningful correction. Many guidance set compounding tolerance limits for the theoretically calculated weight and volume. For example, USP 795 states that compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90.0% and not more than 110.0% of the theoretically calculated weight or volume per unit of the preparation (The United States Pharmacopeial Convention, 2013). Thus, if a formulation requires a very small amount of drug (e.g., 0.1% hydrocortisone, micronized), then the volume contribution may simply be disregarded. The mold preparation would be performed by:

1. First calibrate the mold with an excess of empty vehicle (fill the mold with water for a quick estimate)
2. Recover the well-formed units and determine the average placebo unit weight ($m_{placebo}$)
3. Calculate the amount of vehicle required for the medicated batch, aiming to compound *more* than required (usually double) to account for losses on glassware and broken units:

$$m_{vehicle,batch} = m_{placebo} \times \#\,\text{units required}$$

$$m_{drug,batch} = \text{strength required} \times \#\,\text{units required}$$

4. Compound the medicated batch using the calculations in Step 3.

Suppository vehicle example—polyethylene glycol (PEG) suppository vehicle

The following example traces through how to compound placebo rectal suppositories using a hydrophilic vehicle. A method above should be chosen (e.g., density factor method, calibrated batch volume method, double pour method) in order to cast medicated suppositories, depending on the vehicle and API required.

Ingredient	*Weight percent (% w/w)*	*Mass for 12 × 2.1 g suppositories*
Polyethylene glycol 3350	58.8	20.58 g
Polyethylene glycol 400 (liquid)	39.2	13.72 g
Silica gel, micronized (stiffener)	2.0	0.7 g

Figure 11 The suppository mold cavities are intentionally overfilled to account for contraction upon cooling.

1. Fill a 600 mL Pyrex beaker approximately one-third, of the way with water. Set beaker on a hot plate on high heat. Set a large porcelain dish on top of the beaker.
2. When the water starts to boil, set the hot plate to medium heat. Add the PEG 3350. Stir with a stirring rod until it melts completely clear.
3. Add the PEG 400 and silica gel, and mix until homogeneous. At this point, APIs would be added and thoroughly stirred. Calculation of the correct amount of API should be performed using one of the methods described in the mold calibration section.
4. Using an oven mitt, pour the melted vehicle while stirring into the suppository mold, in a slow, steady stream. Overfill each mold cavity so that there is a thick, continuous bead of mixture overflowing on top of the mold without spilling over the sides. Overfilling the mold cavity compensates for base contraction upon cooling.
5. The mold may be cooled at room temperature, or transferred to a refrigerator to accelerate solidification (1–2 h).
6. Remove the excess vehicle using a metal spatula, by scraping it firmly across the top of the mold. The spatula may be heated by briefly touching it to the hot plate.
7. Smooth out any pits or imperfections on top of the suppository with a gently heated spatula.
8. The suppositories may be dispensed in the mold cavity for the patient to remove prior to use. Alternately, eject the suppositories from the molds by gently pressing directly upwards from the bottom of the mold cavity, until the suppository pulls free from the walls of the mold. Lift the suppository out of the mold. Be careful not to push too hard, or the mold walls will deform the suppository shape. Individually wrap the suppositories in tinfoil.
9. Store the finished suppositories at 5°C.

Notes: Excipients are melted in reverse order of their melting point. Micronized silica gel is used in this formulation as a stiffener (Figs. 11–13).

Figure 12 The suppository mold is scraped across the top with a gently warmed spatula to remove the excess vehicle.

Figure 13 The top of each suppository is smoothed to correct minor imperfections.

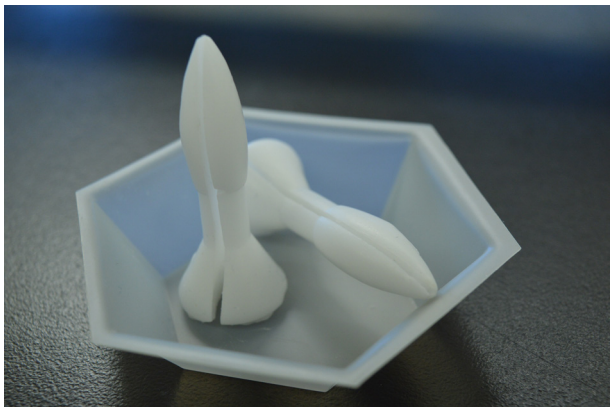

Figure 14 The rectal rocket is uniquely shaped to flank the topical surfaces of the rectum and sphincter. A slit allows the patient to flatulate without concern of ejection.

Rectal Rocket Vehicle Example (Oleaginous)

Ingredients	*Weight percent (% w/w)*	*Mass for ~2 × 6.6 g rectal rockets*
Witepsol 15	63.0	12.6 g
White wax (granulated)	20.0	4.0 g
Stearic Acid	10.0	2.0 g
Almond Oil	5.0	1.0 g
Silica Gel	2.0	0.4 g

The vehicle is prepared by fusion, using the same technique described as rectal suppositories, also over-filling the rectal rocket mold, and scraping excess vehicle across the top before recovering (Fig. 14).

Lollipop Vehicle Example: Sorbitol/PEG 3350

Ingredients	*Weight percent (% w/w)*	*Mass for ~6 × 9 g Lollipops*
Sorbitol (powder) NF	64.7	58.23 g
Polyethylene glycol 3350	32.3	29.07 g
Silica gel, micronized	2.0	1.80 g
Flavorant (water based)	1.0	0.90 g
Colorant (water based)	(Trace)	1–2 drops (optional)

1. Prepare the lollipop mold by lightly lubricating with a fine layer of mineral oil. Insert lollipop sticks into the mold cavity, ensuring the sticks penetrate the center of the lollipop circle.

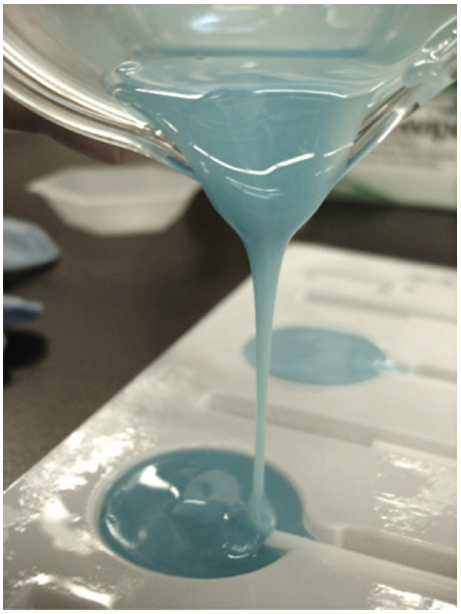

Figure 15 The lollipop molds are filled to ensure the lollipop sticks are completely submerged in vehicle.

2. Fill a 600 mL Pyrex beaker approximately one-third of the way with water. Set beaker on a hot plate on medium heat. Set a large porcelain dish on top of the beaker. Set up a thermometer inside the beaker to monitor formulation temperature.
3. Add the PEG 3350 to the beaker and stir with a glass rod until completely melted.
4. Add the Sorbitol powder. Mix continuously while maintaining a temperature of ~100–110°C, to form a smooth homogenous liquid-like dispersion. The mixture will be opaque, but should not be gritty. If the mixture is overheated, it will separate into two phases. If this occurs, cool the mixture while stirring until the solution thickens and becomes a single phase again, without solidifying.
5. Add the micronized silica gel and flavorant. Stir until homogenous.
6. Remove the beaker from the hot plate. Continue stirring until the vehicle thickens to a white glue-like consistency, and appears uniform.
7. Carefully pour the melted mixture into the mold, while stirring. Fill the entire cavity flush with the top of the mold, being sure to cover the top of the lollipop stick. Rotate the stick in the mold to ensure it is submerged in the mixture (Fig. 15).
8. The mold may be transferred to the refrigerator to accelerate cooling, or may cool slowly at room temperature. It will take 1–2 h for the formulation to completely solidify. Do not attempt to remove the lollipops while not completely solidified, or they will deform upon ejection.
9. Carefully remove the lollipops by pressing gently upwards from the center of the lollipop cavity from the bottom of the mold. Recover and weigh the lollipops to obtain the calibrated weight. Tare the balance with a lollipop stick so the weight of the lollipop stick is not included.
10. Medicated lollipop weights can be formulated using the same technique, adding the API(s) to step 5 to reduce exposure to heat. Calculation of the correct amount of API and vehicle should be performed using one of the methods described in the mold calibration section. The recovered lollipops can be stored in an amber plastic prescription vial (e.g., 60 dram, see Fig. 16), with a suitable-sized hole drilled in the cap to suspend it when capped.

Troche Vehicle Example—Glycerin/Gelatin/Acacia

Ingredients	*Weight percent (% w/w)*	*Mass for ~30 × 0.8 g Troches*
Glycerin USP (softener, preservative)	46.0	46.0 g
Gelatin (225 Bloom or equivalent)	20.0	10.0 g
Purified water	23.4	11.7 g
70% Sorbitol solution (sweetener)	8	4.0 g
Acacia NF (thickener)	1.5	0.75 g
Stevia powder (sweetener)	0.2	0.1 g
Silica gel, micronized (stiffener)	0.9	0.45 g
Flavorant (water-based)	(Trace)	1–2 drops
Colorant (water-based)	(Trace)	1–2 drops (optional)

Figure 16 Various sizes of amber plastic prescription vials. The amber color helps protect the products from light.

1. Consider lubricating the troche mold with a light coating of mineral oil. This step is not required for this formulation, as it is self-lubricating.
2. Using a glass mortar and pestle, gently triturate the silica gel, stevia powder, and acacia to a fine powder. Trituration should be performed lightly with a quick circular motion, allowing the weight of the pestle to reduce the particle size against the mortar. The pestle should not be pounded against the mortar, as this can damage the mortar or pestle.
3. Add purified water, glycerin, and 70% sorbitol solution to a 150 mL Pyrex beaker. Stir with a stirring rod until clear.
4. Set the beaker on a hot plate, set to high heat. Set up a thermometer in the beaker, to monitor formulation temperature. Stir continuously until the mixture reaches 80°C, and is clear.
5. Carefully remove the beaker from the hot plate. Add the gelatin. Mix with a stirring rod until the gelatin dissolves. The mixture will not appear completely transparent. The consistency should be smooth. Use periodic heating on the hot plate to keep the mixture from solidifying.
6. Add the powders from step 2 into the gelatin mixture. Stir with a stirring rod until evenly dispersed, and uniform.
7. Add the colorant and flavorant into the gelatin mixture, mixing thoroughly with a stirring rod.
8. Pour the mixture into the troche mold; ensuring each cavity is completely filled. If the mixture solidifies before or while pouring, gently reheat and mix until pourable.
9. A metal spatula, warmed on the hot plate, may be used to scrape excess vehicle from the top of the troche mold to ensure units solidify independently, to allow for easy separation when cooled.
10. Some troche molds double as the dispensing package, and are designed with a built-in lid. Allow the troches to cool at room temperature with the lid open. Recover and weigh the troches. Turn each unit upside-down in the troche mold to dispense.
11. For the medicated troches, API(s) would be added to step 2, to minimize exposure to heat. Calculation of the correct amount of API and vehicle should be performed using one of the methods described in the mold calibration section (Figs. 17–19).

This vehicle could also be used to compound gelatin-based gummy bears (making ~12 × 3.8 g gummy bears). Gummy bear molds should be slightly overfilled to have a rounded top. The gummy bear molds are *not* scraped across the top to remove excess

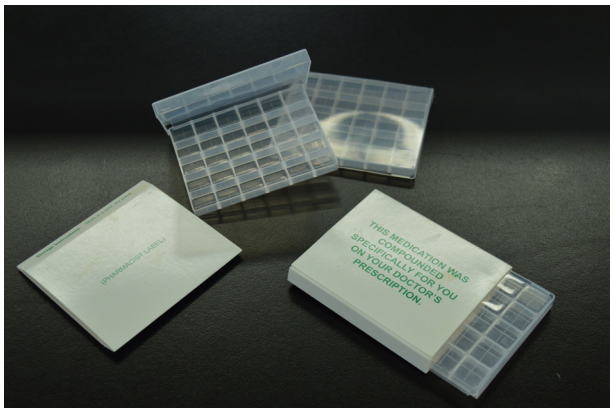

Figure 17 Plastic troche molds, with package sleeve.

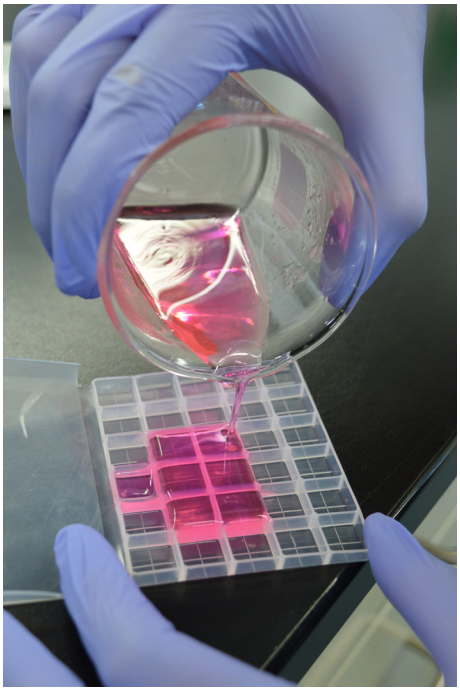

Figure 18 Troches are poured at the mold center then spread outward.

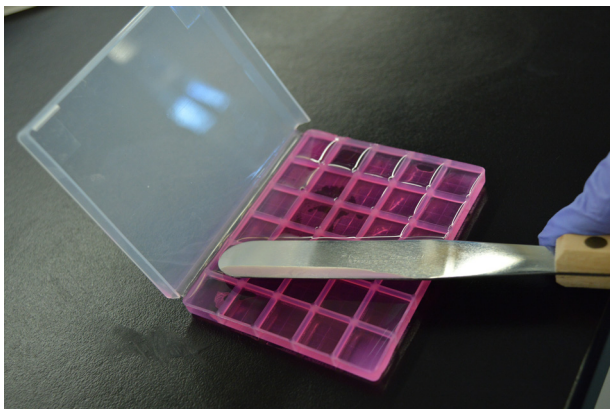

Figure 19 Troches are finished by scraping the vehicle across the top, to ensure each unit is forms separately.

vehicle, or the formulation will be too thin for successful removal. An attempt should therefore made to be consistent when overfilling (without spilling over the borders of the mold cavity, in order to minimize variations in weight. Pouring is best accomplished when the vehicle is cooled close to its melting point, so it is more viscous when poured. Calibration of the mold is required to obtain the correct desired strength.

Lip Balm Vehicle Example—Petrolatum/Beeswax

Ingredients	*Weight percent (% w/w)*	*Mass for ~3 × 4.2 g sticks*
White petrolatum	48.9	12.23 g
Beeswax	20.2	5.05 g
Polyethylene glycol 400	18.6	4.65 g
Lemon oil (fragrance/emollient)	12.3	3.08 g

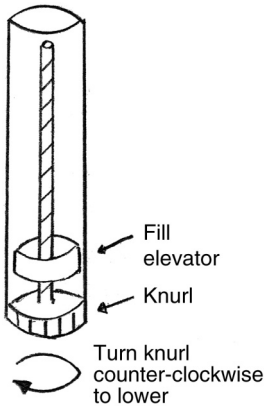

Figure 20 Lip balm casing. Rotate knurl counter-clockwise to lower fill elevator.

1. Set up a steam bath on a hot plate by filling a 250 mL beaker approximately one-third of the way with tap water, and placing it on a hotplate set to high. Set a small ceramic dish on top of the beaker.
2. Remove the caps from the lip balm casings. Verify that each casing has a fill elevator inside. Ensure the elevator is at the lowest-most position by twisting the bottom ring (called the "knurl") counter-clockwise completely, with the knurl facing towards you. Weigh and record the mass of each casing without the cap (Fig. 20).
3. Add the beeswax, petrolatum, and lemon oil to the ceramic dish. Heat the mixture with stirring, until completely melted and homogenous. Do not overheat the mixture.
4. Use polyethylene glycol 400 to levigate the API(s), and transfer the remainder to the ceramic dish. For the calibration procedure, add all of the polyethylene glycol to the ceramic dish. Mix uniformly.
5. Remove the ceramic dish from the steam bath and blot the bottom of the dish to remove any condensate. Carefully pour the melted vehicle into the lip balm casings, completely filling them to the top, without overfilling. The vehicle will contract slightly as it cools.
6. Allow the formulations to cool. Weigh the filled casings to determine formulation weight.

Capsule Filling Calculations

For example, a 100 mg acetaminophen script is to be filled in size 1 capsule. Magnesium stearate (1% by volume) is to be added as a powder glidant to facilitate capsule filling, and lactose powder is to be used as a diluent, occupying the remainder of the capsule volume. The following formulation is desired:

	Tapped density (g/mL)	*Fill weight (mg)*	*Fill volume (%)*	*Mass per capsule*
Acetaminophen	0.343	?	?	100 mg
Magnesium stearate	0.286	143.0	1	?
Lactose (diluent)	0.713	356.5	?	?

Tapped density is used to calculate the fill weights of each ingredient. The tapped density of magnesium stearate is not available, so the formulator completely packs 5 capsules with magnesium stearate, and determines that the average fill weight for magnesium stearate is 143 mg. This corresponds to a tapped density of 0.286 g/mL (=143 mg/0.5 mL per size 1 capsule). The remaining fill weights for a size 1 capsule (volume = 0.50 mL) can now be calculated:

$$\text{Acetaminophen fill weight} : 0.343\,\text{g/mL} \times 0.5\,\text{mL} = 0.1715\,\text{g}$$

$$\text{Lactose fill weight} : 0.713\,\text{g/mL} \times 0.5\,\text{mL} = 0.3565\,\text{g}$$

	Tapped density (g/mL)	*Fill weight (mg)*	*Fill volume (%)*	*Mass per capsule*
Acetaminophen	0.343	171.5	?	100 mg
Magnesium stearate	0.286	143.0	1	?
Lactose (diluent)	0.713	356.5	?	?

Once the fill weights are calculated (or obtained from tables), the percentage of fill volumes can be calculated for each powder. This is the theoretical ratio of volume occupied by each powder in the capsule.

$$\text{Acetaminophen}(\%)\ \text{fill volume} = \text{strength}/\text{fill weight} = 100\ \text{mg}/171.5\ \text{mg} = 58.3\%\ \text{fill volume}.$$

$$\text{Magnesium stearate}(\%)\ \text{filled volume} = 1\%\ (\text{design parameter})$$

$$\text{Lactose}(\%)\ \text{fill volume} = 100\% - (\text{sum of all other}(\%)\ \text{fill volumes}) = 100\% - (58.3\% + 1\%) = 40.7\%$$

	Tapped density (g/mL)	*Fill weight (mg)*	*Fill volume (%)*	*Mass per capsule*
Acetaminophen	0.343	171.5	58.3	100 mg
Magnesium stearate	0.286 (measured)	143.0	1	?
Lactose (diluent)	0.713	356.5	40.7	?

Finally, the theoretical mass per capsule can be calculated as the fill weight x %fill volume for each powder:

$$\text{Magnesium stearate mass per capsule} = \text{fill weight} \times \%\text{fill volume} = 143.0\ \text{mg} \times 1\% = 1.430\ \text{mg}$$

$$\text{Lactose mass per capsule} = 356.5\ \text{mg} \times 40.7\% = 145.1\ \text{mg}$$

	Tapped density (g/mL)	*Fill weight (mg)*	*Fill volume (%)*	*Mass per capsule*
Acetaminophen	0.343	171.5	58.3	100 mg
Magnesium stearate	0.286	143.0	1	1.430 mg
Lactose (diluent)	0.713	356.5	40.7	145.1 mg
Total			100	246.5 mg

The theoretical weight of the filled capsule (not including the capsule body) should be 246.5 mg (=100 mg + 1.430 mg + 145.1 mg). The entire batch may now be prepared by multiplying the mass per capsule of each ingredient by the number of capsules to compound. For instance, if a batch of 50 capsules is to be compounded, the following would be required:

	Mass per capsule (mg)	*Batch mass (to prepare 50 capsules)*
Acetaminophen	100	100 mg × 50 capsules = 5.00 g
Magnesium stearate	1.430	1.430 mg × 50 capsules = 71.5 mg
Lactose (diluent)	145.1	145.1 mg × 50 capsules = 7.255 g
Total	246.5	12.325 g

The batch may now be compounded and be hand filled, or filled using a capsule machine. Capsules are QC'd against their theoretical capsule weight, which is defined as a pass if they are within 10%. For this formulation, a pass would be defined if the measured capsule weight was within (0.9 × 246.5 mg to 1.1 × 246.5 mg =(221.8–271.1 mg), also taking into account the weight of the capsule body by measuring and adding the average empty capsule weight onto those limits (The United States Pharmacopeial Convention, 2013).

Capsuling a Nonstandard Dose: Interesting Example of Dose Taper

It is commonplace in a community pharmacy to encounter the need to formulate a drug taper. The active ingredient may not necessarily be available for purchase as a pure raw ingredient and other capsuling methods are required in this case.

For example, patients that are discontinuing long-term selective serotonin reuptake inhibitors (SSRIs) may require a gradual dose taper. A slow wean is recommended in order to avoid discontinuation reactions like dizziness, insomnia, nausea, vomiting, irritability, and hyperhidrosis (Eli Lilly, 2016). Manufactured formulations of duloxetine exist as 30 and 60 mg strengths. A patient that has been on long-term duloxetine at a dose of 30mg daily would require a steady dose taper to prevent discontinuation symptoms. If switching to a longer acting SSRI like fluoxetine is not an option then compounding a gradual tapered strength is the only option (Attfield et al., 2016). There are no defined SSRI taper guidelines, so it is pertinent for the physician and pharmacist to work closely with the patient in managing their taper schedule. A general guideline is reduced the dose by about 15%–20% each week. This unspecified guideline is established through collaboration with the prescriber, typically on a case-by-case basis. The taper schedule for this patient may look as follows:

- Week 1 of taper: 25 mg capsules daily ×7 days
- Week 2 of taper: 20 mg capsules daily ×7 days
- Week 3 of taper: 15 mg capsules daily ×7 days

- Week 4 of taper: 10 mg capsules daily ×7 days
- Week 5 of taper: 5 mg capsules daily ×7 days and then discontinue

This taper schedule may need to be re-evaluated during the first week if discontinuation symptoms occur. A 10% dose reduction weekly may be more appropriate is sensitive patients. A simple way to proceed with compounding this particular prescription would be to tackle one week at a time. The first week taper schedule is discussed below as an example.

Total amount of duloxetine required for the week

$$25\,\text{mg} \times 7 = 175\,\text{mg}$$

The number of standard capsules required making up this content

$$175\,\text{mg} \times 1\,\text{cap}/60\,\text{mg} = 2.9167\,\text{capsules}$$

The commercially available duloxetine capsules are coated pellets. It is not recommended to crush the contents of the capsules and add fillers in this case. As the enteric coating leads to dissolution resistance until pH >5.5 in the gastrointestinal tract, it is important to maintain this coating. The contents of 3 × 60 mg commercially available capsules should be emptied in a small non-static measuring container.

$$\text{Weight of } 3 \times 60\,\text{mg capsules} = 1.377\,\text{g}$$

$$\text{The theoretical weight of } 2.9167\,\text{capsules} = 2.9167/3 \times 1.377\,\text{g} = 1.33875\,\text{g}$$

Each compounded capsule should have 25 mg of duloxetine, which amounts to

$$1.33875\,\text{g}/7\,\text{capsules} = 0.19125\,\text{g}(191\,\text{mg})$$

This particular weight is the weight of pellets that will be poured into an empty capsule amounting to 25 mg of duloxetine. There is no filler required as the contents of the weigh boat can be placed directly into the empty capsules by hand and sealed immediately after. A recommended quality assurance check after the 7 capsules have been sealed is to weigh the batch and calculate the average capsule weight.

Assume:

$$\text{Weight of 7 empty \# 3 gelatin capsules} = 336\,\text{mg}$$

$$\text{Weight of 7 capsules containing duloxetine pellets} = 1.673\,\text{g}$$

$$\text{Therefore, the weighted duloxetine pellets} = 1.673 - 0.336 = 1.337\,\text{g}$$

Conclusions

Compounding can be a rewarding service provided in community pharmacies, as it can allow for customization in patient treatment, ultimately improving health outcomes. This service is an integral part of pharmacy practice and can be essential in patient care. The compounding of quality preparations requires access to appropriate updated reliable resources and reference materials. Typically these materials include reputable textbooks, relevant research articles, and usually telephone access to a compounding resource center that can provide appropriate aids in formulations and stability data. Depending on the location of practice, government regulation determines the breadth of resources that are required to be kept in the facility for staff to access. From a business aspect, compounding can strengthen the practitioner–patient–pharmacist relationship, ultimately enabling the provision of individualized, safe and effective patient-centered care.

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Global Health and Pharmacy Practice

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Background and Introduction

Global health refers to population health in a global construct. Its principal goals are to improve health status and achieve equity for people in all countries around the world.

Health status is the aggregate product of a nation's wealth, traditions, the climate, priorities, and the degree of democracy. For example, it was in the very late 1890s when Germany popularized the concept of the nation-state. In order to have a strong army for the country, it meant maintaining the health of the population, so that young men called to service would be healthy and fit for battle. In some other countries, maintenance of health was for its own sake. Some medical conditions exist only among certain occupational groups such as farmers being injured by tractor accidents, or construction workers who may fall or have something dropped on them, or office workers whose sedentary activities could lead to obesity, emboli, and lack of exercise. Some conditions such as heat stroke are normally seen only in tropical and very warm climates, whereas frostbite is most usually seen in very northern or extreme southern areas (White et al., 2003).

Pandemics such as bird flu, SARS among many others do not discriminate or respect political borders. They may begin in one area but soon are spread by the traveling public or bird migratory patterns. The strains of the annual seasonal flu immunizations are determined by the strains found in Asia and used all over the world shortly afterwards.

For the last 50 years, a United Nations agency, the World Health Organization (WHO) headquartered in Geneva, Switzerland, has been responsible for global health matters. WHO collects disease statistics and shares them with member nations in an effort to gain an early clue of a likely spreading condition. The WHO is hampered by a few rather serious shortcomings: the reported numbers are accurate and the organization can only recommend or suggest health policies to member countries. If a country depends on foreign tourists for income, it may elect to downplay the incidence of some prevalent local disease so as not to scare away potential visitors. The WHO can make recommendations but no member country can be compelled to follow its policies or guidelines. Here, some of the poorest countries may not have the resources to battle a problem, whereas others have wide-scale corruption and vaccination materials may be diverted or sold.

Yet, in spite of all of these flaws, the WHO has served well as a monitoring and coordination center. The recent Ebola outbreak was tracked by the WHO which reported on new cases in countries, giving health planners valuable information about disease progress by areas, and what resources and precautions would be required in what locations (Learning to Live Together, in press).

While we all live on one planet sharing air, water, and space, there are massive differences in health status, life expectancy, and illness rates in different countries and continents. There are probably at least 50 different variables that determine a person's health status in a region or country. Even gender differences play a role, as do age, ethnicity, housing quality, etc. People who walk barefoot should be expected to have greater health problems, especially if they live in areas where parasites, worms, and amoebic species are present. A pharmacist must understand what types of health problems might be encountered in different practice sites in differing regions. Most pharmacists in North America or Western Europe, for example, have probably never encountered a case of thrush,

Chagas disease, leishmaniosis, or Yellow fever. Pharmacists in South Saharan Africa deal with malaria, dengue fever, and river blindness (AHR, in press).

Industrial Development

Third World Environment: Developing Countries

As the aging population grows bigger over time, many developing countries' health care system do not have the capacity to meet its demand. According to the United Nation, life expectancy globally will "rise from 71 years in 2010–15 to 77 years in 2045–50" (UNDESAPD, 2017). This means that the topic of care for aging population must be addressed more seriously. "The number of older persons in the world is projected to be 1.4 billion in 2030 and 2.1 billion in 2050, and could rise to 3.1 billion in 2100" (UN, 2018). Specifically "by 2050, the projected 434 million people aged 80 or over will account for 21% of the global population over age 60" (UNDESAPD, 2015). This population often suffers from limited access to health care due to many barriers, such as the lack of availability, accessibility, affordability, and acceptability (Odonnell, 2007). Improvement of health care system in developing countries is essential to maintain its demand in the years to come.

China, one of the developing countries with the biggest population in the world, has deaths from multiple diseases, such as cardiovascular disease, cancer, chronic respiratory diseases, and diabetes (WHO, 2016a). Providing education to the population can prevent most of these diseases. WHO is one of the largest health organizations in the world with its mission "to promote health and to prevent and control major chronic diseases and their risk factor" (WHO, 2016b). One of WHO's core functions is to prevent and manage chronic disease (WHO, 2016b). Prevention is the key for developing countries to improve health care as the aging population increases. As the population of the world is shifting from younger toward older, so is the causes of death shifting from acute disease to more of chronic disease. The top death rate in low-income economies in 2015, according to WHO, are respiratory, stroke, heart disease, and HIV. Developing countries are "now living long enough to die of diseases that typically hit in old age" (Tavernise, 2017). These chronic diseases require specific health care systems to support their needs. As aging population increases the need for prevention also increases. Developing countries' health care faces many problems, but prevention is the key for chronic disease control and to improve the quality of life.

Prevention can be divided into three categories: "primary, secondary, and tertiary" (IWH, 2015). Primary prevention can be done through legislation, such as banning a control substance, educate patient on disease state, or immunization against certain disease. Primary prevention is one of the keys to prevent disease in aging population. This is a great challenge for developing countries, many of which emphasize on managing diseases and often ignore patient education. Preventative measures can be taken in the example of tobacco usage. Tobacco usage in the developing countries "are seeing a sharp rise in number of people smoking" (Parry, 2017) compares to the decline in the developed countries. The increase in usage rate can be prevented through primary prevention of education.

Secondary prevention includes "regular exam and screening tests to detect disease in its earliest stages" (IWH, 2015). Secondary prevention can directly improve the treatment success rate of many chronic diseases. The aging population can benefit from screening because early treatment is one of the few ways to prevent the disease or diagnose it in early stage. This is especially important in chronic diseases because screening can raise awareness for patients to be more careful with certain lifestyle. For example, diabetes, patient can be diagnosed as prediabetic. This does not require treatment but more of a lifestyle modification. This crucial step will lower the overall cost of health care, as insulin or any other medications for chronic disease is rather expensive. The average "Indian family earns an income of only US$ 28 per month" while insulin can cost up to US$ 15 for a "month supply of 40-unit human insulin" (Anderson, 2015). This cost can be challenging for patients and health care system in developing country to handle.

Tertiary prevention can be used to "soften the impact of an ongoing illness or injury that has lasting effects" (IWH, 2015). This step is one of the possible ways to help elderly patients to cope with their new lifestyle. This is one of the most important steps of prevention, as relapse or rehospitalization can be costly to the overall health care system.

Prevention is the key to a better health care system for the developing countries. It is possible for a developing country to lower the cost of health care yet still have a good quality of patient care. The overall population of the world is growing, so is the elderly population. This population is expected to grow even more according to the researchers at WHO. This can be detrimental to the health care system that is already weak in the developing countries. Major changes in implementation of prevention can help decrease the pressure that is pressing on the health care system.

First World Environment

By first world, we are referring to the most highly developed, industrialized nations, such as those seen in North America, Western Europe, Australia, New Zealand, Japan, Taiwan, Israel, Brazil, Argentina, and South Africa, as a few examples. Life is basically different in these countries. Residents have access to convenient, affordable medical care especially preventive services such as pediatric immunizations and nearly all babies are born in hospitals under the supervision of skilled experts. Denizens of such areas have indoor plumbing and running safe water supplies. One might say that life is easy in such areas, but that may not be entirely true, as a different set of lifestyle diseases are seen in these populations. While one might not have to walk 2 km to fetch water, city people sit at an office desk all day without participating in sufficient levels of physical exercise; they breathe in the

pollution from factories and automobile exhaust. They work and live in cities with high levels of particulate matter in the air causing asthma, COPD, allergies, and their work leads to chronic low back pain, emboli, and the pressure of work may lead to depression, hypertension, and related diseases.

Workers at industrial factories, such as chemical, iron and steel, electronics, and a host of other industries are faced with exposure to heavy metals and other toxic substances along with repetitive motion disorders such as carpel tunnel disorders found in secretaries and keyboardists. Due to often long commuting times and competition at work, these persons often eat commercially prepared foods containing preservatives, color enhancers, high levels of salt, and other chemicals, not to mention the leaching of substances from tin cans and elasticizers from plastic containers (ILO, 2010).

As the ownership of automobiles is so large, many people walk or exercise very little. This leads directly and indirectly to a series of lifestyle diseases as type II diabetes, hypertension, heart failure, gout, obesity, and the need for hip and knee prosthetics, GERD, among many others. In these areas, food is abundant, plentiful, and relatively cheap. People snack sometimes all evening while watching television, night after night.

On a related topic, professional medical care services are readily available in most areas and especially in large urban areas where there are high concentrations of all of medical specialists and tertiary care hospitals. The availability of these resources leads to greater use to a point where some say that there is overt overmedicalization, where someone with a cough may be referred from their primary care physician to an ear, nose, and throat specialist, who may order an MRI or other imagining along with laboratory tests. Some false positives may lead to unwarranted biopsies and surgeries, and at a minimum, time away from work, additional expenditures and perhaps adverse events related to the drug therapy, which requires further diagnosis and treatment.

Persons in such affluent areas spend money on esthetic interventions, such as wrinkle removal, removal of varicose veins, plastic surgery of the breasts and nose, laser treatments of the eyes to negate the need for spectacles, bariatric surgery, liposuction, hair transplants, and a host of recent antiaging treatments. As one might expect, each of these treatments results in some small fraction of adverse events requiring medical or even hospital attention.

Store-prepared or catered-takeout meals often contain high quantities of sodium and/or sugar and frequently include little or no fresh fruits or vegetables. Some cancers are seen at higher incidence levels in industrialized countries in certain neighborhoods near factories expelling toxic pollutants, or near previous industrial dump sites. Stress, which causes elevated catecholamine levels, may increase other CNS disorders.

Affluent living standards may result in persons hiring others to handle routine tasks as cutting the lawn, shoveling snow, painting the house, or other landscaping tasks (PEW, 2018).

Age

Age is an important determinant of health status. Babies and small children are affected by numerous bacterial and viral infections. Many are upper respiratory with the typical colds, coughs, runny noses along with ear infections, diarrhea, falls with scraped skin, playground accidents with bumps and bruises. We witness falls from bicycles and skateboards, broken bones from sporting accidents.

Adolescents are sometimes afflicted by acne and skin disorders, injuries from automobile crashes due to inexperience, eating disorders, and other problems due to risky behaviors such as sexually transmitted diseases and substance abuse.

There is a period from the early 30s into the 50s when most persons are fundamentally healthy for their age peer group. Beginning sometime in the 50s we see most people of this age group using eyeglasses in order to read, with the use of hearing aids not seen as much until the population is in their 70s. Now we find the major burden of chronic conditions, such as congestive heart failure, type II diabetes, hypertension, gastritis, inflammatory diseases, arteriosclerosis, various cancers, eye cataracts, prostate enlargement, dyslipidemias, among many others.

Recently, one cannot avoid seeing "memory care" institutions. The conditions of dementia and Alzheimer's disease are contributing to a huge number of nursing home admissions, and it is predicted that these conditions will be responsible for the greatest number of long-term care patients in institutions. They are expected to exceed the number of stroke and Parkinson's disease patients presently residing in nursing care facilities. The bones of the elderly are less flexible and strong than those found in younger persons, leading to broken femurs from falls. Declines in sensory prowess continue gradually with poor vision or challenged hearing and memory leading to morbidities. Moreover, it is speculated that a weaker immune response may permit the growth of cancer cells. Such weaker immune systems are found in many elderly persons.

Gender

Factors, such as age, sex, race, and ethnicities, can influence the prevalence of diseases in the population. Sex characteristics and gender have proven to impact the development and severity of certain diseases that manifest differently in men and women. The incidence of many health conditions and diseases among males and females varies throughout the world and this is most likely due to the physiologic differences that lie in gender. According to the National Institute of Health (NIH), sex and gender can influence the development, presentation, progression, and management of certain diseases and can have different impacts on the overall health of an individual. Some of these diseases are further discussed.

Alcohol Use

According to the Global Information System on Alcohol and Health (GISAH), about 3.3 million people die each year from inappropriate alcohol consumption. The excessive use of alcohol around the world has been linked to 100% of fetal alcohol syndrome cases, 22% of suicides, 15% of traffic injuries, 25% of pancreatitis, 10% of colorectal cancer, 8% of breast cancer, and 8% of heart disease (WHO, 2014a). In the year 2010, the consumption of alcohol reported by people around the world was equivalent to 6.2 L of alcohol per individual of 15 years or older. The pattern of alcohol consumption varied from one country to another, that is, the countries with the highest incomes reporting the highest consumption of alcohol per capita. Interestingly, WHO reports that females tend to abstain from consuming alcohol more often than men. As a result, there are marked differences in alcohol-related death in men and women. In the year 2012, alcohol claimed the lives of 7.6% of men globally and 4% of women (WHO, 2014b). In 2010, the total alcohol consumption among male around the world was 21.2 L while for female it was 8.9 L. The proportion of current drinkers reported in that same year among individuals 15 years and older in the world was 47.7 males and 28.9 females (WHO, 2018a). In the United States, the 2015 National Survey on Drug Use and Health (NSDUH) reported that 9.8 million men (8.4%) and 5.3 million women (4.2%) of 18 years and older had an alcohol use disorder (NIAAA, 2017). As a result, the WHO has proposed to reduce the harmful use of alcohol in the world by 10% by the year 2020 (WHO, 2014b).

Cancer

Cancer can affect all persons regardless of their gender, race, or ethnicity. Nonetheless, the prevalence of cancer varies among individuals and variations in individual characteristics may be the reason why. These differences can be attributed to genetics, hormones, environmental factors, etc. Therefore, the risk of developing cancer among men and women varies significantly, and the types of cancers men and women develop can be quite different (NIH, 2018). In 2012, breast cancer claimed the lives of 521,900 women in the world, and as a result it was categorized as the most common type of cancer in women. Nonetheless, when examining the prevalence of cancer in developed countries, it was noticed that lung cancer deaths exceeded those of breast cancer. Meanwhile, lung cancer seems to be the number one cancer seen in men worldwide killing 1,241,600 men around the globe in 2012. Although, in developed countries, the number of prostrate cancer cases was higher (ACS, 2015). In the United States, the three most common cancers in men are prostate cancer (95.5), lung cancer (68.1), and colorectal cancer (44.0) (CDC, 2015a). Meanwhile, the most common cancers in women are breast cancer (123.9), lung cancer (50.8), and colorectal cancer (33.7) (CDC, 2015b). According to statistics published by the Center for Disease Control (CDC), the rate of new cancer cases for all cancer types was 472.3 for males (471.2–473.3) and 413.6 for females (412.6–414.5) of all races and ethnicities for the year 2014 (CDC, 2015c).

Depression

Depression is said to be one of the leading causes of disability around the world, as it can affect an individual's personal, professional, and social life. It is one of those diseases influenced by gender since according to many studies it is most prevalent among women than men. Physicians often fail to diagnose patients with depression due to stigma or due to the fact that it can be potentiated and eclipsed by other diseases, such as cancer, Alzheimer's disease, autoimmune conditions, etc. (NIH, in press). According to data from the National Health and Nutrition Examination Survey, from 2009 to 2012, 7.6% of Americans 12 years of age and older suffered from depression. Of these, 20.4% of were men while 36.1 were women (CDC, 2014). World statistics also reveal that depression is more common in women (5.1%) than in men (3.6%). According to WHO region estimates for 2015, age was also a factor contributing to this prevalence with more 7.5 % of females and more than 5.5% males from 55–47 years suffering from depression (WHO, 2017a).

Cardiovascular Risk

Cardiovascular disease continues to be the leading cause of death among men and women. However, gender is one of the factors associated with differences in prevalence of this disease, its presentation and progression (NIH, 2014). Paying attention to the risk factors and managing them appropriately in men and women can have a huge impact on morbidity and mortality. Well-known risk factors for cardiovascular disease are smoking, diabetes, high cholesterol, and obesity among others (NIH, 2005). Nonetheless, there are specific risk factors that make women more prone to suffer from such complications. For instance, some estrogen receptors have been associated with heart function and cardiovascular disease, there exist differences in the way men and women age with regards to the cardiovascular system, sex hormones play crucial roles in maintaining blood pressure, pregnancy can affect the heart in different ways, etc. (NIH, 2014). According to the CDC, heart disease claimed the lives of 321,000 men in 2013 killing 1 in every 4 men in the nation (CDC, 2017a). Meanwhile, in the same year 289,758 women died. This represented 1 in every 4 female deaths (CDC, 2017b). Russian Federation, Ukraine, Romania, Hungary, Cuba, Brazil, Czech Republic, Argentina, Mexico, and the United States are the ten top countries in the world with the highest number deaths due to heart disease, stroke, and high blood pressure. The following table summarizes the death rates among men and women between the ages of 35–74 years in these countries (AHA, 2018).

Countries	*Men (death rate per 100,000)*	*Women (death rate per 100,000)*
Russian Federation	1173	466
Ukraine	1067	454
Romania	657	312
Hungary	524	218
Cuba	359	209
Brazil	347	205
Czech Republic	347	142
Argentina	305	139
Mexico	261	137
United States	235	117

Obesity

The prevalence of obesity in the word has increased more than 2 times from the 1980s until today. It continues to be one of the leading causes of preventable morbidity and mortality in the United States and in the world. The World Obesity Federation reported in 2014, about 15% of men and 15% of women in the European Union were classified as obese (World Obesity, 2016). In most countries, obesity is more prevalent among women than men. Countries such as Korea, Italy, Spain, and England saw an increase in such gender inequality regarding to obesity between 2010and 2014 and reports show that less educated men and women were more likely to be obese than those with higher educational levels. Nonetheless, in the United States the rate of obesity has increased the most among educated individuals (OECD, 2017). In 2014, 10.8% of males and 14.9% of females of 18 years or older were classified as obese worldwide (WHO, 2018c). In the United States, data from the National Health and Nutrition Examination Survey from 2011 to 2014 revealed that rates of obesity were higher among women (38.3%) compare to men (34.3%). Interestingly, the prevalence of the disease was similar among men and women in terms of age with men between the ages of 40 and 59 (38.3) having a higher prevalence of obesity compared to men 20–39 years of age (30.3%). Meanwhile, women between the ages of 40–59 years of age showed a higher prevalence of obesity of 42.1% and those between the ages of 20 and 39 showed a prevalence of 34.4% (CDC, 2015d).

Alzheimer's Disease

According to CDC, Alzheimer's disease is the most common form of dementia. It is a progressive disease that limits a person's ability to live a normal life and to perform day-to-day activities individually. The risk of developing Alzheimer's disease varies among men and women (ALZ, 2016). According to a study included in the World's Alzheimer's Report in 2015, a significant difference in disease prevalence was observed between men and women in certain geographical areas, such as East Asia, South Asia, the Caribbean, Latin America, and Western Europe. In such places, the prevalence of Alzheimer's was 14%–32% lower in men (ALZ, 2015).

In the United States, men 65 years old have a 9.1% risk of developing the disease while women have a 17.2% risk. At age 75, men have a 10.2% risk and women have an 18.5% risk. Finally, at age 85, men present with a risk of 12.1% while women present with a risk of 20.3%.

Occupation

Occupational work-related illnesses have become one of the social matters that is alarming and need to be addressed. According to Global Estimates of Occupational Accidents and Work-related Illness, the three most concerning work-related illness are circulatory disease, malignant neoplasms, and communicable disease; which respectively accounted for 35, 29, and 10% of total work-related mortality (WSHI, 2014).

Depending on an individual's lifestyle, occupation, or social economic status, these factors can precipitate different work-related illness. For instance, occupational injuries and respiratory diseases occur more often in industrialization countries (MacLeod, 2016). Agriculture has adapted to the advancement of technology where machinery is utilized for every step of the process. This development introduces crucial threat to the health of many. Industrial chemical wastes and pollutants provoke global warning that cause disturbances to the ecosystem, in addition, elicit precipitation to serious respiratory infection. According to WHO's recent study in 2011, respiratory disease was one of the top three occupational diseases globally, specifically in the low, middle, and even high income (WSHI, 2014). Second, recent data suggests that there is a different disease pattern between developed and developing countries. Developed countries in Western Pacific region are most likely to contract malignant neoplasms while developing countries in South-East Asia region are more likely affected by circulatory diseases (WSHI, 2014). For malignant neoplasms, an estimates of total 204,215 cases in Western Pacific region while there were only 94,834 cases in South-East Asia (WSHI, 2014). Respectively, there were a total of 110,399 cases of circulatory diseases in Western Pacific region compares to 223,872 cases in

South-East Asia region (WSHI, 2014). Given the supported data from the study, there seems to a correlation between occupational-related illness and environmental/personal factors, such as: occupation, lifestyle, country regions, etc.

Since work-related mortality has become a more concerning social matter globally, WHO's new project—a global plan that has different directions but ultimately accomplish a mission—to control the escalation in number of workers affected by these work-related illnesses (WHO, 2013; WHO, 2007). WHO emphasizes on the implementation of workers' health policy by enhancing protection and communication at the workplace about health and work safety (WHO, 2013; WHO, 2007). Fundamentally, an improvement in the occupational health services translates to a reduction in occupational-related diseases.

Climate

Global warming is becoming a major threat to the health of many. According to CDC, there has been a steady rise in temperature since 1991. Pattern of extreme temperature, such as: heat waves, winter storms contribute to 10% of earth surface in 2012 compare to 0.1% back in 1981 (WHO, 2017b). This is partially due to the rise in consumption of fossil fuel, which cause a release of high concentration of carbon dioxide. Carbon dioxide traps and keeps the heat in the atmosphere, hence a rise in temperature. Variation in temperature affects many aspect of life, including: ecosystem, crops, water supplies, etc. which can further precipitate into serious health issues.

The change in climate has a big impact on human health. A rise in temperature translates to flooding, water contamination, abnormal migration pattern, etc. According to WHO, the changes in pattern of the environment evidently show a correlation between a shift in climate and serious health-related diseases, such as vector-borne diseases, airborne diseases, and waterborne diseases. First, vector-borne disease is account for 17% of all infectious disease globally; malaria and dengue seize more than 3 billion cases alone (WHO, 2017b). There has been much research which shows an extension during summer months due to a rise in temperature can result in a prolong season for vector-borne diseases and opportunity for these diseases to migrate further to the north region (Climatenexus, 2017). Specifically, suitable climax conditions allow for optimal survival and reproduction for these vectors. WHO estimated that there were 212 million cases of malaria worldwide in 2015, and Africa is accounted for 90% of the cases (WHO, 2017c). Second, the frequent heat waves have recently put a tremendous crisis on the water source. A decline of water supply, water sanitation places underdeveloped countries at a much higher rate at contracting these infectious diseases (WHO, 2014c). Cholera affected more than 42 countries along in 2015, cultivated approximately 172,454 cases (WHO, 2016c). Likewise, the incidences of Lyme disease were also significantly high during 2015. It was one of the sixth most common national notifiable diseases (CDC, 2017c). There were a total of 38,069 confirmed cases reported to CDC with additional notes of expansion evidence in term of geographic distribution (CDC, 2017c). Third, global warning accelerates the melting glacier process, which gives rise to a sea level. The combination of both torrid heat and a rise in sea level place a major role in the migration of bird species. A recent study shows that if ruddy turnstones—a bird species reaches Delaware Bay several weeks earlier than its normal migratory schedule, then the influenza infection rate increased significantly (Erickson, 2012). According to CDC, there is an increase in influenza-related death since 2011 (CDC, 2018). The outcome of the study and the data provided from CDC suggest a correlation between influenza infection rate and migration of bird species.

WHO situates an emphasize on fossil fuels consumption, which plays a major role in the contribution toward global warming (WHO, 2014d). A reduction of pollutants and greenhouse gas distribution can suggest a positive health impact (WHO, 2018b). Additionally, a source of safe water is also important in risk reduction in the transmission rate of certain diseases (Beard, 2014). A program called WASH FIT, Water and Sanitation for Health Facility Improvement Tool was developed by WHO and UNICEF; this program aims to educate on the importance of safe water management and its impact on health globally (Beard, 2014).

Lifestyle

Lifestyles are frequently interwoven with income, wealth, and social class. Simply stated, lifestyle is a way an individual or group lives. Impoverished persons are unlikely to travel long distances to famous ski resorts, resulting in few ski accidents among that demographic, and many more such ski accidents among the wealthy/leisure classes. Conversely, fewer wealthy persons have automobiles fall on them and crush arms, hands, or legs. When the oil in their cars must be changed, they take the car to a service establishment where a professional completes that task. If one in a lower social class notes the need for an automobile oil change, they do it themselves to save the money, but unfortunately some are ill-prepared for the task in front of them.

The indigent have little risk of contracting Norwalk virus GI problems commonly acquired on cruise boats, simply because they do not take cruises. Lifestyle is often partially determined by peer groups. Persons in young suburban communities ride bicycles more often than inner city dwellers who may not have a secure storage area for the bicycle and who may fear its "disappearance." We see the impact of peer pressure on lifestyles in so many ways. When you are landing at an airport, you notice a swimming pool in the backyard of a house. But look more carefully next time you are on a flight. Rarely will you see a single, isolated pool. There will be clusters of pools adjacent to each other in neighborhoods. The same is true in those young suburban communities with bicycle riders. It starts with one person riding a bicycle to the grocery store or train station, and shortly thereafter, there will be many bikes parked at these places. Lifestyle is also partially dictated by environment. Persons in senior communities may be more willing to use a

hearing aid when they see that hearing aid use is the usual situation or what is considered normal in that community. This is due to humans' need and desire to conform and possibly a little peer pressure involved as well.

Lifestyles dictate the probability of certain medical issues. Husband and wife violinists are more likely to have a child, a violin-playing offspring. Sumo wrestler parents are more likely to have a sumo wrestler child than a violin-playing child. Lifestyle is also partially determined by social class. Usually, one's neighbors are in the same social class. We get ideas for home decorations, clothing, hobbies, etc. from our neighbors and through this process, the likes and preferences of an area where there is a single social class become close to the others. Illnesses of that social class population are determined by their habits and behaviors. For example, families that take trips to exotic places are more probably to return with amoebic or parasitic diseases than a family that stays closer to home-playing badminton or horseshoes in their backyards.

Lifestyles, social class, income, and occupation type influence the use of health care services in a large way. Consider the outdoor construction worker who can tolerate cold or hot weather extremes, minor cuts, scratches, bruises, sprained muscles, and other problems. As this person is paid on an hourly basis, he or she will be reluctant to miss time from paid work to visit a physician's office, costing 3 h or more plus the doctor's fee or insurance copayment. That person might be expected to depend on their community pharmacist for advice and recommendations. The consultation is free, less time consuming, and any recommended over-the-counter (OTC) drugs are generally not terribly expensive. The highly paid executive who gets a paper cut in a finger might go to a leading surgeon or dermatologist specialist physician since they are salaried and will not lose any pay for the time away at the physician's office. Moreover, they usually have very complete, robust health insurance with a minimal personal expense to them. Fewer of this latter group will be consulting the pharmacist for professional services or OTC product recommendations.

In warm climates, people go to the beach, go swimming, diving, boating, and partake in other water sports leading to the obvious potential health problems, such as drowning, fish bites, infections from polluted water, bug bites, etc. In other areas, people have ski and snowboard accidents, heart attacks after shoveling snow, falls on the ice, and car accidents on slippery pavement. It should not take long for a pharmacist to determine which, if any, areas he or she may want to study in greater depth based on all of these factors describing the residents in close proximity to their pharmacy employment location.

Discussion

There should no longer be any doubt in the minds of readers of this chapter that global health is complex and that it is not an example of "one size fits all." If we as pharmacists truly desire to participate in the health team, we must be proactive and identify unmet health needs and then prepare ourselves to be able to satisfy those currently unmet needs. Unfortunately, we cannot wait for someone else to identify such gaps, as their groups will claim that area for itself. We cannot, similarly, develop a common global health course for pharmacy students since global health, as abundantly pointed out in this chapter is defined differently in different geographic areas and even differently within smaller boundaries, such as neighborhood wealth, social class, age, population density, proportion of families with young children, etc.

The alternative is unattractive, for us to stand behind the counters of our shops and sell pills to people. That scenario makes us more as merchants/shop owners rather than as health care professionals. For the student or coworker who has been in practice for some number of years, the path ahead could not be clearer. We need to learn from local health authorities what are the most pressing health problems in that community. Let's say that it is an alarming increase of the incidence of hepatitis C. Then, we need to explore the age group and location of patients. When we learn that it is most common in 50 years and older persons who participate in international travel, we now have a target. We can suggest testing to our patients in this sociodemographic and/or we can prepare educational materials in print and distribute them. We could also write a health column for the local newspaper, or have a local weekly television show where the pharmacist can educate and promote healthy behaviors.

Pharmacists have missed many opportunities for expanded professional services scope in the past. Let us hope this time will be different. The community pharmacist is the ideal person to assist communities with their global health needs.

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Pharmacy Practice in the UK

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Introduction

What is Pharmacy Practice?

Modern pharmacy practice incorporates not only elements of clinical pharmacy and the legal and ethical aspects of professional practice, but also addresses the psychological drivers of patient behavior and the wider social determinants of health. As such, pharmacists require a blend of clinical skills, scientific knowledge, and communication and coaching skills to assess and respond to patients' pharmaceutical and health needs.

Good Pharmacy Practice (GPP) is defined by the International Pharmaceutical Federation (FIP) as "*the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care.*"

GPP is organized around four major roles for pharmacists

1. Prepare, obtain, store, secure, distribute, administer, dispense, and dispose of medical products.
2. Provide effective medication therapy management.
3. Maintain and improve professional performance.
4. Contribute to improve effectiveness of the healthcare system and public health.

Pharmacy practice research explores GPP and encompasses topics such as social pharmacy, behavioral medicine, medicines' use, medicines' safety, health economics, pharmacoepidemiology, and pharmacovigilance.

As a field of research, pharmacy practice is relatively new and reflects the profession's evolving priorities and new applications to healthcare delivery. The changing landscape of pharmacy practice, as with all healthcare professions, has been driven by technology, as well as by political, economic, and social factors. In response, modern pharmacy has undergone an identity shift from a medicines' supply-focused profession to a patient-centered profession. While the transition is far from complete, and has been fraught with outward interprofessional tensions and, at times, an inward "identity crisis," the role of the pharmacist continues to evolve beyond the dispensary to make better use of pharmacists' extensive and expensively acquired skills.

The Face of Pharmacy in the UK

The United Kingdom of Great Britain and Northern Ireland (England, Scotland, Wales, and Northern Ireland) has a population of approximately 66 million people. In the UK, 1.8 million people visit a pharmacy each day, and on average a person will visit a pharmacy more than 14 times over a year. Unlike many other countries, approximately 89.2% of the population can reach a pharmacy within a 20-minute walk, making pharmacies highly accessible and central to communities (Todd et al., 2014). In urban areas, it is 98.3% of the population, while for rural areas it is much lower at 18.9% of the population. However, a study (Todd et al., 2014) showed that the areas of highest deprivation have the greatest access, with 99.8% of the population within a 20-min walk of a pharmacy. Contrary to the inverse care law, which states that "the availability of good medical care tends to vary inversely with the need for it in the population served," there is good evidence to demonstrate a positive pharmacy care law in the community pharmacy context (Todd et al., 2014).

As a result, in future, pharmacies may be at the forefront of public health strategies aimed at reducing health inequalities, as pharmacy density is highest in the regions with the most underserved populations. Overall, in the UK, access to medicines is good, as the National Health Service (NHS) funds over 90% of the prescriptions dispensed; thus the cost barrier around medicine use is significantly reduced. Approximately 10% community pharmacies are open for 100 h a week, and many are open longer than GP surgeries, again improving access to out-of-hours care. There are approximately 50,650 pharmacists and 13,000 community pharmacies, with approximately 70% working in the community sector, 20% in hospital pharmacy, and 6% in primary care (FIP, 2015). Pharmacy is the third largest healthcare profession after medicine and nursing in the UK. In addition, some pharmacists visit patients in care homes and in their own homes, and are increasingly taking on more specialized roles on advisory boards and at the health authority level.

Patients visit the pharmacy more than any other health facility to access medicines and healthcare advice, yet the opportunistic interventions delivered are often not remunerated and go unrecognized. In the 1980s the "Ask Your Pharmacist" campaign was launched to raise awareness around the role of the pharmacist and to address the issue of underutilization of the pharmacists' skill set. Other public health campaigns such as "Change 4 Life" and "Smoke Free" actively refer the public to pharmacists for smoking cessation services in their televised and printed adverts. Despite such efforts, it is probable that the scope of pharmacy is still not clearly understood by the general population and even by some healthcare professionals today. Although some improvements have been made, pharmacy leaders must continue to adapt to meet modern consumer needs and unite the profession around the future of pharmacy.

Pharmacists are the experts in medicines and their use in disease management. They play a crucial role in supporting medicine adherence as part of a shared decision-making process, as well as in improving cost-effective measures aimed at reducing medicine waste. The pharmacist's central aim is to use their pharmaceutical expertise to enhance patient care. In addition to supporting patients with their prescribed medicines, pharmacists also help patients to manage minor and common ailments and prescribe over-the-counter medicinal products. Pharmacists can also train as independent prescribers (see pg 15 for Nonmedical Prescribing).

Many pharmacies across the UK are now commissioned to provide public health services, and increasingly, the role of the pharmacist in public health is being recognized. For example, the quality payment scheme, a form of remuneration made to

pharmacies based on contractors fulfilling certain quality criteria, is now linked with Healthy Living Pharmacies (HLPs) (see pg 13 for Healthy Living Pharmacy). With the advent of HLPs, pharmacists are increasingly taking on roles such as health coaching to support patients with weight loss, smoking cessation, and encourage healthy lifestyles to reduce the growing burden of noncommunicable diseases.

However, pharmacists' role in public health is not limited to the community sector with hospital pharmacists also providing smoking cessation and nicotine replacement therapy in secondary care. Despite these advances across both sectors, the 2016 Royal Public Health Society "Building Capacity: Realising the potential of community pharmacy assets for improving the public's health," highlights a lack of awareness among commissioners, and the public has persisted and hindered service uptake.

In the community setting, pharmacists have further clinical roles in delivering services such as cardiovascular screening, substance misuse and needle exchange programs, travel clinics, flu vaccines, medicines' use reviews, new medicines' service, and others (see pg 16 for Pharmacy Services). Pharmacists also assist patients in their journey through the health care system, for example, by signposting to relevant patient support groups as well as refer patients to clinics, general practitioners and accident emergency units where appropriate. A key role of the pharmacist is to differentiate between the minor ailments that can be treated with over the counter products and more serious conditions that require specialist care or immediate attention in the case of a medical emergency.

A Brief History of Pharmacy

Pharmacy is one of the oldest professions in the world, with origins dating back to antiquity when the role of healer was equal parts priest, pharmacist, and physician, and their medical art was practiced in temples. Moving into the first century AD, pharmacy evolved into a scientific field, and by the eighth century, the first privately owned drug stores were established by the Arabs in what is modern day Baghdad. The Arab influence spread across Europe, and many of the pharmaceutical teachings from the East were treated as authoritative up until the seventeenth century.

The legal separation of pharmacy from medicine in Europe can be traced back to the Edict of Palermo 1231 AD, which distinguished the differing roles and responsibilities, as well as regulations for practice. However, in the UK, medicalization of the apothecary, and ultimately the evolution of pharmacy, occurred over the twelfth to the twentieth century.

In England, as well as in most European countries, apothecaries developed from the Pepperers and Spicers, and traded in spicery, which included crude drugs and prepared medicines. Pharmacists and physicians have a shared history as apothecaries, and as such diagnosed patients and prescribed medicines that they sold and dispensed. Apothecaries became a distinct occupational group from the Pepperers and Spicers in the thirteenth century, and the Society of Apothecaries, the first organization of pharmacists in the Anglo-Saxon world, was formed in 1617.

However, another group, the chemists and druggists, not only dispensed medicines, but also manufactured, packaged, and wholesaled drugs. The Apothecaries Act of 1815 further defined the separation of roles, with apothecaries evolved into general practitioners. The business of sale and supply of medicines was left to pharmacists (Harding and Taylor, 2016).

Finally, the modern history of pharmacy has been shaped during years of great social change, leading up to the establishment of the welfare state in 1911, and later the establishment of the NHS in 1948. Prior to the NHS, dispensing prescriptions accounted for less than 10% of income generated, whereas by 2011, 88% of the revenue of independent pharmacies came from the NHS, and approximately 96% of work flow in the community pharmacy centered around dispensing and supply of medicines. As the volume of NHS prescriptions increased over time and dispensing became the main form of revenue for the pharmacy, pharmacists retreated further and further behind the dispensary and away from patients. However, with the introduction of remuneration for enhanced service delivery, such flu vaccines and cardiovascular screening the future of pharmacy are changing (Harding and Taylor, 2016).

How Pharmacy Became a Profession in the UK?

The professionalization of pharmacy in the UK began with the foundation of the Pharmaceutical Society of Great Britain in 1841, today known as the Royal Pharmaceutical Society. In 1842 the Society set up its own School of Pharmacy within its Bloomsbury Square headquarters marking the beginning of organized pharmacy education in the UK. In 2012 this original School of Pharmacy, merged with University College London (UCL), and is now known as the UCL School of Pharmacy.

The Pharmaceutical Society set registration examinations and established the first register of "pharmaceutical chemists" under the Pharmacy Act of 1852 (Harding and Taylor, 2016). The Society acted as both the professional body and regulator until 2010. Following the split, a newly formed body, the General Pharmaceutical Council, took on full regulatory function, and the Royal Pharmaceutical Society evolved into the professional leadership body (see pg 23 General Pharmaceutical Council, and Royal Pharmaceutical Society).

In addition to the establishment of the professional body, both the transformation of pharmacy education and the introduction of a register further formalized pharmacy as a profession. Other factors such as the emergence of retail chains and mass manufacture of medicines have also challenged and shaped modern pharmacy practice. Although the single largest historical factor in creating a volume-driven dispensing model was the shift away from extemporaneous preparation of products in the pharmacy to the wholesaler, and finally to the domination of the manufacturer producing original packs (Harding and Taylor, 2016).

In the UK, multiple chain community pharmacies first entered the market in the 1880s. The first limited company was established by an unqualified druggist, Jesse Boot. By 1883 Jesse Boot owned 33 branches and by 1897, 126 pharmacy chains. Today Boots is by far the largest retail chemist chain in the UK, if not the world. In 2014 Boots merged with Walgreens to form the Walgreen Boots Alliance Inc. comprising manufacture, wholesale, distribution businesses, and retail pharmacies. In the 2016 fiscal year, total sales reached $117.35 billion. The merger with one of the largest American pharmacy chains signifies further entrenchment of the monopoly model in Britain and raises the issue of professionalism versus commercialism.

Healthcare Landscape

Origins and Values of the National Health Service

The NHS was established on July 5th, 1948 by the Minister of Health, Aneurin Bevan, based on the ethos that quality healthcare should be available to all, regardless of wealth. The vision of the NHS is underpinned by three core principles:

- that it meets the needs of everyone
- that it be free at the point of delivery
- that it be based on clinical need, not ability to pay

These principles have guided the development of the NHS and remain at its core despite the many reforms in systems and structure over time. The NHS is free at point of use for all UK residents; however, in England, there is a prescription charge (currently £8.60 per item), as well as charges for optical and dental services. Under devolution, Wales was the first part of the UK to make prescriptions free in 2007, Northern Ireland followed in 2010, and Scotland in 2011.

The prescription fee only applies to England and was introduced in 1952; however, many groups are exempt from payment including patients over the age of 60, children under the age of 16, full-time students aged 16, 17, or 18, pregnant women, patients on low income, prisoners on release, and patients with a medical exemption certificate.

The NHS employs more than 1.5 million people, putting it in the top five of the world's largest workforces, together with the US Department of Defence, McDonalds, Walmart, and the Chinese People's Liberation Army. The NHS in Scotland, Wales, and Northern Ireland employs 161, 415; 84,000; and 66,000 people, respectively. However, a 2015 report by the King's Fund "Workforce Planning in the NHS" reveals severe shortages in the healthcare workforce, which could jeopardize quality of care (Addicott, 2015).

This pressure on the healthcare workforce has resulted in innovative ways of working such as incorporating skill mix and a team approach to managing health. For example, due to the GP shortage, pharmacists work alongside GPs in surgeries resolving problems with medicines, leading on high-risk prescribing, managing patients' long-term conditions, and liaising with local pharmacies (see pg 14 for Primary Care Pharmacy—GP and Pharmacist Partnerships).

NHS Reform and Structure

In the UK, healthcare is primarily accessed via the NHS. The Department of Health (DH) is a department of the UK government responsible for strategic leadership for both health and social care matters and for the NHS in England. The ministerial department, comprising 23 agencies and public bodies, develops policies and guidelines to improve the quality of healthcare. Across Northern Ireland, Scotland, and Wales, the responsibility for healthcare is devolved to the Northern Ireland Assembly, the Scottish Government, and the Welsh Assembly Government, respectively. The Chief Pharmaceutical Officer for each region is responsible for providing specialist advice on medicines and pharmaceutical issues to the Department of Health and for the development of policy relating to medicine optimization and pharmacy.

The NHS is funded directly through public taxation and is managed by the Department of Health. The Secretary of State for Health heads the department and is accountable to Government on all health-related issues. In 2013 the NHS underwent structural reform, and The Health and Social Care Act 2012 transferred full statutory responsibility for pricing from the Department of Health to NHS England and NHS Improvement jointly. Prior to this, all NHS planning and delivery was done by the Department of Health, Strategic Health Authorities, and Primary Care Trusts.

NHS Performance Ranking

The Commonwealth Fund study (Schneider et al., 2017) rated the NHS as the best overall healthcare system compared to 10 other countries including Australia, Canada, France, Germany, Netherlands, New Zealand, Norway, Sweden, Switzerland, and the USA. This study evaluated the NHS as the best healthcare system with regards to equity, safe care, coordinated care, and preventative care measures, but it was ranked 10th for healthcare outcomes despite the UK having the fastest reduction in deaths amenable to health care in the past decade, see **Table 1** and **Fig. 1**.

Table 1 Healthcare system performance rankings

	AUS	*CAN*	*FRA*	*GER*	*NETH*	*NZ*	*NOR*	*SWE*	*SWIZ*	*UK*	*US*
Overall ranking	**2**	**9**	**10**	**8**	**3**	**4**	**4**	**6**	**6**	**1**	**11**
Care process	2	6	9	8	4	3	10	11	7	1	5
Access	4	10	9	2	1	7	5	6	8	3	11
Administrative efficiency	1	6	11	6	9	2	4	5	8	3	10
Equity	7	9	10	6	2	8	5	3	4	1	11
Healthcare outcomes	1	9	5	8	6	7	3	2	4	10	11

Bold to highlight the overall ranking according to the study by Schneider et al.

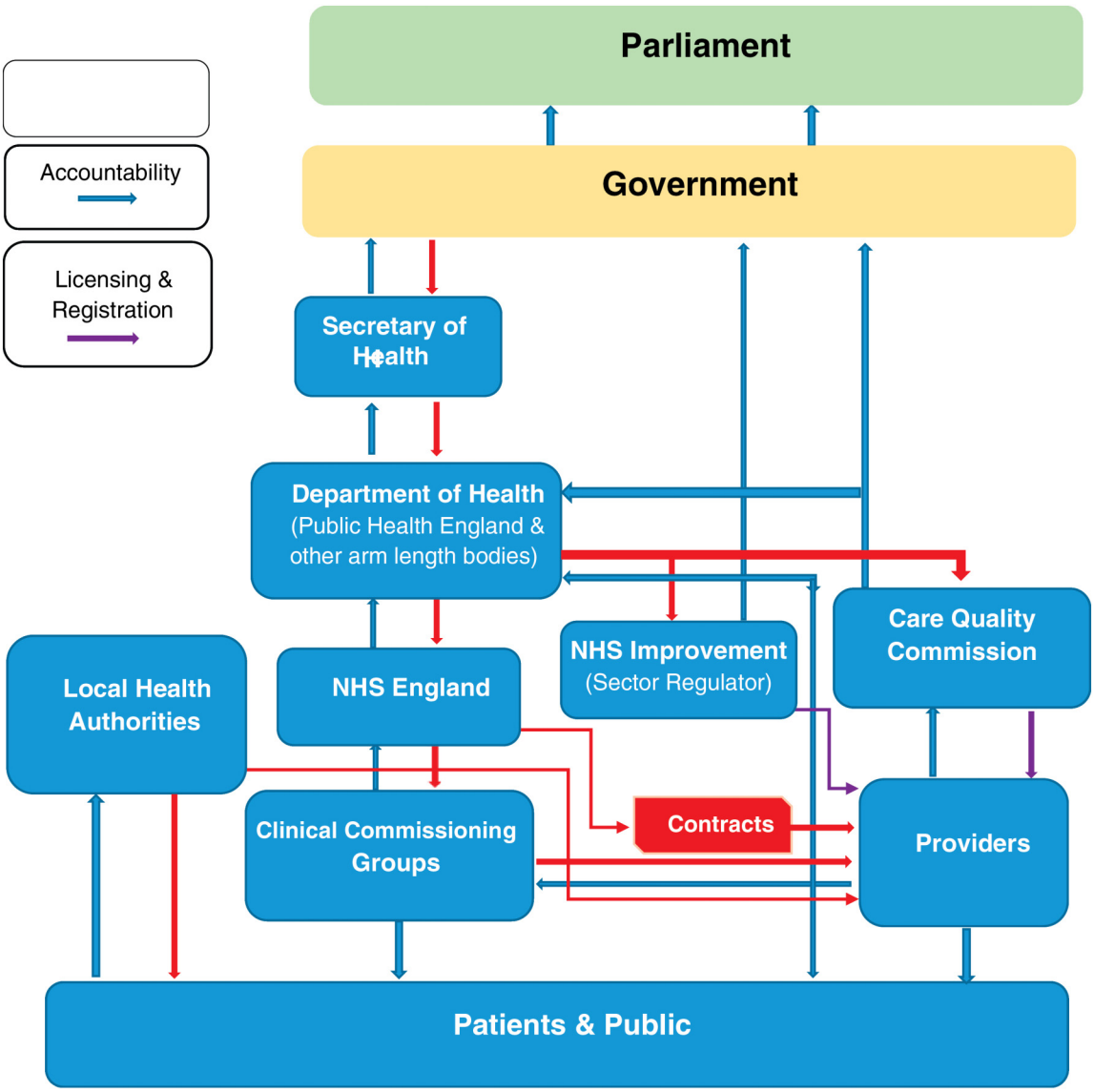

Figure 1 Basic NHS structure and funding.

NHS England

NHS England is an independent body, at an arm's length to the government, and was established in 2013 to set the direction and priorities of the NHS. It acts as the commissioner for primary care services to pharmacists, dentists, GPs, and other specialized services such as military health. NHS England oversees approximately £100 billion of the total NHS budget and works to ensure

efficient use of allocated funds via clinical commissioning groups (CCGs). NHS England is responsible for the direct commissioning of services outside the remit of CCGs, with a focus on specialized services.

NHS Improvement

NHS Improvement was created in 2016 to oversee NHS foundation trusts and independent providers delivering NHS funded care. It is an umbrella organization that brings together monitoring groups such as the monitoring, NHS Trust Development Authority, Patient Safety, the National Reporting and Learning System, the Advancing Change team, and the Intensive Support teams with the overall aim of improving quality of care.

Clinical Commissioning Groups

Clinical Commissioning Groups (CCGs) replaced primary care trusts on April 1, 2013 and are clinically led statutory NHS bodies. These bodies are responsible for commissioning healthcare services by region and comprise GPs and other clinicians. CCGs are responsible for 60% of the NHS budget and largely commission secondary care services, as well as GP services. The secondary services commissioned are:

- Planned hospital care
- Rehabilitative care
- Urgent and emergency care
- Most community health services
- Mental health services
- Learning disability services

CCGs can commission any service provider that meets NHS quality standards and budget, such as private sector providers, NHS hospitals, and charities.

Fig. 1 illustrates the basic NHS structure around funding, licensing, and accountability between government and the arm's-length bodies and other groups that work within the umbrella structure.

Fig. 2 further illustrates the NHS structure in relation to Public Health England, Regulatory Groups, healthcare professionals, and their duty to the general public.

NHS Sectors

Primary Care

The NHS is divided into three main sectors: primary care, secondary care, and tertiary care. Primary care is the largest sector of the NHS and is the backbone of patient care. It is mainly provided by general practitioners, community pharmacists, opticians, and dentists. Most primary care is delivered via a local practice where a patient will be registered for treatment by a number of healthcare professionals. In this sector, community pharmacists are key to medicines' supply and provide healthcare advice. However, pharmacists are increasingly working in an integrated model of general practice alongside GPs and taking on a greater clinical role.

Secondary Care

Secondary care is organized into different levels and types of services for patients known as "Trusts," mainly comprising hospitals, and together deliver a comprehensive service for patients. A wider variety of healthcare professionals work in secondary care including doctors, nurses, pharmacists, radiographers, physiotherapists, and dietitians. Patients enter secondary care through referral via the primary care systems, although in urgent cases patients may access secondary care through the accident and emergency department.

The Urgent Treatment Centres (UTCs) are open 12 h a day, seven days a week, and are integrated with local urgent care services. These centers will be rolled out for patients who do not need hospital accident and emergency care but require treatment by clinicians with access to diagnostic facilities, for example, X-ray machine. By 2018 approximately 150 designated UTCs will be available via GP referral.

Tertiary Care

Tertiary care includes more specialized medical centers, for example, specialist centers in pediatric cardiac surgery or cancer care.

Pharmacists and pharmacy technicians work in all three areas providing advice, guidance, and the supply of medicines and medical devices and appliances.

In rural areas of the UK where patients live over a mile from a pharmacy, patients may obtain medicines from a dispensing doctor as part of their NHS service. GPs often employ a pharmacy technician to provide support with dispensing services.

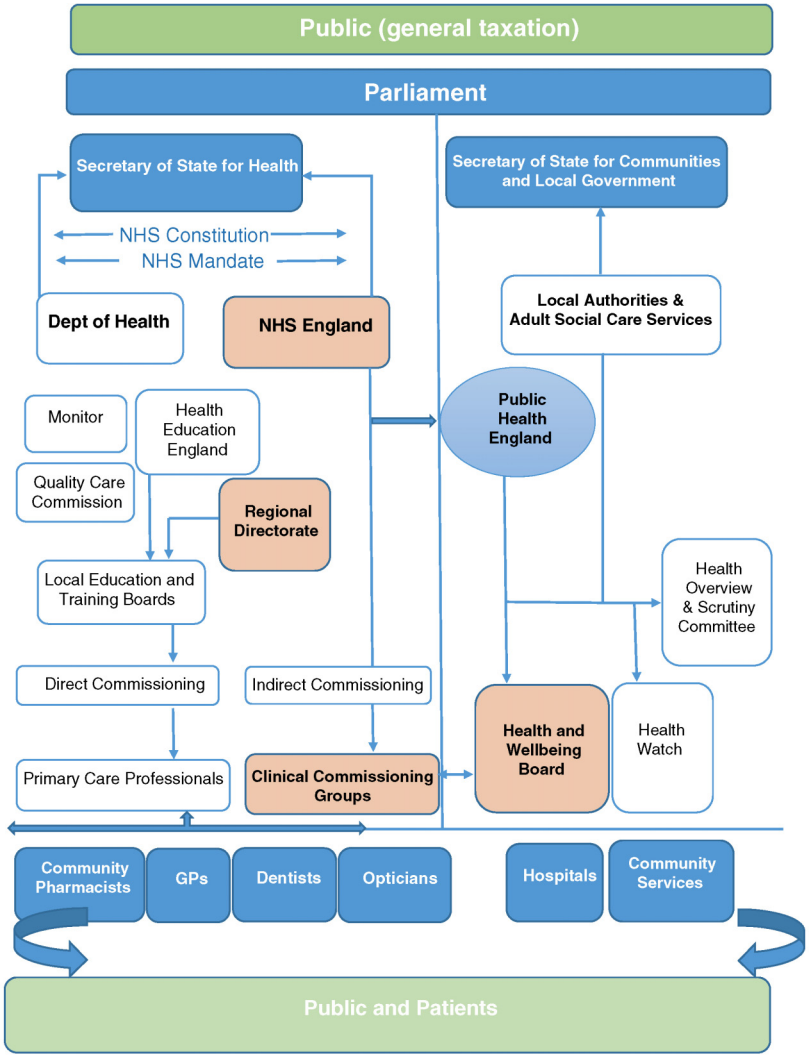

Figure 2 NHS structure (PSNC, 2017).

Private healthcare is structured in a similar way, as patients can access private care in the community through GPs and other healthcare professionals. These practitioners may provide solely private services or joint NHS and private services. Private secondary care is provided in private hospitals and treatment centers in a similar way to the NHS (Fig. 3).

NHS Budget for Medicines

As a provider of universal health coverage, the NHS is an expensive healthcare system to sustain. To reduce cost in the UK, certain medicines have been placed on the blacklist and are not available on an NHS prescription but can be purchased privately. The blacklist was introduced in 1984 in an attempt to economize; however, over time drug costs continue to rise due to improved diagnostics, an ageing population, and patient demand. Over the past decade, the number of prescriptions written has increased by 30%, and the cost of general practitioner prescriptions has risen by over 50% in real terms, driving up NHS expenditure on drugs and thus straining the budget (Harding and Taylor, 2016).

As part of a wider effort to reduce the NHS budget for medicines, a drive toward self-medication with the support of community pharmacists was introduced in the 1990s through a series of legislative changes. The European directive 92/26/CEE stated that medicines should be classified as prescription-only medicine (POM) only if they are frequently taken inappropriately, dangerous without medical supervision, or normally injected. Thus it was argued that medicines with a proven safety and a low-toxicity profile could be used to treat minor ailments. This deregulation process started slowly in the UK, but with the support of the Royal Pharmaceutical Society (RPS) and to some extent the Royal College of General Practitioners, it now has the widest range of over-the-counter medicines available in the world (Fig. 4).

Figure 3 Context of the RPS professional standards. *Adapted from RPS Report 2014.*

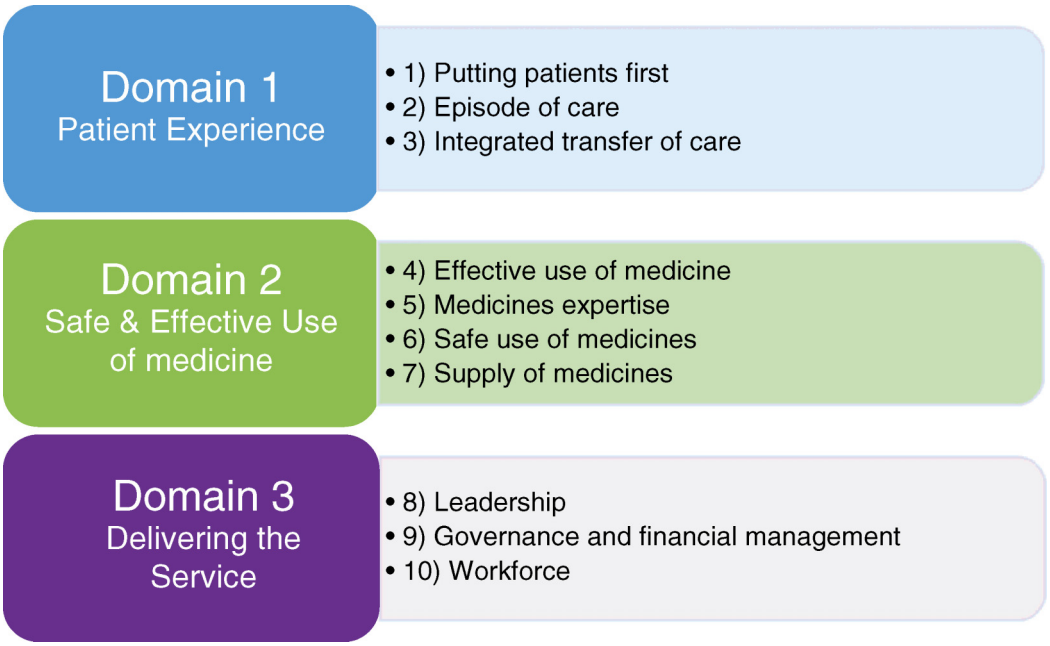

Figure 4 The RPS 10 standards for pharmacy services. *Adapted from RPS Report 2014.*

This move toward deregulation of medicines has further reduced the cost to the NHS as over-the-counter (OTC) medicines are purchased out-of-pocket. In the UK, the first POMs to be deregulated to P status was loperamide and ibuprofen in 1983. The deregulation of 1% hydrocortisone cream saved patients in the UK £2 million pounds in 1987 alone (Harding and Taylor, 2016). Since then, over 80 POM to Pharmacy medicine (P) switches and 50 P to General Sale List (GSL) have been reclassified. In recent years, the rate of deregulation of GSL medicines has increased with most P medicines now available at all retail outlets. The extension of medicines available as OTC and the pharmacists role in advising patients on their use have come under criticism following the *"Which?"* report that exposed up to 43% of all patient consultations in community pharmacies were unsatisfactory and potentially dangerous (Royal Pharmaceutical Society and General Pharmaceutical Council, 2013).

However, the RPS Minor Ailment Study showed that patients receiving treatment in a community pharmacy for the management of one of four minor illnesses had similar outcomes compared to patients managed by GPs. The study also found that patient satisfaction was high and the pharmacy service was significantly more cost-effective than alternative providers (Watson, 2013).

As more medicines continue to become available OTC, pharmacists have a wider advisory role to play in supporting patient self-care for common conditions and minor ailments. It is estimated that minor ailments cost the NHS £2 billion annually in GP visits. A further 8% of Emergency Department consultations involve minor ailments, and this translates up to a cost of £136 million to the NHS annually (Watson, 2013).

Beyond supporting patient self-care, pharmacists help to improve cost-effective medicines use and support in quality, prescribing at a strategic and practice level. In the UK, pharmacists work with interdisciplinary teams to develop drug formularies and appraise the available evidence for inclusion. In the community setting, pharmacists monitor and review repeat prescriptions, which make up 80% of all prescriptions. Repeat dispensing is an essential service under the pharmacy contractual framework. It is a process that allows a patient to collect repeated supplies of their medicines without the need for a prescriber to hand sign prescriptions on each occasion. The prescriptions are then available for dispensing for up until one year or until the next patient review. The repeat dispensing service is most suitable for patients on stable and/or multiple therapies, with chronic conditions, and patients who can appropriately self-manage seasonal conditions. The pharmacist must ascertain the patients' need for a repeat supply, and as such, pharmacists are well placed to make prescribing recommendations and improve prescription quality (Rees et al., 2014).

Pharmacy Regulation in the UK

General Pharmaceutical Council

Pharmacy in the UK is regulated by the General Pharmaceutical Council (GPhC) whose main function is to safeguard patients by upholding standards and public trust in pharmacy. However, in Northern Ireland, the Pharmaceutical Society acts both as the professional body and the regulator.

The GPhC was established in 2010 to set the standards for conduct, ethics, proficiency, education and training, and continuing professional development. Prior to 2010, the Royal Pharmaceutical Society acted as both the regulator and the professional body. Following the demerger, the GPhC is now responsible for the register of pharmacists, pharmacy technicians, and pharmacy premises and monitors pharmacy professionals' fitness to practice requirements. In addition, the GPhC approves qualifications for pharmacists and pharmacy technicians and accredits education and training providers.

Medicines and Healthcare Products Regulatory Agency

The Medicines and Healthcare Products Regulatory Agency (MHRA) is an executive agency of the Department of Health. The agency works to ensure that medicines, medical devices, and blood components for transfusion meet quality standards and issue market authorization for the sale of medicines. In addition, the MHRA influences UK and EU international public health regulatory framework.

Pharmacy Leadership

Royal Pharmaceutical Society

There are a number of general organizations that support and represent pharmacy and pharmacists, such as the RPS. The RPS is the professional leadership and membership body whose aim is to promote pharmacy and support its members to improve the health of the public across England, Scotland, and Wales.

In Northern Ireland, the regulatory and professional leadership functions of the pharmacy profession in Northern Ireland are currently performed by one organization only, the Pharmaceutical Society of Northern Ireland.

General Pharmacy Organizations in the UK

Organization	*Function*
Association of Pharmacy Technicians UK (APTUK)	APTUK is the professional leadership body of registered Pharmacy technicians.
Centre for Pharmacy Postgraduate Education (CPPE), Wales Centre for Pharmacy Professional Education (WCPPE), NHS Education Scotland (NES)	CPPE and the Welsh and Scottish equivalents function as a provider of continuing professional development courses and resources linked to national priorities, which are centrally funded. CPPE also provides postgraduate education.
National Pharmacists' Association (NPA)	Trade association for community pharmacists.

(*Continued*)

Organization	*Function*
Pharmacists' Defence Association (PDA)	The Pharmacists' Defence Association supports the needs of individual pharmacists and provides indemnity insurance. It defends pharmacists in conflict and is a lobbying organization.
Pharmacists Support	Independent charity providing support to pharmacists and their families.
Royal Pharmaceutical Society (RPS)	Professional membership and leadership body in the UK.
RPS Local	The RPS local is the regional branch of RPS members including pharmacy employers, pharmacy education providers, and pharmacists.
British Oncology Pharmacy Association (BOPA)	BOPA is a registered charity and works to promote excellence in the pharmaceutical care of patients with cancer.
UK Clinical Pharmacy Association (UK CPA)	Promotes excellence in clinical practice, leadership, medicines management, and specialist clinical areas.
Pharmacy Voice	It is an association of trade bodies representing community pharmacy contractors. The umbrella organization includes National Pharmacy Association, Company Chemists' Association, and Association of Independent Multiples.

Community Pharmacy

In the UK, the community pharmacist is one of the main providers of medicines and healthcare advice in primary care. Community pharmacists are based in pharmacies either on the high street, grocery stores, or as part of a GP practice. The business model includes independent pharmacies, as well as small chain or large multiple chain pharmacies. Over the years, the number of independent pharmacies in the UK has begun to decline as large multiples have come to dominate the market. Multiples have the necessary economies of scale and resources to invest in infrastructure. In some cases, they are also able to achieve supply chain efficiency with the vertical integration of wholesale operations. These large multiples are achieving more than double the net retail profit margins in their pharmacy operations (Anscombe and Thomas, 2012).

Use of Technology in Community Pharmacy

Summary Care Record

While hospital pharmacists in the UK have had access to summary care records (SCR) for some time, in the community setting, the introduction of the SCR is relatively new. The SCR is a "centrally held electronic record containing key clinical information including a patient's medication, known allergies and any adverse reactions to medication." Over 96% of the population has an SCR that can be reviewed by healthcare professionals 24 h a day, seven days a week. Until recently, community pharmacies did not have access to the SCR. Following a proof of concept pilot launched in April 2014 across 140 pharmacies, SCR access was granted to all pharmacies across the UK. At this stage, pharmacists have "read" only access to the SCR and cannot add notes "write access" to document side effects or other serious problems patients may experience with their medicines and health.

Currently, over 93% of community pharmacies have access to the SCR, and over 24,000 pharmacy professionals have completed the SCR eLearning training. In the 2017–18 financial year, community pharmacies received funding through the Quality Payments Scheme if they were able to demonstrate that they are using the SCR to aid patient counseling and queries where necessary. Pharmacy staff must ask patients for their explicit verbal consent before accessing a patient's SCR.

The privileges gained by community pharmacy, such as SCR "read" access, signifies a further move toward the integration of pharmacists within the primary healthcare team and in particular with GPs. In future, if "write" access is permitted, it will further enhance the scope of pharmacy practice, but this may have legal ramifications.

Community Pharmacy Services

The NHS community pharmacy contract for England and Wales outlines all the NHS services to be provided by pharmacists. There are four service domains: optimizing the use of medicines, public health services, supporting people to live independently, and supporting self-care.

The scope of service provision is expanding, and over 90% of pharmacies in the UK have a private consultation room; however, in community pharmacy, dispensing remains a core part of daily practice.

There are two levels of pharmacy services delivered at the community level:

1. Essential Services
    a. Dispensing appliances
    b. Dispensing medicines
    c. Disposal of unwanted medicines
    d. Public health and promotion of healthy lifestyles

e. Repeat dispensing
f. Managed repeats
g. Signposting
h. Support for self-care

2. Advanced Services

a. Appliance Use Review
b. Flu Vaccination Service
c. Medicines Use Review (MUR)
d. New Medicines Service (NMS)
e. NHS Urgent Medicine Supply Advanced Service (NUMAS)
f. Stoma Appliance Customisation (SAC)

Locally commissioned services in community pharmacies can be contracted by local authorities in response to the needs of the regional population.

Medicines' Use Review

The MUR is one of the most significant innovations in community pharmacy in delivering medicines' optimization and improving patient knowledge and medicines' adherence. In 2015 3.2 million Medicine Use Reviews (MURs) were carried out by 10,916 community pharmacies (Pharmacy Voice, 2017).

In England and Wales, it is an advanced service funded by the NHS and is both a diagnostic and educational intervention (Blenkinsopp et al., 2012). As part of the consultation, the pharmacist explores the patient's understanding of how their medicines should be used and why they haveprescribed it. The pharmacist identifies any problems and provides feedback to the prescriber where necessary. Thus the MUR complements the work of the GPs and fosters interprofessional collaboration between pharmacists and GPs.

To deliver the MUR service, the pharmacy and pharmacist must undergo accreditation and meet certain criteria such as competency assessment, and the premises must have a consultation area that meets NHS standards of privacy. In 2011, national targets groups for selection of MUR were introduced for patients taking high-risk drugs, patients with respiratory disease, and patients recently discharged from hospital. MURs should be conducted on an annual basis, and at the time of publication, the remuneration rate per MUR conducted equates to £28.

In Scotland, a similar service, the Chronic Medication Service (CMS), is part of the core community pharmacy contract. It is more comprehensive than the MUR service and includes a full pharmaceutical care assessment, plan, and implementation. The CMS allows for repeat prescribing of long-term medication, and all data storage is electronic, thereby facilitating communication between the pharmacist and GP.

There is good evidence to show that MURs improve prescribing outcomes, for example in the reduction of polypharmacy, and as such, GPs have accepted most pharmacist recommendations and interventions in the UK (Blenkinsopp et al., 2012).

New Medicine Service

The New Medicine Service (NMS) was added to the Community Pharmacy Contractual Framework as an advanced service in 2011, and since then more than 90% of pharmacies in England have provided this service to patients. The service provides support for people who have been prescribed a new medicine for a long-term condition with the aim of the patient-centered identification of problems with treatment and providing support if needed. The intervention consists of two consultations with the patient: 7–14 days after presentation of new medicine prescription and 14–21 days thereafter. A randomized control trial demonstrated that the NMS significantly increased the proportion of patients reporting adherence to their new medicine by 10.2%–70.7%, compared with normal practice, 60.5% (Elliott et al., 2016).

The NMS aims to:

- improve patient adherence and health outcomes;
- increase patient engagement with their condition and medicines;
- support patients in making decisions about their treatment and self-management;
- reduce medicine wastage;
- reduce hospital admissions due to adverse events from medicines;
- lead to increased reporting of adverse reactions via the Yellow Card scheme, thereby supporting improved pharmacovigilance;
- receive positive assessment from patients;
- support the development of outcome and/or quality measures for community pharmacy.

At time of publication, the remuneration rate per NMS equates to £25. Some limitations of the service include insufficient integration, underdeveloped relationships between pharmacist and GP, and in some cases, unwillingness by pharmacists to implement the service (Elliott et al., 2016).

The Role of Pharmacy in Health Promotion

Healthy living pharmacy

In efforts to further public health interventions in a community pharmacy setting, the "Healthy Living Pharmacy" was piloted in 2009. The vision for the scheme was born out of a government 2008 White Paper, "Pharmacy in England: building on strengths, delivering the future." Among the recommendations made in the White Paper, a call for community pharmacy to play a greater role in prevention and early detection of disease and management of chronic conditions was outlined. In addition, it encouraged pharmacy to take greater clinical responsibility for patients such as prescribing and, in turn, broaden the role of pharmacies beyond dispensing volume-driven activities.

Health Living Pharmacy (HLP) framework is a tiered commissioning framework designed to improve the health and well-being of the local population and reduce health inequalities via public health services delivered in community pharmacies. Furthermore, the framework aims to develop a pharmacy as a community hub for healthy living and develop the pharmacy workforce as a skilled team to promote behavior change and thereby improve health and well-being. Central to the HLP concept is further engagement with the local community, GPs and other health professionals, social care and public health professionals, and local authorities. There are three levels of service delivery within the HLP framework:

- Level 1: Promotion—Promoting health, well-being, and self-care (in July 2016, Level 1 changed from a commissioner-led process to a profession-led self-assessment process)
- Level 2: Prevention—Providing services (commissioner-led)
- Level 3: Protection—Providing treatment (commissioner-led)

In the UK, the healthy living pharmacy framework has been developed to support pharmacies to provide a wider array of public health services tailored to local need. This includes offering accessible and effective interventions around smoking cessation, weight loss, sexual health, alcohol, and other harm reduction services. Pharmacy Voice have identified that 60% of patients using HLPs would have otherwise visited a GP for health improvement advice and 20% would not have changed their lifestyle (Holden, 2015).

To be awarded HLP status, pharmacies must demonstrate the suitability of their premises, systems and resources, and a commitment to a healthy living ethos illustrated by a proactive approach to self-care and healthy lifestyles in their community. Each HLP must have at least one "Health Champion" trained and accredited to provide health and well-being advice to customers. By January 2016, 2100 pharmacies were accredited as HLPs, and 3500 pharmacy staff qualified as Health Champions (Public Health England, 2016).

Around 70% of people who visit pharmacies do not regularly access other healthcare services, thus HLPs can provide health and well-being support to people in their community that may be outside the reach of other resources. Improved choice and access to early interventions on issues such as common ailments, optimal medicines use, and lifestyle could improve outcomes in the longer term and therefore positively impact cost of care in the future. (Holden, 2015)

Primary Care Pharmacy—Pharmacist and General Practitioner Partnerships

From the 1990s onwards, pharmacists began working more closely with the general practice based primary healthcare team. As pressures and demands on GPs have increased over time, clinical pharmacists have begun to work as part of the general practice team to resolve day-to-day medicine issues and treat patients directly.

In this integrated model of care, clinical pharmacists provide health checks, counsel patients on complex medicine regimens, and manage patient's chronic and long-term conditions. In addition, pharmacists have advised on GP formularies and take responsibility for anticoagulant and *Helicobacter pylori* assessment clinics. The role of the clinical pharmacist in GP practices helps to improve the quality of prescribing and care. Furthermore, the integrated model allows for GPs to focus on diagnosing and treating patients with complex conditions. According to the Pharmacy Voice, 92% of GPs would like more support from community pharmacy teams to help their patients take their medicines correctly. Following the successful pilot in 2015 that placed 490 clinical pharmacists in 650 GP practices, a further £100 million has been invested to support an extra 1500 clinical pharmacists to work in general practice by 2020.

To support this transformation, a new Pharmacy Integration Fund was established with a budget of £42 million secured for 2016–18. The fund will drive the greater use of pharmacists and pharmacy technicians in a variety of settings such as general practices, care homes, urgent care settings, and further support the development of clinical pharmacy. Further development of digital integration between settings is required.

Out of Hours Services

NHS is a free-to-call single nonemergency phone number and medical helpful that operates in England and Scotland. The equivalent in Wales is NHS Direct Wales, which was rolled out in 2016. It is a 24 h a day service and triages urgent but nonlife threatening health issues. Audits of the calls have shown that a high number of queries are linked to medicines use and as such pharmacists are employed to give direct online healthcare advice (Rees et al., 2014).

Patient Group Directions

An alternative strategy to improve patients' access to medicines is the use of Patient Group Directions (PGD). PGDs allow for medicines to be accessed without a prescription and is supplied by a pharmacist or other healthcare professional, usually in planned circumstances. PGDs require significant resources and time to implement and should be developed by a multidisciplinary group of healthcare professionals as well as the prescribing advisory boards. The legal definition of a PGD is "A written instruction for the sale, supply, and/or administration of named medicines in an identified clinical situation. It applies to groups of patients who may not be individually identified before presenting for treatment" (MHRA, 2017).

The PGD allows the supply of prepacked licensed POMs only to patients who meet the inclusion criteria. The DH has enforced that the PGD should only be used for short courses of standard treatment of, for example, sildenafil for erectile dysfunction and orlistat for weight loss. While emergency hormonal contraception is not a POM, it is also available under the PGD and in certain instances is free of charge.

NonMedical Prescribing

In the UK, improved access to medicines has been a significant driver of the legislative changes enabling pharmacist prescribing. Making better use of pharmacist's skills and pharmaceutical expertise, as well as the specializations of other healthcare professionals, was the focus of the two Crown Reports. The 1999 Crown Report critically changed the landscape of prescribing with the recommendation that pharmacists, nurses, midwives, physiotherapists, podiatrists, optometrists, and radiographers should gain prescribing privileges. To qualify as a nonmedical prescriber, additional assessments and accreditation is required. Nurses were the first to become nonmedical prescribers, followed by pharmacists in 2003. By this time, about 24% of pharmacists worldwide had already incorporated "some form" of prescribing into pharmacy practice. In the UK, the legal framework emerged at a later stage to support the work that clinical pharmacists were already undertaking (Baqir et al., 2012).

Supplementary Prescribing

In the supplementary prescribing model, a diagnosis must first be made by either a doctor or dentist, and a clinical management plan (CMP) must be agreed in collaboration with the independent prescriber and the patient. The patient must give their consent to the transfer of care to a supplementary prescriber. The extent of the allowances for prescribing dictated by the CMP is largely determined by the therapeutic area expertise of the supplementary prescriber, and the relationship with the doctor. Most importantly, the CMP sets out the terms of agreement between the independent and nonmedical prescriber and can vary in specificity and detail. There are few restrictions around what nonmedical prescribers can prescribe to patients, and in May 2005, certain controlled drugs and unlicensed medicines were added to the list of medicines that can be prescribed by supplementary prescribers (Rees et al., 2014).

Now that pharmacists can become independent prescribers (IP) in the UK, supplementary prescribing is less common, although important in creating the foundation and framework for independent prescribing.

Independent Prescribing

The IP regulations came into effect in 2006 and allowed pharmacists to prescribe autonomously for any condition within their clinical competence (Harding and Taylor, 2016). The independent prescriber is responsible for the assessment of patients with undiagnosed or diagnosed conditions, and accountable for clinical management decisions, including prescribing. At time of publication, an IP may be a specially trained nurse, optometrist, physiotherapist, therapeutic radiographer, podiatrist, or pharmacist. Nurse and pharmacist-independent prescribers can also prescribe unlicensed medicines and controlled drugs apart from three types of controlled drugs for the treatment of addiction.

To qualify as an IP, the pharmacist must have practiced for a minimum of 2 years and complete a GPhC accredited programe that is typically run over a period of 6 months. In addition, there are conversion courses available to allow supplementary prescribers to qualify as independent prescribers.

There is a single competency framework for all prescribers including doctors, see **Table 2** for a summary table of the prescribing competency framework. In the table, there are ten competencies split into two domains, the consultation and prescribing governance. However, it does not list individual outcomes for each competency area.

IP pharmacists may also run their own clinics or prescribe in wards such as intensive care or medical administration units. However, currently there is a vast variation (2.5%–71%) in the rates of prescribing pharmacists as a proportion of hospital pharmacists.

Pharmacy education is also changing to reflect the extended role of the pharmacist and prescribing competencies will become core components to the pharmacy undergraduate curriculum. In future, a multifactorial prescribing model will be more likely to encompass activities such as the Medicines Use Review, New Medicines Service, Chronic Medicines Service, and repeat dispensing (Harding and Taylor, 2016).

Table 2 Prescribing competency framework

Consultation	*Prescribing Governance*
1. Asses the patient	7. Prescribe safely
2. Consider the options	8. Prescribe professionally
3. Reach a shared decision	9. Improve prescribing practice
4. Prescribe	10. Prescribe as part of a team
5. Provide information	
6. Monitor and review	

Hospital Pharmacy

In the UK, hospital pharmacy is the second largest employer of pharmacists, in both NHS and private hospitals. In general, the hospital pharmacist's role is not only more specialized than in the community setting, but also includes similar functions such as the purchase, preparation, dispensing, and supply of all the medicines. Beyond the supply of medicines, hospital pharmacists play a key role in providing clinical and pharmaceutical expertise to patients and healthcare professionals alike. The pharmacy department works closely with other healthcare professionals and advises staff on the safe and effective use of medicines with regard to dose, formulation, administration, and drug monitoring.

In the UK, hospital pharmacists also provide medicine information services such as writing medication-related guidelines and developing hospital formularies. The medicines information team also supports healthcare professionals and patients on all aspects of medicines and have access to a wide range of reference material to respond to queries.

While clinical pharmacy is not practiced in a uniform manner across the UK, most hospital pharmacists will speak to patients during ward rounds to improve patient understanding and adherence to their medicines and conduct medicine reconciliation (i.e., taking a medication history from patients and resolving any discrepancies.) NICE has recommended that pharmacists complete this as soon as possible after patient admission to hospital. A 2009 report from the General Medical Council highlighted that 8.9% of orders across UK hospitals contained a prescription error. Furthermore, the evidence suggests that pharmacists take more accurate drug histories than medical staff, and so pharmacists have been identified as central clinical staff in improving prescription quality (Harding and Taylor, 2016).

The 2016 Carter Report, which was launched to review efficiency improvement in hospitals, recommended that the pharmacy workforce drives outcomes and achieves optimal value from the £6.7 billion it spends on medicines per year. Overall, the NHS is expected to deliver efficiencies of 2%–3% per year with a 10%–15% real terms cost reduction target by April 2021.

As part of this strategy to heighten operational productivity and performance, recommendations have been made for pharmacists and pharmacy technicians to spend more time delivering clinical patient facing activities such as medicine optimization. Furthermore, the Carter Report has emphasized skill mix and enhanced efficiency to build in medicine optimization as part of daily practice with the aim of reducing unwarranted variation in productivity and efficiency.

According to the Royal College of Physicians, in the UK, there has been a cumulative rise of 37% in patient visits to hospital over the past 10 years (Harding and Taylor, 2016). To accommodate this significant rise in patient numbers and the complexity of admission services, recommendations have been made for seven days a week service. However, there is still widespread variability in pharmacy departments' delivery outside of the standard working hours, particularly on weekends, and this presents as a significant challenge for hospital pharmacy. In response, NHS trusts have launched hospital transformation programs (HTTP) to prepare clinical pharmacy staff for seven-day healthcare service delivery and deploy clinical pharmacists onto wards to ensure optimal use of medicines.

Hospital Pharmacy Standards

The regulations around the use of medicines in hospital settings are intricate, and hospitals are required to register with the Care Quality Commission (CQC) in England. The CQC's role is to ensure that hospitals, care homes, and dental and general practices provide people with safe, effective, and high-quality care.

In the wake of the Francis Report 2013, which exposed serious neglect of patients in the Mid Staffordshire NHS Foundation Trust, the issues of patient safety, quality of care, and leadership are at the forefront of public and policy debate. As a result, the organizational culture of the NHS has responded with an emphasis on value-based recruitment for all staff. Values such as empathy and compassion are screened for from point of university entry across most UK pharmacy universities, and in the workplace pharmacists must demonstrate empathy and compassion.

In addition, the Royal Pharmaceutical Society is reviewing the current set of Professional Standards for Hospital Pharmacy Services to improve patient safety for 2017. These standards serve as a broad framework to support pharmacy departments in improving the quality of service delivery. It also outlines future pharmacy services and pharmacy roles designed to reduce incidents of avoidable harm within organizations. The standards are aimed at giving patients a clear picture of what to expect from their pharmaceutical care. There are currently 10 standards for pharmacy services divided into three domains: Patient Experience, Safe and Effective Use of Medicine, and Delivering the Service (see Table 2, p. 24).

Use of Technology in Hospital Pharmacy

In continental Europe and the US, the use of pharmacy-based automated dispensing machines for original pack selection became commonplace in the 1980s. However, robotic dispensing and automation was adopted more gradually in the UK due to a traditional mixed dispensing profile. Although the use of robotics in dispensing is now common, it was not until the European Community Directive 92/97 became law in 1999 that the automated system became viable in UK hospital pharmacies. (Goundrey-Smith, 2008)

In addition to the use of robots, electronic prescribing (EP) is a further safety measure that is used in hospital settings. While there is variation in the definition of EP from country to country, the NHS Connecting for Health has defined EP as the "utilisation of electronic systems to facilitate and enhance the communication of a prescription or medicine order, aiding the choice, administration and supply of a medicine through knowledge and decision support and providing a robust audit trail for the entire medicines use process" (Ahmed et al., 2016).

With the drive toward a "paperless NHS" by 2020, there has been significant investment in digital infrastructure; however, currently, the overall uptake is still low in comparison to other European countries. A new report from Digital Health Intelligence concludes that at the current rate of implementation, NHS hospitals will not become paperless before 2027.

The EP hospital system includes a range of different functions, and is more complex than the systems used in Primary care. EPs may be implemented in a wide range of organizational contexts and are accessed by different healthcare professionals at different stages of care.

Healthcare Organizations and Pharmacy Groups

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) is an Executive Non Departmental Public Body (ENDPB) and, while accountable to the DH, operates independently of the government. The primary responsibility of NICE is to provide evidence-based guidance on health and social care to help practitioners deliver the best quality of care. The guideline recommendations are targeted toward individual health and social care professionals, but should be used alongside professional judgment and after discussion with service users.

It was originally established in 1999 as a special health authority to review efficacy and cost-effectiveness of medicines. It publishes recommendations around medicine use by prescribers. Over time, the NICE has evolved to include added functions, for example, health technology appraisals and guidelines around quality standards.

NICE publishes quality standards and guidelines on the following:

- Health technologies
- Health promotion
- Clinical Practice
- New and existing medicines and treatment.
- Treatment and care of people with specialist diseases and conditions.

While NICE guidance is specific to England, certain NICE services are shared with Wales and Northern Ireland. The devolved administrators from each country are consulted with in the development of their own NICE guidance that is relevant to their local context. In Scotland, it is the Scottish Intercollegiate Guidelines Network (SIGN) that develops evidence-based guidelines. The guidelines are developed by a committee of unbiased experts with at least two lay members who have an illness that the guideline pertains to, or have personal experience using the relevant healthcare service as a patient or carer.

A 2016 Medication Error report from the World Health Organization identified discrepancies in discharge medication following hospitalization in 43%–60% of items leading to a 77% error rate in transfer from secondary to primary care. In an attempt to reduce error at point of patient transfer, NICE recommends that medicines' discharge information should be shared with the community pharmacy. Some electronic tools help facilitate this process, for example, the Refer-to-Pharmacy tool allows bedside referral of inpatients to their community pharmacist for a post-discharge medicine adherence consultation, or to update a patient's pharmacy record with medication changes.

NICE has developed guidelines around medicines' optimization and adherence and is used by both hospital and community pharmacists for the most up-to-date diagnostic, treatment, counseling, and referral information.

Health Education England

Health Education England (HEE) is part of the NHS and is a national leadership body responsible for ensuring that education, training, and workforce development drives the highest quality public health and patient outcomes.

Pharmacy and pharmacists come under the remit of HEE, which is an executive nondepartmental public body sponsored by the Department of Health. As the national leadership organization for education and training, HEE is responsible for workforce planning and development. This body is further divided at the local level with Local Education and Training Boards (LETB) developing the NHS workforce locally.

In Scotland, the equivalent body and special health board responsible for developing and delivering education and training is NHS Education for Scotland.

Currently in the UK, the pharmacy degree is a 4-year Masters of Pharmacy (MPharm) program, which is classed as an "undergraduate masters program" under the Bologna agreement for educational equivalence across Europe. To qualify as a pharmacist, graduates complete a one-year preregistration training program and pass the General Pharmaceutical Council registration exam.

Public Health England

Public Health England (PHE) is an executive agency of the Department of Health that was introduced in the 2013 reform of the NHS, replacing the Health Protection Agency and the National Treatment Agency for Substance Misuse as well as 70 other health bodies. PHE has operational autonomy to advise and support the government, the NHS, and local authorities with professional independence. Public Health England works closely with public health professionals in Wales, Scotland, and Northern Ireland, and strives to improve the public's health and well-being, build capacity and capability of the public health system, and protect the public from threats and emergencies (Public Health England, 2016).

Pharmaceutical Services Negotiating Committee

The Pharmaceutical Services Negotiating Committee (PSNC) is recognized by the Secretary of State for Health as the representative negotiating body representing community pharmacy contractors on NHS matters in England. It was established in 1976 and works to promote and support community pharmacies by lobbying parliamentarians and policy makers. The PSNC primarily negotiates the terms and conditions of the NHS community pharmacy contractual framework and agrees the distribution of funds. In England, 11,600 pharmacies with an NHS contract fund PSNC through levies paid to their Local Pharmaceutical Committee. Across the UK, the PSNC works closely with its sister body Community Pharmacy Wales (CPW) which represents community pharmacy contractors in Wales. The PSNC also negotiates the remuneration that community pharmacy contractors receive for NHS dispensing services and other pharmaceutical services such as MURs, and promote further opportunities for service development. The remuneration is a financial reward for pharmaceutical service provision and is paid as fees and allowances, and the cost is charged to NHS England.

Future of Pharmacy

The Department of Health cuts to the pharmacy budget in 2015 and 2016 have already resulted in a growing number of independent pharmacy closures. However, in October 2017 it was announced that Lloyds Pharmacy, a major multiple chain, will cease trading in 190 branches across the UK due to commercial unviability (Torjesen, 2017). Up until now, the multiples have had a stronghold on pharmacy despite the often-challenging market conditions in the UK. As a result, there may be a rapid rise in the number of Internet Pharmacies, and with early signs, albeit not confirmed, that the corporate megalith Amazon may be entering the pharmacy business in the American market, it may not be too long before the UK follows.

Pharmacy will have to continue branching out beyond medicine supply and undergo a rebranding as a neighborhood health and well-being hub. This is already happening with the expansion of the Health Living Pharmacy model across the UK; however, more aggressive marketing measures may be required for public buy-in. Key to its success will be strong pharmacy partnerships across a broader range of local leaders and groups, ranging from charities to patient support groups.

Furthermore, as the global burden of noncommunicable diseases continues to grow, pharmacists are key healthcare workers in supporting personalized care for people with chronic conditions. The "Pharmacy First" services may be accessed by a variety of routes ranging from online to face-to-face, and the community pharmacy will serve as a triage center referring urgent cases to the GP or to the hospital. Community pharmacy staff will be able to book people directly into other services and fast-track them if necessary. Also with access to patient medical files via the SCR, pharmacists are better equipped now more than ever to give comprehensive healthcare advice. The next step for pharmacy will be to gain "write" privileges to record and update pharmacy-led interventions, building on the evidence base around the value of pharmacy.

In some ways, pharmacy is returning to its roots prior to the establishment of the NHS, with pharmacists positioned in a heightened patient facing role, and selling a broader range of services. However, as the scope of pharmacy service provision is widened, the remuneration must follow for future sustainability. As lessons of recent history show, pharmacy must adapt to technological, social, and political change at a faster pace to avoid further loss of self-determination as a profession. Perhaps most importantly, in order for pharmacy to thrive in a highly competitive and service provider saturated market place, the profession will have to demonstrate added value directly to the public and use each patient interaction as an opportunity to do so.

List or Relevant Websites

England

The Department of Health	www.dh.gov.uk
NHS England	www.england.nhs.uk
NHS Digital	www.digital.nhs.uk

NHS Improvement	www.improvement.nhs.uk
NHS Evidence	www.evidence.nhs.uk/
Public Health England	www.gov.uk/government/organisations/public-health-england
Health Education England	www.hee.nhs.uk
Royal Pharmaceutical Society	www.rpharms.com
General Pharmaceutical Council	www.pharmacyregulation.org
Medicines and Healthcare products Regulatory Agency	www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
British Society for the History of Pharmacy	www.bshp.org/
Pharmaceutical Services Negotiating Committee	www.psnc.org.uk/
National Patient Safety Agency	www.npsa.nhs.uk/
British National Formulary	www.medicinescomplete.com
Association of Pharmacy Technicians UK	www.aptuk.org/

Northern Ireland

NHS Northern Ireland (Health and Social Care)	www.online.hscni.net/
http://www.psni.org.uk/	www.psni.org.uk/
Community Pharmacy Northern Ireland	www.communitypharmacyni.co.uk/what-is-community-pharmacy/
Department of Health Northern Ireland Pharmacy	www.health-ni.gov.uk/topics/pharmacy
Pharmacy Forum Northern Ireland	www.health-ni.gov.uk/topics/pharmacy
Northern Ireland Association for Mental Health	www.inspirewellbeing.org/

Scotland

NHS Health Scotland	www.healthscotland.scot/
Scottish Government	www.gov.scot/
Health Protection Scotland	www.hps.scot.nhs.uk/
Scottish Public Health Network	www.healthscotland.com/resources/networks/scotphn/about.aspx
Health Improvement Scotland	www.healthcareimprovementscotland.org/
NHS Education for Scotland	www.nes.scot.nhs.uk/
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk/
The Improvement Hub	www.ihub.scot/
Scottish Medicines Consortium	www.scottishmedicines.org.uk/Home
Scottish Health Council	www.scottishhealthcouncil.org/about_us/about_us.aspx#.WfpI3YeDOUk

Wales

Health in Wales	www.wales.nhs.uk/ourservices
Community Pharmacy Contract Wales	www.wales.nhs.uk/sites3/page.cfm?orgid(498&pid(7552
Royal Pharmaceutical Society Wales	www.rpharms.com/making-a-difference/wales
Community Pharmacy Wales	www.cpwales.org.uk/
General Pharmaceutical Council in Wales	www.pharmacyregulation.org/about-us/who-we-are/organisation/gphc-wales
Wales Centre for Pharmacy Professional Education	www.wcppe.org.uk/about-us
Local Pharmaceutical Committee Wales	www.lpc-online.org.uk/regions/wales/
Primary Care Services Wales	www.primarycareservices.wales.nhs.uk/home

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Pharmacy Practice in Western Europe

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The Backdrop

Pharmacy in Western Europe has changed dramatically from the time of monastic pharmacy in the middle ages and the first apothecaries in Spain, Italy, and France to the present patient-centered pharmacy practice. Nowadays, in community pharmacy, the pharmacist is practicing independently, albeit in collaboration with other health care professionals, to provide primary care services to society. Documents, such as the Nuovo Ricettario from Florence, attesting to standardization of substances used as medicines, were the precursors of pharmacopoeias and pharmaceutical regulatory sciences, including the practice of pharmacovigilance. The evolvement of the concept of clinical pharmacy and later pharmaceutical care in the 1960s led to advances in pharmacy practice first in hospital pharmacy and subsequently in community pharmacy. The elaboration of pharmacy practice research is the foundation for the present evidence-based pharmacist interventions in health care. The concept of clinical pharmacy may actually trace its roots to Europe, at the time of the Knights of the Order of St. John of Jerusalem, who were a military-religious hospitaller order. There is evidence that the pharmacist participated in ward rounds with physicians to discuss the treatment to be given to patients in the Sacra Infermeria in Malta, at the time a state-of-the-art hospital established in 1574, which was run by the Knights.

This overview of pharmacy practice in Western Europe is analyzed by approaching advancements in the professional practice in community and hospital pharmacy with the impact of the concepts of clinical pharmacy, pharmaceutical care, and pharmacovigilance, as drivers of change. The influence of education and practice research on shaping these advancements is considered.

It is difficult to establish a geographical definition of Western Europe, because it is not a formal region, as is the European Union. There have been major transformations in the region post-World War II to date. Europe consists of a number of countries in terms of economic forces, political influences, and military successes. This geographical and nation-state, not to mention languages situation, makes the region unique in terms of an attempt of convergence of systems for countries within the European Union while there are also other significant models for the other countries, which are European although not members of the European Union. A broad outlook that goes beyond the geopolitical definition is adopted in this chapter where the outlook is embracing the advancements and innovations in pharmacy practice within Europe.

Data from the PHARMINE study undertaken by the European Association of Faculties of Pharmacy (EAFP) among 25 EU member states in 2008, established that there were 419,353 pharmacists working in these countries (Atkinson and Rombaut, 2011). Patterns of practice for pharmacists reported in the PHARMINE study are similar to the data presented in the 2017 report by the International Pharmaceutical Federation (FIP) "Pharmacy at a glance" where principal areas of practice for pharmacists in Europe identified are: 78.5% in community pharmacy, 8.9% in hospital pharmacy, and 12.6% in other areas. In terms of pharmacists density per population, the European median is 8.28 pharmacists per 10,000 population. The number of pharmacists per population is highest in Europe when compared to the figures for other regions: western Pacific region, 4.96; Pan American region, 4.67; eastern Mediterranean region, 4.28; southeast Asian region, 2.31; and African region, 0.61 (International Pharmaceutical Federation, 2017). According to 2012 data, the range of pharmacists density per 10,000 population varies from 5.25 in Norway to 24.82 in Malta (**Table 1**) (International Pharmaceutical Federation, 2015). There could be a geographical trend in that: the higher density (12–25) of pharmacists is seen in the southwest Mediterranean countries (France, Portugal, Spain, Italy, and Malta) and the lower density (5–6) is seen in the Nordic countries of Norway and Finland.

Table 1 Pharmacists density per 10,000 population in European countries

Countries	*Pharmacists per 10,000 population*
Austria	6.93
Belgium	11.63
Croatia	7.17
Czech Republic	7.62
Finland	5.80
France	11.57
Germany	9.58
Hungary	5.70
Ireland	10.46
Italy	13.47
Malta	**24.82**
Norway	**5.25**
Portugal	12.56
Spain	13.74
Switzerland	8.45
United Kingdom	8.08

International Pharmaceutical Federation (FIP), 2015. Global pharmacy workforce intelligence: Trends report. The Hague, The Netherlands: International Pharmaceutical Federation.

Forces of Change

Over the past 50 years, there have been multiple changes in European countries that have impacted on the evolvement of pharmacy practice models. A significant impact was the transition from compounding of medicines in community pharmacies to the industrial manufacture of medicines (Higby, 1996).

A consequence of the industrialization of the manufacture of medicines was a change in the practice of community pharmacy: the dimensioning of the community pharmacist as a caregiver rather than as a producer of the medications (Azzopardi, 2000). The community pharmacist has a tradition of playing a central role in the social network of the community being served, and this role also encompassed accessibility to medications. The introduction of medicines that were produced within a pharmaceutical industry under a trade name presented a challenge to accessibility of medicines. Governments intervened in some countries to oversee that medicines were available to different social strata. Industrialization from a broader perspective was seen as a driving force for national economic growth. Governments in Europe, through different approaches, were addressing disease from various angles including access to medicines. Poverty was central to access to health care and in some instances ensuring equitable access to medicines was considered a key performance indicator in the successful redistribution of wealth (Szreter, 2004). Health care models were developed across European countries post-World War II. The introduction in the United Kingdom of the National Health Service in 1948 was seen as an innovative social service model targeting national coverage of health care, including pharmaceutical services (Lopes et al., 2010). Europe retained a characteristic trait of variability in health services delivery. This diversity in its health services structure is very relevant when reflecting on how the economic driving force of industrialization impacted on the models of pharmacy practice. Switzerland is an example highlighting this variability that transcends to a national level. In Switzerland, the national health system relies on regional laws and regulations adopted by the 26 different cantons (Simonet, 2009). The evolvement in health care systems in European countries is an on-going strategy, which needs to take into account the continuous reshaping of the region, starting in the 1990s with the reunification of Germany and expansion of the European Union (Ridic et al., 2012). The impact of Brexit on the National Health Service in the United Kingdom and an influence of Brexit on health care systems in other countries may be a driving force for future transformations impacting on pharmacy practice.

Forces of change taking place in other regions outside Europe, especially in the United States, impacted on the evolvement of pharmacy practice in Europe. In the United States, with a backdrop of economical prosperity and an expanding repertoire of industrially manufactured medications, leaders of hospital pharmacy from the American Society of Hospital Pharmacists instigated a survey on the status of pharmacy practice in hospitals. In the report of the findings of the survey, the authors take forward this initiative by presenting innovative clinical pharmacy services that pharmacists could develop in hospitals where the focus moves toward the patients (Francke et al., 1964). The survey and the resulting publication sowed the seeds for the germination of the philosophy of clinical pharmacy in the United States, which at the time was envisioned to be affiliated with institutional care settings (Higby, 2014). The philosophy of clinical pharmacy practice took longer to germinate in Europe (Gums, 2013). An explanation for this delay is that in addition to change resistance inherent to human nature, pharmacy leaders in Europe were engrossed in developing health system models of accessibility and delivery of medicines as a priority to convincing European governments of the benefits of clinical pharmacy services.

Medicines regulatory sciences, particularly aspects of quality assurance started to become formalized. The thalidomide disaster brought to light in 1961, is seen as the driving force to the evolvement of pharmacovigilance, as a patient-safety strategy, which relies

on the remodeling of pharmacy practice (Routledge, 1998). Pharmacovigilance, which broadened the description of pharmacy practice beyond community and hospital settings, is seen as a pharmaceutical science reflecting a practice that looks at safety in whichever platform of care a pharmacist is performing.

Community Pharmacy

In Europe, community pharmacy is represented by a median of 3.06 community pharmacies and 6.26 community pharmacists per 10,000 inhabitants (International Pharmaceutical Federation, 2017). The Pharmaceutical Group of the European Union (PGEU) is an international nonprofit organization that represents community pharmacists in Europe and plays an advocacy role at the European Union level to advance community pharmacy practice as a contributor to health systems and society well-being. Community pharmacy practice in Europe may be described as having a common trend of transforming the practice to focus on public health, patient care, and quality services, albeit with terms of diversity in the regulation of the profession (Anderson, 2007).

Regulation of community pharmacy practice in Europe is influenced by different ways of ensuring accessibility and sustainability, such as an exclusive ownership of pharmacies by pharmacists, pharmacies run by chains, control of establishment of new pharmacies based on distance and/or population, and exclusive rights to sell non-prescription medicines (Chave, 2014). The European Commission is in support of liberalization, but European court cases have ruled that restrictions at national levels are justified and lawful, as the restrictions are in the interest of protecting delivery of quality health care (Lluch and Kanavos, 2009). Liberalization or deregulation of distribution of community pharmacies in Europe may not necessarily lead to increasing access to medicines in rural areas, where the service is perhaps lacking. Quality and expansion of pharmacy services, particularly beyond dispensing of prescription-only medicines, may be challenged if opening of pharmacies is not controlled (Vogler et al., 2014).

The legal frameworks governing community pharmacies highlight requirements related to premises, dispensing of medications, storage of medicines, and some description of professional services. Patcheva et al. (2012) describe legal requirements in Germany, Slovenia, Croatia, and the Republic of Macedonia. Quality systems for community pharmacy practice and the relevance of adopting key performance indicators of professional services to identify areas of improvement were established (Azzopardi, 2000; Azzopardi et al., 2003; Halsall et al., 2008; Mark, 2008; Vo et al., 2017). The strengths of quality systems for community pharmacy practice serve to identify the professional intervention of the pharmacist as it impacts on patient care and promotion of health. Accessibility to medicines by requiring a pharmacist to manage a community pharmacy does not present a legal restriction on accessibility to medicines (Community Pharmacy Section, International Pharmaceutical Federation, 2005).

Community pharmacists are active players in the primary care setting to support patients in the selection of non-prescription medicines and identifying signs or symptoms requiring referral. The elaboration of protocols to support a standardized approach by community pharmacists is a means of measuring the intervention of the community pharmacist in patient care while promoting evidence-based practice (Vella et al., 2009). Community pharmacists are empowering patients in choosing non-prescription medicines rationally based on scientific evidence (Galea et al., 2014).

The need for the formal establishment of cognitive pharmaceutical services that should be remunerated and recognized as contributing to health outcomes is acknowledged as strengthening the community pharmacy model. As the concept of pharmaceutical care, coined by Hepler and Strand in 1990 gained ground in Europe, non-remuneration for pharmaceutical care services provided by community pharmacists was identified as a barrier to the implementation of professional services focusing on pharmacotherapy management and patient monitoring (Van Mil et al., 2001). The concept of pharmaceutical care within community pharmacy practice led to the development of pharmacy practice research aimed at demonstrating value of the cognitive services provided by community pharmacists in monitoring patient adherence to treatment, in undertaking medicines use reviews, and in patient counseling. The Pharmaceutical Care Network Europe was established in 1994 to stimulate pharmaceutical care and pharmacy-related outcomes research in Europe. The network serves as a collaborating platform for pharmacists interested in developing community pharmacy practice research.

The barrier of the need for reimbursement for professional pharmacy services has been overcome in a number of countries. Reimbursement by health insurances for cognitive pharmacy services including pharmaceutical care services and disease management was started in Germany in 2003 (Eickhoff and Schulz, 2006). In the United Kingdom, the Medicines Use Review (MUR) community pharmacy service was introduced in 2005 (van den Berg and Donyai, 2010). In Switzerland, the provision of pharmaceutical services by community pharmacists is reimbursed by health care insurers (Schneider et al., 2009). The Swiss Polymedication Check, which is a pharmacist-led medication review implemented in Switzerland and reimbursed by health care insurers, was shown to identify drug-related problems related to adherence by the patient to treatment and improved patient knowledge about the medicines (Messerli et al., 2016). In Italy, medicines use review for patients with asthma (I-MUR) was launched as the first nationally reimbursed cognitive pharmaceutical service (Manfrin et al., 2017). The positive results and validated protocols from the countries where pharmacists are reimbursed for cognitive services serve as tools for the development of such services in other countries (Swieckowski et al., 2017).

Consumer satisfaction studies of community pharmacy services indicate a good degree of satisfaction for the services received related to conventional professional pharmacy services (Wirth et al., 2011). The consumer perception regarding extended professional services provides information about priority areas to be considered for innovative community pharmacy services. The participation of the pharmacist in interdisciplinary collaboration in the management of chronic conditions and the provision of diagnostic testing was reported by consumers as key areas of evolvement (Vella et al., 2015). The incorporation of point-of-care

testing within a cognitive service provided by community pharmacists is feasible and contributes to improved management of drug therapy (Geerts et al., 2013). The introduction of a community pharmacist-led anticoagulation management service was shown to be sustainable and contribute to the improvement of management of patients on warfarin (Mifsud et al., 2014). Application of point-of-care testing of urine analysis for microalbuminuria in diabetic patients may be incorporated within diabetic patient monitoring services (Ungaro et al., 2015). Topics described in Scotland as requiring prioritization in community pharmacy services development included appropriate supply of non-prescription medicines, patient counseling for prescribed medication, pharmaceutical care to promote medication adherence, responding to minor symptoms, and pharmaceutical care of vulnerable patients (Newlands et al., 2017).

The development of new services within community pharmacy practice may be examined through the application of risk management intervention (Pereira Guerreiro et al., 2012). Studies on the risks in prescribing by pharmacists, for example, antibacterial drugs as perceived by physicians are an indication of the need for community pharmacists to disseminate the positive contribution of pharmacist prescribing in enhancing patient safety and timely access to medicines (Attard Pizzuto et al., 2016). Pharmacist prescribing was developed in the United Kingdom since 2003, first through supplementary and later through independent prescribing (Baqir et al., 2012). Professional services evolved for the past 14 years in different forms and aspects. There is room for further development of the service within the community pharmacy context even in the United Kingdom (Stewart et al., 2011).

Community pharmacy practice has come a long way since its apparent threat of deprofessionalization with the industrialization of production of medicines. Transformation is ongoing and is seen by community pharmacists as a means to contribute significantly to patient care and to social health care models. The drive of transformation is evolving and there are many challenges coming along in the future.

Hospital Pharmacy

European data stands at 4.08 hospital pharmacists and 0.94 hospital pharmacies per 100,000 population. There is a wide variation of percentage of pharmacists holding a principle employment as a hospital pharmacist on a national level in Europe. The United Kingdom and Malta top the list where 19.8% and 19.2% of the total pharmacists population are practicing in a hospital setting. Bulgaria and Greece represent the other end of the spectrum with 1.6% and 2.3%, respectively (Atkinson and Rombaut, 2011). Hospital pharmacy practice consists of: (1) administrative services related to procurement and distribution of medicinal products, medicines preparation, such as compounding and intravenous admixtures, and quality assurance; (2) clinical services related to drug information, therapeutic drug monitoring, direct-patient services, and patient safety. The European Association of Hospital Pharmacy represents national associations in Europe of hospital pharmacists and promotes networking between hospital pharmacists to promote continuous improvement of hospital pharmacy services.

Hospitals in Western Europe tend to procure medicines directly from the manufacturing industry, whereas hospitals in Eastern Europe in general go through wholesale dealers (Frontini et al., 2012a). Challenges particularly relevant to small hospitals and islands, with regards to procurement of medicines include accessibility, drug shortages, and pricing. The centralized distribution model requires a large operational structure in the hospital pharmacy that includes non-pharmacists to handle stock distribution and management. Hospital administrators are looking into models that provide the best efficiency and clinical outcome from the pharmacist manpower. This is leading to circumstances where the number of pharmacists contributing to administrative pharmacy services is being reduced or some of the services are being subcontracted or outsourced. The production of sterile and non-sterile medicines in hospital pharmacies in Europe has decreased over the past 17 years (Frontini et al., 2012b).

In the 1967 issue of the journal Drug Intelligence published in the United States, Don E. Francke refers to the emerging role of the hospital pharmacist as a member of the health care team contributing to the patient care area (Francke, 1967). The contribution of the emerging clinical pharmacists was identified as reducing medication errors, monitoring adverse effects, and contributing to unit dose dispensing and pharmacist participation in intravenous admixtures preparation (Francke, 1969). Anthony Serracino-Inglott, a pharmacist from Malta who was following a residency and a postgraduate doctor of pharmacy degree at the Cincinnati General Hospital was working with Don Francke and his team between 1969 and 1972. He worked on improving intravenous administration of drugs by the patients' bedside (Kramer et al., 1971). Serracino-Inglott went back to Malta after completing his doctoral studies and was instrumental in developing clinical pharmacy services at the acute and rehabilitation hospitals in Malta and in giving the strategic shift of pharmacy education in Malta toward a patient-centered approach. Graham Calder, the first Regional Director of Pharmacy Service in Great Britain, Birmingham Region, participated in the ASHP-AACP workshop on clinical pharmaceutical practice and education held in Kansas City, United States in 1971 (Calder, 1971). Calder reflects on the experience as enlightening and in fact he was another European pioneer who witnessed clinical pharmacy beginnings in the United States and went on to contribute to the spread of clinical pharmacy models in the United Kingdom. These encounters may well explain the highly clinical pharmacy-oriented services in the hospitals in Malta and the United Kingdom. In the United Kingdom, the movement of clinical pharmacy practice in the hospitals spread throughout the country, and in 1981, the UK Clinical Pharmacy Association was established.

The clinical services in hospitals in Europe are expanding. For example, in a rehabilitation hospital in Malta, 61% of the pharmacist time is dedicated to clinical activities, 27% to administrative services, and 12% to other activities (Wirth et al., 2009). In Malta, a number of studies have shown the impact of clinical pharmacy services in the acute hospital setting within particular specialties, including cardiology (Agius Decelis et al., 2015), psychiatry (Bugeja et al., 2015), and rheumatology (Grech et al., 2013).

Standardization of clinical pharmacy practice in the hospital contributes to quality of patient care (Mamo et al., 2013). The development of Medication Assessment Tools as evidence-based instruments intended to support clinical pharmacy services in ensuring appropriateness of drug therapy was started by the research group led by Professor Steve A. Hudson from the University of Strathcylde, Scotland (McAnaw et al., 2003). Innovatively developed Medication Assessment Tools were implemented in Maltese hospitals for stroke (Gauci et al., 2017a), atrial fibrillation (Gauci et al., 2017b), and rheumatology (Grech et al., 2016). Pharmacist contribution to patient care includes the contribution of the pharmacist in rational drug therapy selection based on predictor models, such as prediction of analgesic consumption postcesarean (Buhagiar et al., 2011) use of antibacterial agents in peripheral arterial disease (Zammit et al., 2011; Vella et al., 2016) and pharmacogenetic testing (Wirth et al., 2016).

The evolvement of clinical pharmacy services in hospitals in Italy followed a different pattern of development. Hospital pharmacists initially carved a unique contribution related to the strengthening of clinical pharmacology and epidemiological studies. This was an indirect excellent contribution for Italian pharmacists to participate in the generation of scientific data that contributes to improved pharmacotherapy selection and access to therapy (Adami et al., 2012). One of the early centers that spearheaded this scientific development of pharmacy practice was the Mario Negri Institute, founded by Silvio Garattini in 1963 to undertake clinical research related to cancer chemotherapy, transplants, rare diseases management, and clinical trials. The perspective in Italy was that by bringing to the forefront the value of pharmacokinetic studies, pharmacoepidemiology studies, and clinical trials data, the pharmacist contributed to innovation in drug therapy (Garattini, 2006). In 1998, the Mediterranean Institute for Transplant and Highly Specialized Therapy (ISMETT) was developed in Palermo in collaboration with the University of Pittsburgh Medical Center Health System (Johnson et al., 2007). ISMETT was one of the earlier models of hospital pharmacy services with a major focus on clinical pharmacy services that was developed in Italy. Hospitals in Italy are developing clinical pharmacy services, such as the one by Francesco Cattel at the San Giovanni Battista Hospital in Torino (Uomo et al., 2012).

Clinical pharmacy practice in hospital settings in Europe is developing at different rates and in varying extents across the region. Reflections on the status of the pharmaceutical services in the hospital settings and identification of processes that will enhance the evolvement of the clinical services are steps taken up by countries, which are identifying appropriate approaches for a successful start up in extending clinical pharmacy interventions (Pawlowska et al., 2016). Services focusing on specific areas of clinical pharmacy include (1) medication reconciliation at admission—Ireland (Byrne et al., 2017); (2) integrated medicines management during patients' hospital stay—Sweden and Norway (Horvei Andersen et al., 2014), Germany (Lenssen et al., 2016), and the Czech Republic (Rychlickova et al., 2016); and (3) medication reconciliation at discharge—France (Van Hollebeke et al., 2016). The development process in some instances is directed to specific specialties, for example, cardiology—Northern Cyprus (Al-Baghdadi et al., 2017). In a number of instances, the service development starts off from pharmacy practice research projects many of which are a result of collaboration between faculties of pharmacy and practice settings.

Pharmacovigilance

The thalidomide tragedy in the 1960s and the shift of focus in community and hospital practice from product to the patient contributed to the notion of evidence-based medicine. Evidence-based medicine is a broad concept where the evidence is covering aspects of rational selection of the drug, including pharmacoeconomic aspects, as well as aspects of patient safety. The notion of "evidence" is sometimes questioned as to how much knowledge and clarity one can ascertain to achieve evidence (Lilja et al., 2008). The weakness of evidence provided to prescribers and pharmacists led to the inability to empower health care professionals to realize the risk-benefit attributes of the drugs in the individual patients. Some drugs, which were withdrawn in the late 1990s, such as Terfenadine, Astemizole, and Cisapride could perhaps be still useful medication for some patients if present pharmacovigilance processes were in place in pharmacy practice settings (Raine et al., 2012). The rapid developments which have taken place in the area of pharmacovigilance over the past years may be considered as an answer from pharmaceutical regulators and stakeholders to the lack of transparency and the limitations of the "evidence" notion.

The European Pharmacovigilance Research Group (EPRG) was established in 1993 with the support of the European Commission, actually before the foundation of the European Medicines Agency (Anon, 1993). The EPRG was coordinated by Sir Michael Rawlins, who today chairs the Medicines and Healthcare Products Regulatory Agency of the United Kingdom. The European Commission took the lead to review the processes of medicines safety monitoring and this led to the EU directive specific to the process of pharmacovigilance, which came into effect in 2012 (Borg et al., 2015). The practice of pharmacovigilance is driven by the European Medicines Agency through the national medicines agencies of the EU member states. There is an element of reliance on the pharmaceutical industry to design and put forward risk management plans through safety specifications elaboration and the development of risk minimization plans and risk management plans (Wiktorowicz et al., 2012). Such an approach is a characteristic to the European process of pharmacovigilance in contrast to the United States. The pharmacovigilance directive encourages prescribers, as well as patients to communicate signals, which contribute to the compilation of real-time data on medicine use. The impact of pharmacovigilance on pharmacy practice is the greater transparency and solid evidence that is generated which empowers prescribers, pharmacists, and patients to make an informed decision as to the risk-benefit of the drug therapy.

Pharmacovigilance processes are generating complex data from different sources (health care professionals, patients, marketing authorization holders). This concoction of data highlights the need for the participation of experts who can analyze this data and interpret the benefit-risk ratio with a macro- and micro-level of patient-safety perspective (Anelli et al., 2017). Pharmacists can contribute to the comprehensiveness of following pharmaceutical regulatory processes while keeping the patient safety perspective.

Pharmacy practice expanded to include pharmacovigilance activity when it is undertaken at the patients' bedside or when the pharmacist is fulfilling this contribution in a regulatory position.

The proactive approach taken in the 2012 EU directive has reduced the strict definition between pre- and post-authorization data (Hidalgo-Simon and Arlett, 2012). There is an apparent trend to favour even more such an approach and to shift pharmacovigilance processes earlier in a medicine life cycle with suggestions to consider replacing stages of clinical trials with pharmacovigilance (EU Commission Conference Report, 2015). The substitution of a part of the extensive preregistration processes with a robust pharmacovigilance activity is especially relevant with respect to orphan drugs and rare diseases where access to medications may be limited. Health care professionals and patients should have the opportunity for informed access taking into consideration that the data is limited for the specific medicinal product. The success of this model relies on good practice by health care professionals, and hence the positioning of the activity of pharmacovigilance at the center of pharmacy practice models becomes unquestionable. The challenges are not limited to how far the proactive approach for identifying unwanted effects should extend. The increasing use of advanced therapies, such as biological agents, including the advent of biosimilars and stem cell technology, pose questions in terms of applicability of the pharmacovigilance current process primarily due to the differences in the manufacturing process (Cilia et al., 2017). Advanced therapies may indicate the need for specially designed pharmacovigilance methodology and pharmacists should participate in this design using their experience in pharmacy practice scenarios.

Pharmacy Education: The Motor for Pharmacy Practice

The European Association of Faculties of Pharmacy (EAFP) was established in 1992 when a group of academics met at the Faculty of Pharmacy Paris-Sud, France. In 1994, EAFP Secretary General Professor Pierre Bourlioux prepared a report on curricula mapping in European schools of pharmacy. The report showed that chemistry was the major component of pharmacy courses covering 25%–46% of the programs. Topics of biological sciences (physiology, biochemistry, and anatomy) contributed to 12%–32% and medical sciences (pharmacology, pharmacy practice, clinical pharmacy) contributed to 11%–30% of the curriculum. In the 2011 PHARMINE study, medical sciences (28%) were the major area constituting a pharmacy course followed by chemistry (24%) (Atkinson and Rombaut, 2011). Over the period of 17 years, there was a shift in pharmacy education in Europe toward the clinical sciences supporting the trends identified in the practice of pharmacy in the areas of community and hospital pharmacy. European pharmacy schools present an element of variability in terms of curriculum distribution across the subject areas (Atkinson, 2014). The data for individual schools of pharmacy show that some curricula are still more chemistry-oriented than others. There is a tendency that the medical sciences content is allocated toward the end of the program rather than as an integrated feature of the curriculum. Nunes-da-Cunha et al. (2016) compared the extent of patient focus in pharmacy curricula in Europe with the curriculum in the United States. In the United States, the Accreditation Council for Pharmacy Education (ACPE) establishes standards for pharmacy education that focus strongly on patient-centered care. The data from the Nunes-da-Cunha et al. study indicate that in the United States, 51% of the course content is patient-centered. In Europe, the range varies from Malta (54.2%) and The Netherlands (50.3%) to Macedonia (21.1%) and Greece (19.7%).

Pharmacy education in the European Union is described through an EU directive that was established in 1985. The directive relates to subject areas included in courses leading to a degree in pharmacy. The 2005 EU directive provides for mutual recognition of professional qualifications within member states. The EU directive stipulates a duration of studies of at least 5 years and highlights the requirement of at least 6 months traineeship in a community or hospital pharmacy. Yet the directives aiming at homogeneity in the pharmacy curriculum in the European Union allow for heterogeneity in the framework adopted for the pharmacy courses. Some programs are offered as integrated 5-year courses leading to a Master-level degree. Other programs adopt the Bologna Convention consisting of a two-cycle program, the first cycle is of 3 or 4 years leading to a Bachelor degree, which constitutes an academic scientific degree; and the second cycle is of 1 or 2 years, respectively, that leads to a Master-level degree in pharmacy. Variability also exists in the extent of experiential learning or internships offered in the program. Some programs in Europe provide internships in pharmaceutical industry and pharmaceutical regulatory settings in addition to the community and hospital practice.

Heterogeneity, which is contributing to functional pharmacists mobility in the European Union, provides for flexibility and opportunities for fine-tuning of pharmacy education toward specific national needs. At the same time, pharmacy educators are aware of the forces of change and transformations taking place in pharmacy practice, which inevitably have to be taken into consideration in the shaping of a contemporary pharmacy education program. EAFP has an advocacy role to liaise with stakeholders from the hospital, community, industrial, and international partners in pharmacy education. EAFP provides a network among educators and stakeholders to reflect on the needs and expectations of society from pharmacy schools. There are a number of dilemmas that are faced when navigating shifts in pharmacy programs to reflect a move toward patient-centered course content. It is painful to identify course content that is no longer relevant. It takes hard work, diplomacy, and leadership to support academic staff to reorient their discipline to embrace a patient-centered approach while maintaining the characteristics of a science-based approach. During the 2017 EAFP Annual Conference in Helsinki, a stakeholders' roundtable discussion was organized to identify consensus areas of needs that pharmacy educators should address. The four areas identified were: (1) maintaining a science-practice curriculum, (2) adopting teaching methods that maintain student involvement, (3) supporting students to become team members, and (4) sowing the seed of curiosity to instill the quest for lifelong learning. Transcribing intelligently fundamental sciences into medical sciences remains a challenge facing tomorrow's evolvement of pharmacy education to satisfy the needs of pharmacy practice integrating clinical pharmacy and pharmaceutical care.

Postgraduate education acts as a catalyst of change by supporting pharmacists in career development and providing them with leadership skills. Innovative perspectives nurture pioneering teams that will steer advanced pharmacy practice models to meet the transformations necessary to navigate the forces of change. There are a number of specialized Masters programs offered by faculties of pharmacy, which present opportunities for further education to pharmacists. Specialized Masters, which are relevant to pharmacy practice are offered in areas of clinical pharmacy, community pharmacy, hospital pharmacy, pharmacovigilance, and pharmacoeconomics. Programs, which incorporate aspects of experiential reflections are valuable in empowering the graduates with a practice analytical skill that makes them proactive toward enlightening and remodeling pharmacy practice.

There are countries in Europe where a specialization in hospital pharmacy is required to be followed before pharmacists are engaged as hospital pharmacists. The programs for the specialization vary in duration (2–4 years postgraduate) and in content (administrative vs. technical and clinical). Many programs focus on the administrative processes linked to hospital pharmacy. The European Association of Hospital Pharmacy is working on a project to achieve a common framework for hospital specialization so as to ensure recognition of the specialization between countries signatories to the common framework.

The emerging trends of a patient-centered education at the undergraduate level and the increased needs for patient focus in the pharmacy practice settings are a force to entice pharmacy educators to take the lead and guide the profession to move towards homogenized skills for patient-centered pharmacy practice. The increasing clinical pharmacy services required to provide the professional services, which are unique for the community pharmacist and the distinctive contribution of pharmacists to pharmacovigilance, indicate that clinical pharmacy aspects are not exceptional to hospital pharmacy settings. The situations where patients are discharged from hospital to community care earlier compared to previous years and patients in the community are using complex medication, such as self-administering biological agents for the management of rheumatoid arthritis, inferr an aspect of shared care between the hospital and community pharmacy practice scenarios. The developments of professional doctorates in pharmacy, which focus on a patient-centered approach, are a means of providing level 8 doctoral study for pharmacists. Professional doctorate programs are postgraduate courses, which rely on three pillars (1) enriching the graduate with advanced clinical skills; (2) providing the opportunity to develop reflective and analytical skills through experiential learning at pharmacy practice rotations in areas of hospital pharmacy, community pharmacy, and pharmacovigilance; and (3) undertaking advanced pharmacy practice research. A doctorate in pharmacy program, which encompasses practice and a research component was launched in 2014 leading to a Doctorate in Pharmacy degree is offered by the Department of Pharmacy at the University of Malta in collaboration with the College of Pharmacy of the University of Illinois at Chicago, United States. Pharmacists following the program experience the perspectives of health-systems and the implementation of clinical services for European and US models. The program has an international audience and currently pharmacists from 16 countries have embarked on the course. This strengthens the dynamics of learning where students share their pharmacy practice experience from different countries. Graduates from this program are taking the lead to pioneer innovation in pharmacy practice services when they return to the home countries.

Pharmacy Practice Research: Pioneering the Transformations

The European Society of Clinical Pharmacy (ESCP) was founded in 1979 with the intention of supporting quality and innovation in clinical pharmacy. During ESCP conferences, scenario analysis workshops are organized to identify driving forces of change for clinical pharmacy and the profile for the pharmacist as a "care manager" was described (Leufkens et al., 1997). Experimentation to create a profile, which provides an additive contribution to positive patient care outcomes and not a meager mirror of a physician or the nurse, is essential. A care manager profile for the pharmacy practice professional prepares a pathway for acceptability of such a role by the pharmacy profession and other players (health care professionals, administrators, patients), and for engaging economic support. The care profile is not a static status which, once achieved, the profession can rejoice and sit on its laurels, as it needs a continuously dynamically changing status. The profession requires drivers to ensure that the quest to establish an advanced practitioner profile fits the upcoming requirements of society. Pharmacy practice research is a resourceful tool to ensure sustainability. Research is pivotal to testing, refining, and implementing innovative pharmaceutical service developments. Audit and quality system checks, incorporated within a practice research, complement to the advancement of pharmacy practice models. The next step forward in pharmacy practice research is the direct application to practice of the outcomes and deliverables of scientific-driven studies.

An innovative characteristic to the pharmacy course, introduced in the 1970s by the Department of Pharmacy of the University of Malta, is a pharmacy practice project, which pharmacy students undertake over a period of 3 years as part of their studies. The project is developed as a study unit within the course and is intended to provide development of skills in pharmacy practice research and at the same time students are encouraged to immerse in projects that lead innovation of pharmacy practice interventions. This experience in introducing pharmacy research at the undergraduate level has now been introduced by a number of pharmacy schools in Europe.

Managing the Forces of Change

Pharmacy practice has evolved rapidly in the past 50 years when compared to the practice during the last thousand years. New advanced therapies, such as the biologicals combined with fast developments in information technology, which led to restructuring of data

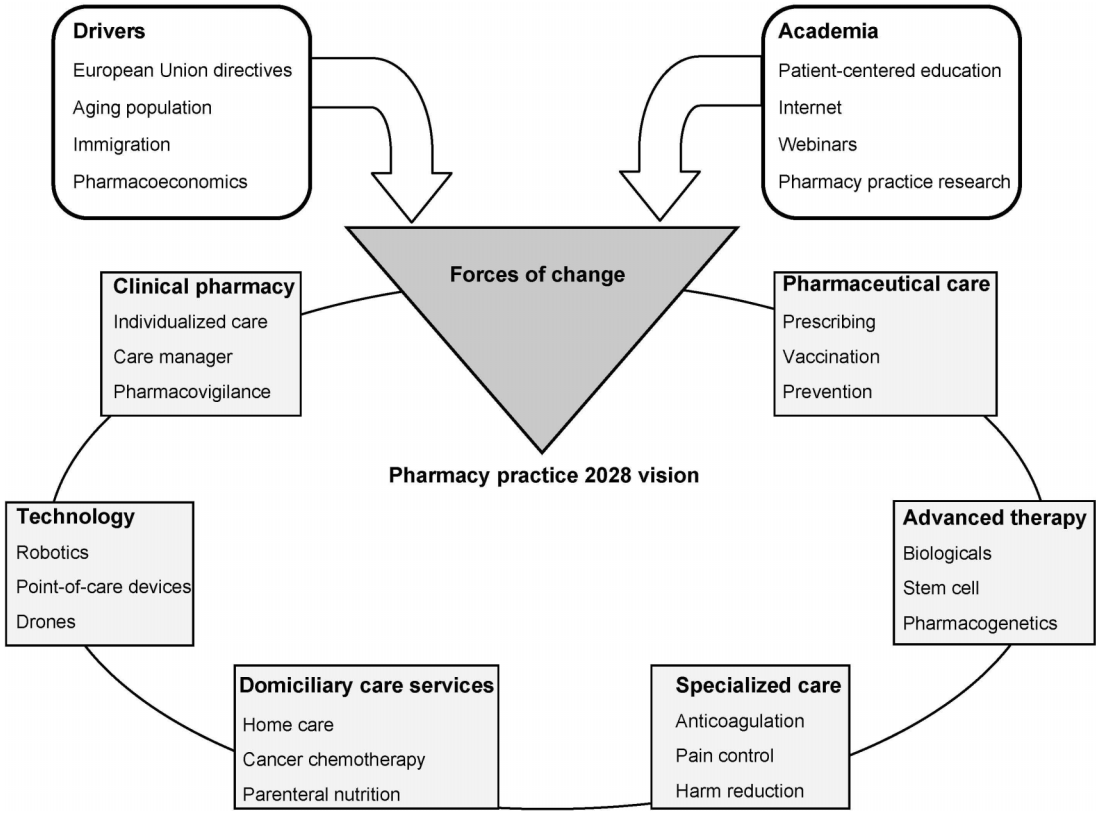

Fig. 1 Pharmacy practice 2028 vision.

storage and retrieval, drug information systems, and big data influence significantly decision-making. The political changes in Europe, led to dropping of barriers between countries, had their effect on health care and consequently on pharmacy practice especially with regards to accessibility to medicines. Political considerations influenced the harmonization of regulatory sciences, which in Europe led to the establishment of the European Medicines Agency. The European Medicines Agency served as a significant force resulting in advancements in pharmacy practice. Reimbursement schedules, the aging of the population, cultural, and social influences, such as immigration, and, not least, the accomplishments of many pharmacists will have an impact on the profession in the next years.

Fast-forward to 2028, forces of changes that can be predicted include metamorphosing concepts of clinical pharmacy and pharmaceutical care, technology, domiciliary services, specialized care, and advanced therapies (Fig. 1). The concept of clinical pharmacy is moving to individualized care where pharmacists need to intervene, as the care manager, to holistically manage a patient. Pharmaceutical care services are expanding beyond traditional aspects to include vaccination, prescribing, patient empowerment, and disease prevention. Pharmacy practice will need to catch up with technology where robotics are incorporated in service developments changing the landscape of the operations of pharmacy practice models, point-of-care devices for biological parameters monitoring are expanding and relying on information technology for real-time data transfer, and drones may be the upcoming tool to be considered in health system delivery. The need for domiciliary services to cater for patients receiving drugs that were previously looked at as hospital items, such as parenteral nutrition, cancer pharmacotherapy, palliative therapy, and medical oxygen therapy, is on the increase. With the expansion of drug therapy, patient management is truly becoming highly specialized for diabetes, anticoagulation, harm reduction, drug misuse, and pain control to name a few examples. The introduction of advanced therapies, such as biologicals, stem cells, and the application of pharmacogenetics to guide therapy form an element of the forces of change in pharmacy practice.

Multiple factors which range from geopolitical forces in the European Union, including the much needed revisiting of directives related to health that are aligned with contemporary scenarios, social factors, such as an aging population, delay in parenthood, smaller families, immigration, and financial factors including pharmacoeconomic aspects are driving forces of change. Academia, through education and research, is a fundamental structure that needs to be on the lookout to support the profession to steer through the forces of change and recognize the contemporary drivers. Patient-centered orientation in pharmacy and striking the optimum balance between the science and practice skills are the challenges academia is handling. Taking up the opportunities presented by technology to alter classic methods of teaching to incorporate distance learning, online learning, hybrid models, and webinars gets academia closer to today's students and pharmacists who are open to further academic opportunities. Liaising with pharmacy practice sites to support pharmacy practice research provides the impetus for the profession to test the waters into new models of pharmacy practice for the vision 2028.

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Relevant Websites

European Association of Faculties of Pharmacy (www.eafponline.eu)
European Association of Hospital Pharmacists (www.eahp.eu)
European Medicines Agency (www.ema.europa.eu)
European Society of Clinical Pharmacy (www.escpweb.org)
International Pharmaceutical Federation (www.fip.org)
Pharmaceutical Care Network Europe (www.pcne.org)
Pharmaceutical Group of the European Union (www.pgeu.eu)
University of Malta, Department of Pharmacy (www.um.edu.mt/ms/pharmacy)

Pharmacy Practice in Australia and New Zealand

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History of Pharmacy Practice in Australia and New Zealand

Australia: The development of pharmacy practice in Australia followed the English tradition from the time of the First Fleet (Hattingh et al., 2013). There was no recognized role for pharmacists, and they competed with doctors, grocers, and retailers for professional recognition. The first pharmacist of Australia was John Tawell who started his chemist shop business in 1820 (Hattingh et al., 2013). A medical board certified him to work as an apothecary and to compound and dispense medicines (Hattingh et al., 2013). The pharmacy practice was casual and did not require qualifications, and activity was unregulated. It was not until the late 19th century that the first major legislative controls to regulate pharmacy practice were introduced (Hattingh et al., 2013). In 1901, the six colonies or states of Australia had a licensing system for selling poison, and groups of druggists and chemists established an organized pharmaceutical society colonially to protect the public from untrained quacks (Hattingh et al., 2013; PSA, 2017b). These colonial societies were modeled on the Royal Pharmaceutical Society (Pharmaceutical Society of Great Britain) and exerted a powerful force on the establishment of pharmacies and pharmacy practice in Australia. These societies developed the first written standards in pharmacy education, ethics, and qualifications, and influenced the development of pharmacy legislation in each state. It is assumed that they also maintained the first pharmacy schools in Australia. Through pharmacy registering authorities, state and territory legislation regulated the profession all over Australia until the pharmacy board was established. This authority was also responsible for registering pharmacists in each jurisdiction, until later when national registration was implemented under a Pharmacy Board of Australia (PBA) (Hattingh et al., 2013). The Pharmacy Act 1956 also introduced restrictions on titles to own pharmacies and rights to practice as a pharmacist. The enforcement of the legislation was later assigned to the pharmacy boards.

A significant contribution in developing pharmacy practice in Australia was made by three-core professional organization, namely, the Pharmaceutical Society of Australia (PSA), the Society of Hospital Pharmacists of Australia (SHPA), and the Pharmacy Guild of Australia (PGA). PSA is the national professional pharmacy organization representing Australia's pharmacists working in all sectors and across all locations. Their main aim is to improve pharmacy practice via an extensive program of education and professional development activities across Australia (PSA, 2017a). SHPA is the national professional organization representing pharmacists, interns, students, and technicians practicing in public and private hospitals and other health services in Australia. PGA is a national employers' organization that represents and promotes the value of the role of community pharmacy in Australian health care system (The Pharmacy Guild of Australia, 2017).

New Zealand: Pharmacy practice in New Zealand was also significantly influenced by the British model. Alexander Eccles was the first pharmacist in New Zealand, who opened the pharmacies in Napier and Hastings (Otago, 2013). The New Zealand Pharmacy Act (1880) introduced the registration of pharmacists, which was superseded by the Pharmacy Act (1939) (Mclintock, 1966). The Pharmacy Act (1939) gave power to the Board of Pharmaceutical Society of New Zealand to oversee regulation and advertising of medicines, and prohibited pharmacist from specified methods of selling drugs. To practice as a pharmacist, membership of the society was compulsory (Analyst, 1940).

The Pharmacy Board of New Zealand is composed of registered pharmacists acting as proprietors, pharmacists (members) of pharmaceutical society, and a barrister assigned by the Ministry of Health. The pharmacy board controls the training, registration, disciplining, and examinations of pharmacists, and appoints a board of examiners and a disciplinary committee. A board of examiners consists of six members where three are nominated by pharmacy board, two by the approved schools, and one by the

Ministry of Education. All pharmacies must be under the provision of the Pharmacy Act (1970), the Poison Act (1960), and the Dangerous Drugs Act (1927). Pharmacists are restricted for retail sale of a huge number of drugs and poisons. The Pharmaceutical Society of New Zealand is a professional, membership-based association representing pharmacists and technicians in New Zealand. They provide training, education, ethics, and status of pharmacists for continuing the professional development (Benrimoj and Frommer, 2004). The Pharmacy Council of New Zealand (PCNZ) was established under Health Practitioners Competence Assurance Act 2003 (HPCAA), which is responsible for the registration of pharmacist and promotion of good pharmacy practice (Pharmacy Council of New Zealand, 2017). In addition to the legal issues that need to be considered when making decisions about patient's clinical management and care, pharmacy practice also involves wide range of decisions about professional and business responsibilities and obligations. The existing legislations and acts ensure that the specified standards of pharmacy practice are met.

Health Care System and Funding

A good health system is one that delivers quality services to all people, when and where they need them (Health Systems, 2017). Health systems in Australia and New Zealand aim to offer universal coverage and publicly funded access to essential health services. Australia and New Zealand have implemented national medicine policies that aim to provide equitable access to cost-effective and safe medicines. Australia's National Medicines Policy is a well-established endorsed framework that aims to improve positive health outcomes for all Australians, focusing mainly on easy access and wise use of medicines (Policy, 2017). "Medicines New Zealand," New Zealand's medicines policy, was launched in 2007 with the aim to promote quality, effective, and optimal use of medicines (Francis, 2014). Although each country has adopted a different approach, both are globally recognized for their execution of national medicines policies (Babar and Vitry, 2014).

Australia: The health care system of Australia is a multifaceted web of both public and private health service providers, participants, settings, and supporting mechanisms (Benrimoj and Frommer, 2004). The responsibility for health care is shared between Australia's Federal, State and Territory, and local governments. Each has roles in funding, policy developments, regulation, and timely delivery of health care service. Some responsibility of funding and regulating the health system between the commonwealth and the state and territory governments are as follows (Biggs, 2013).

Commonwealth government is mostly responsible for

- Medicare, the national scheme, which provides free or subsidized access to clinically relevant medical, diagnostic, and allied health services;
- Pharmaceutical Benefits Scheme (PBS), which subsidizes universal access to thousands of prescription medicines;
- purchasing of vaccines for the national immunization program;
- medical research grants;
- subsidizing for aged care services, such as residential care;
- health professionals education; and
- therapeutic goods and medical devices regulation.

States and territories are mainly responsible for

- management and administration of public hospitals;
- preventive services delivery such as immunization programs, cancer screening;
- ambulance and emergency services;
- community and mental health services funding and management; and
- public dental clinics.

Health care services are provided by a variety of public and private organizations and health care professionals who can be employed by either or both sectors. Examples of services include public health and preventive services in the community, primary health care, emergency health services, hospital-based treatment in public and private hospitals, and rehabilitation and palliative care. Public sector health services are operated by all levels of government, which include public hospitals, visits to outpatient clinics, and general practitioners (GPs). Private sector health service providers comprise private hospitals, community pharmacies, medical practices, and a mix of public and private services (Benrimoj and Frommer, 2004; Remuneration and Regulation of Community Pharmacy, 2016). Private health insurance and out-of-pocket payments by patients mostly fund the activity of private hospitals, which is successively subsidized by the government of Australia by 30% reductions on member contributions to private health insurance (Pharmacy Guild of Australia, 2010). Local governments deliver community-based health and home care services. They also facilitate public health and health promotional programs such as nutrition awareness and weight loss programs, immunization services, and smoking cessation.

In 2015–16, health expenditure in Australia accounted for 10.3% of gross domestic product (GDP) (Australian Institute of Health and Welfare, 2017). Health care expenditures are funded through taxes, a Medicare levy, and private health insurance financing. Australia introduced Medicare in 1984, which is a universal public health insurance scheme funded by the Australian Government, with copayments by users when services are not "bulk-billed." Bulk billing is a payment option under the Medicare system where a GP bills Medicare directly for the services provided to patients, so patients have no out-of-pocket expenses. Medicare provides free treatment to Australians, permanent residents, and some overseas visitors in public hospitals, subsidization of wide

range of prescription medicines costs under PBS, and payments for professional health services itemized in the Medicare Benefits Schedule (MBS). Medicare mostly covers subsidized or free treatment by medical practitioners, optometrists and also dentists in specific circumstances, and allied health professionals. Private health insurance covers fully or partly the cost of health care as a private patient. It is available as hospital cover or ancillary or extras cover (general treatment cover). Hospital cover helps the cost of some or all in-hospital treatment including hospital accommodation and fees of a doctor as a private patient. General treatment cover pays the cost of nonmedical health services such as dental treatment, optometry, chiropractic ambulance, and physiotherapy (Moles and Stehlik, 2015; Public and Private Healthcare, 2016). Similarly, private health hospital cover insures patients against some or all of the additional costs of being a private patient in either a public or private hospital. Medicare will cover 75% of the MBS fee for associated medical costs (Private Health Insurance Ombudsman, 2015).

The key components of Australia's health system related to medicines are the PBS Schedule and Repatriation Schedule of Pharmaceutical Benefits Scheme (RPBS). These aim to facilitate timely, affordable, and reliable access to wide range of life-saving pharmaceuticals with government subsidized price. The Australian Government negotiates medicine price with the supplier to subsidize medicines that are necessary to maintain the health of the community. This is achieved by carefully assessing the therapeutic benefits and costs of medicines, including comparisons with other treatments where appropriate. PBS and RPBS are an integral part of Australian Government's broader National Medicines Policy that aims to deliver medication and other necessary services to achieve optimal health outcomes (Hattingh et al., 2013; The Pharmaceutical Benefits Scheme, 2016). Both PBS and RPBS are governed by Medicare Australia. Eligible people to receive this fund for health must be a citizen of Australia, or those who hold permanent resident visa, or those with verified relationship with Australian citizen such as on spousal visas, as well as certain foreign visitors covered by reciprocal health care agreement (Hattingh et al., 2013; Moles and Stehlik, 2015). The PBS was started in 1948 that includes "life saving and disease preventing medicines" available free of charge for Australian community (Moles and Stehlik, 2015; The Pharmaceutical Benefits Scheme, 2016). It is regulated by the National Health Regulations, governed under the National Health Act 1953 (Commonwealth). The pharmaceutical manufacturer makes an application for a PBS listing, which is assessed by Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC examines the efficacy, safety, and cost-effectiveness of the proposed listing. They also make recommendation of medicines to the Federal Minister for Health about its availability as pharmaceutical benefits, maximum quantity, number of repeats available for each item, and recommend restrictions in some cases. To perform its function, PBAC has two subcommittees: Economics Subcommittee and the Drugs Utilization Subcommittee. The former committee advises on cost-effective policies and evaluations of cost-effective aspects of major submissions, and the latter committee monitors the patterns and trends of medicines used within the PBS. To improve transparency of the PBS listing process, "public summary documents" are published to make aware and inform the stakeholders about the rationale of specific recommendations and enhance the understanding of overall listing process (Hattingh et al., 2013). The RPBS established in 1919 is subsidized by the Department of Veterans' Affairs (DVA), under the Veterans Entitlements Act 1986, which provides pharmaceutical benefits to veterans having DVA card and to the eligible dependents (Hattingh et al., 2013; The Pharmaceutical Benefits Scheme, 2016).

For Australia's Aboriginal and Torres Strait Islander people with existing, or at risk of having chronic diseases, the closing the gap (CTG) PBS copayment program was established to reduce the cost for PBS medicines. If a prescriber believes that patient did not take prescribed medicines and experienced setbacks in the management of chronic disease or are unlikely to adhere to medicines regimen without support through the program, then they endorse prescription with CTG to allow the pharmacist that dispensing of the prescription should be done with copayment relief. CTG prescription for medicines listed on the PBS schedule draws a lower or nil patient copayment, that is, general patients with CTG prescription will pay the present concessional rate for every PBS medicine and concessional patients with CTG prescription will not be charged the patient copayment for any PBS item (Moles and Stehlik, 2015).

New Zealand: The New Zealand health care system includes a complex network of organizations and people. The health care system is funded primarily by the central government through the Ministry of Health. New Zealand has universal health coverage system which is publicly funded predominantly and services are provided via public, private, and nongovernmental sectors (Health Systems in Transition, 2014). There are 20 District Health Boards (DHBs) responsible for planning, funding, and delivering most publicly funded health services in their districts. DHBs arrange funding for primary care, hospital services, public health services, aged care services, and services provided by other nongovernment health providers. Public hospitals are owned and funded by DHBs, and the hospital care is provided free of charge to patients. Private hospitals offer elective services on contract to DHBs and on a private basis. Since 2002, primary health organizations (PHOs), a local structure designed to establish networks of GPs and other primary health providers, started providing primary health care services. The 36 PHOs deliver comprehensive primary health care in the community where children below 6 years of age pay no fees (Health Systems in Transition, 2014). PHO is funded on the basis of their enrolled population where most patients pay additional fees for service. However, significant additional government funding has later reduced the fees for most patients and has increased the consultation rates.

Uses of pharmaceuticals in New Zealand are governed by the New Zealand Medicines and Medical Device Safety Authority (Medsafe) and the Pharmaceutical Management Agency (PHARMAC). Medsafe administers the Medicines Act and Regulations ensuring that medicines used in New Zealand are safe and effective. PHARMAC on the other hand decides subsidy levels on medications approved by Medsafe. PHARMAC is responsible for managing the New Zealand Pharmaceutical Schedule and negotiates the purchase of drugs from suppliers, successfully controlling supply-side expenditure (Health Systems in Transition, 2014).

The Pharmaceutical Schedule includes a list of subsidized medicines, appliances, and other relevant products that can be prescribed by general practitioners, nurses, dentists, and midwives. Although patients have to make small copayments, concession procedures ensure that they are affordable. Copayments for most prescriptions is NZ$5 per item. PHARMAC is the only procurer of publicly subsidized medicines, and is successful in negotiating costs and controlling supply-side expenditure. It decides which medicines to fund, sets subsidy levels and conditions, and ensures that expenditures are within the allocated budget (Health Systems in Transition, 2014).

New Zealand has slightly higher health expenditures as a percentage of GDP than the Organization for Economic Cooperation and Development (OECD) average. Health expenditure as a percentage of GDP rose from 6.8% in 1990 to 10.1% in 2010 to 11% in 2014 (Health Systems in Transition, 2014). Health expenditures are funded through taxes, private health insurance financing, and by those receiving the services (direct payment). In addition to the funding from Ministry of Health and DHBs, Accident Compensation Corporation (ACC) is the other major public funder that provides comprehensive, no-fault personal injury cover for all New Zealand residents and visitors injured in New Zealand (Statistics New Zealand, 2010). They are funded through employer, employee, and car-licensing levies. They also provided funding for hospitals that has incurred accident-related care costs and pays care-related expenses to private health insurances or providers for approved treatment. This scheme has been highly successful in New Zealand (Health Systems in Transition, 2014).

The health care landscape around the world is changing and facing similar challenges to those seen in Australia and New Zealand such as the ageing population, the increasing prevalence of chronic diseases, increasing cost of medicines, new technologies and products, and the rising costs for human resources and other workforce issues (Pharmacy Guild of Australia, 2010). Future affordability of services and equitable health care is a challenge. The traditional approaches and models of health care service delivery require transformation. Some countries have recognized that the prominent ways to tackle this problem is to start with cost-effective implementation of primary health care. One approach would be to involve pharmacist to deliver public health interventions as pharmacists have been identified as having an increasingly important role in the primary care team (Duckett and Breadon, 2013; Page and Somers, 2015; Pharmacy Action Plan, 2016).

Practice Standards and Guidelines

Professional practice standards (PPS) and guidelines related to pharmacy practice provide the framework to maintain and improve the quality of pharmaceutical services, forming an essential aspect in regulating the profession (Hattingh et al., 2013).

Australia: In Australia, practice standard and guidelines are developed by major pharmacy organizations such as the PSA, the SHPA, and the PGA. The PSA's Code of Ethics and PPS articulate the expected standards of professional behavior of pharmacists in Australia. A number of practice guidelines are also developed by the PBA. PBA endorses the PPS. Pharmacists are advised to ensure that, in addition to complying with the code of conduct for registered health practitioners, they be guided by the code(s) of ethics relevant to their practice (Pharmacy Board of Australia, 2014). The PPS lies within a broader hierarchy of guidance underpinning and supporting the practice of pharmacists as shown in **Fig. 1**. Commonwealth, State and Territory Legislation forms the foundation on

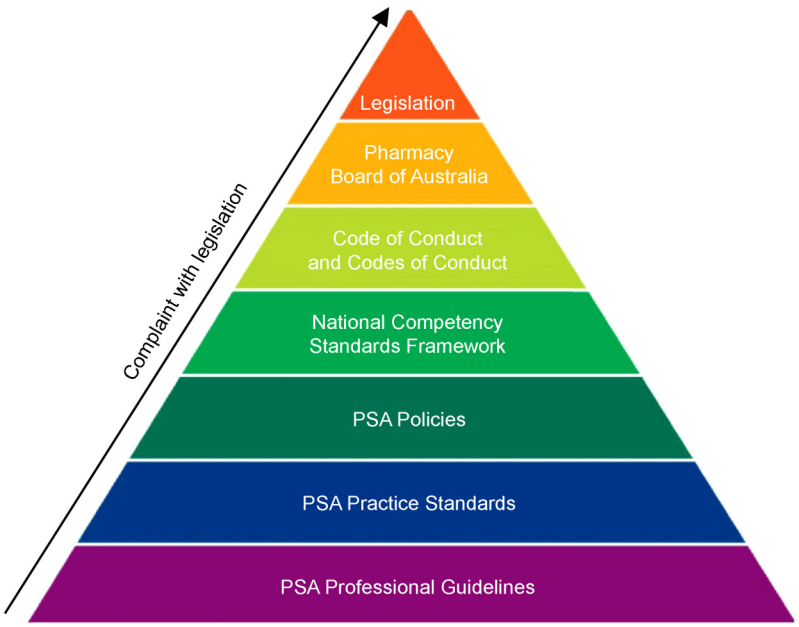

Fig. 1 Hierarchy of guidance and regulation of pharmacy practice in Australia.

which pharmacy practice is based. It is portrayed at the top of the pyramid (Fig. 1) depicting the various hierarchies of guidance and regulation. PPS reinforces the professional practice of all pharmacists in Australia, regardless of the role, scope, level, or location of practice. It encompasses both professional services such as dispensing and counseling, and selected specialty standards such as specialized medicine information services (Hattingh et al., 2013).

Practice in accordance with the PPS must not be interpreted as permitting a breach of the law, or discouraging compliance with legal requirements. At all times, the pharmacist must comply with legal obligations. The PBA is the registering authority of pharmacists in Australia. The board develops standards, codes, and guidelines for the pharmacy profession and also involves in approving accreditation standards and accredited courses of study. These guidelines and standards articulate the values of the pharmacy profession and expected standards of ethical behavior of pharmacists toward individuals and community (PSA, 2017a). The competency standards describe the skills, attitudes, and other attributes (including values and beliefs) attained by an individual based on knowledge and experience that enable the individual to practice effectively as a pharmacist (PSA, 2016). Professional practice and quality standards ensure that professional services deliver optimal health outcomes. Finally, practice guidelines support pharmacists and their staff in the implementation of quality professional services. These guidance and framework support pharmacists to practice professionally and ethically so that expected standards are met, and health and well-being of patients are improved. A collaborative forum to progress tasks and initiatives associated with the national competency standards for pharmacists was established in 2011 known as Advanced Pharmacy Practice Framework Steering Committee. This later in 2014 transitioned into the Pharmacy Practitioner Development Committee (PPDC) which focuses on the development of pharmacist practitioners through consideration of competencies and scopes of practice (Advanced Pharmacy Practice, 2017). PPDC mainly focuses on issues around pharmacist prescribing, implementation of an advanced pharmacy practice recognition model, strategies relating to competencies, and scopes of practice in the context of overall pharmacist practitioner development.

New Zealand: In New Zealand, regulation of the pharmacy profession is achieved through the Health Practitioners Competence Assurance Act 2003 (HPCAA) which dictates that clinical, cultural, and ethical competencies must be integrated into the learning objectives of pharmacy programs. The Pharmaceutical Society of New Zealand (PSNZ), PCNZ, and NZ Hospital Pharmacist' Association (NZHPA) develop and implement PPS and guidelines for pharmacists. The PCNZ is established under the HPCCA with a duty to protect the public and promote good professional practice by pharmacists. It achieves this through a range of roles including review and promotion of the competence of pharmacists, prescribing the qualifications required for scopes of practice within the profession, and accrediting and monitoring educational institutions and the programs of study they provide (Australian Pharmacy Council, 2012). The Health and Disability Services—Pharmacy Services Standard is the basis for relating good practice and promoting constant advancement in the quality of pharmacy services (New Zealand Standard, 2010). The Pharmacy Services Standard aims to provide safe and appropriate services which complies with the legislation, timely services which are planned and delivered in an appropriate manner, and clean and safe environment to provide service to the consumers. This standard defines the quality and safety requirements for the provision of community and hospital-based pharmacy services and clinical pharmacy services not provided from a pharmacy.

Pharmacists around the world are facing new challenges related to an increasingly complex health care system and their roles are changing significantly. Therefore, it is important that pharmacists follow defined practice standards and guidelines to protect themselves against potential litigation, and to respond to the specific needs of individuals and the community (Hattingh et al., 2013). Pharmacy practice standards and guidelines, therefore, aim to achieve consistency in service delivery and maintain continuous quality improvements so that the risks of misadventures are minimized.

Pharmacy Education

Formerly, pharmacist training in Australia and New Zealand was based on an internship system. From early 1960s, this has continuously advanced into a high standard university program producing qualified pharmacists with advanced clinical skills (Hattingh et al., 2013; Marriott et al., 2008; Otago, 2013). Individuals are eligible for registration as pharmacist when they complete their program of study accredited by the Australian Pharmacy Council (APC) and approved by the PBA or the PCNZ and registered on the Board or Council's website (Australian Pharmacy Council, 2012). Accredited programs are offered either as an undergraduate degree or postgraduate entry with bachelor's degree being the minimum requirements for registration.

Australia: The duration of pharmacy program that is eligible for accreditation should be consistent with the "volume of learning" descriptor of the Australian Qualifications Framework (Australian Pharmacy Council, 2012). University program of study exposes students to real pharmacy practice through placement programs, thus enabling them to provide patient-focused services (Hattingh et al., 2013). These placements form a significant element of several pharmacy programs and are obligatory requirement for accreditation of the program by the APC (Hattingh et al., 2013). Currently, the APC is the designated independent accreditation agency for Australian pharmacy under the National Registration and Accreditation Scheme (Hattingh et al., 2013). Graduates after completing their qualification from an approved Masters or Bachelors programs are required to complete a 12-month internship to get registration with PBA or PCNZ (Australian Pharmacy Council, 2012; Hattingh et al., 2013). This internship contains supervised practice, with an approved preceptor, continuous assessment, and participating in education program proposed by an Intern Training Program (ITP) provider approved by the APC (Australian Pharmacy Council, 2012; Hattingh et al., 2013). The ITP providers include some universities, the Pharmacy Guild of Australia/New Zealand, and the Pharmaceutical Society of Australia/New Zealand. The final requirement of all intern pharmacists to achieve a registration as a pharmacist is to undertake examinations

that are designed to test their level of competency (Australian Pharmacy Council, 2012). In December 2016, there were total of 30,368 registered pharmacists in Australia, which comprises 27,452 as general registration, 1777 as provisional registration, 1132 as nonpracticing registration, and 7 as limited registration (Pharmacy Board of Australia, 2017). A 2016–20 Action Plan of New Zealand Ministry of Health reported that there are about 3500 registered pharmacist across New Zealand (Pharmacy Action Plan, 2016).

In Australia, pharmacy education has experienced major structural changes over the past decade because of the substantial increase in the number of pharmacy schools and the number of pharmacists entering the workforce (Marriott et al., 2008). In 1997, there were 6 universities offering 6 undergraduate degrees, and in 2015 there are 18 universities offering 24 pharmacy degrees (Marriott et al., 2008; Pauline et al., 2004). The increasing number of pharmacy schools may be due to the large shortfall in the pharmacy workforce to meet the demand particularly in the regional and rural areas all over Australia (Marriott et al., 2008). None of the pharmacy school offers doctor of pharmacy (PharmD) degree in Australia; however, in addition to the research degrees like research masters or PhD degrees, many universities offer a range of postgraduate programs such as doctor of clinical pharmacy, master of clinical pharmacy, graduate diploma, or graduate certificate (Marriott et al., 2008). Majority of students directly enter into the pharmacy program from secondary school where their results from the previous study are the key selection criterion (Marriott et al., 2008; Pauline et al., 2004). The selection criteria may vary in different Australian school of pharmacy. Large number of students enter the undergraduate program following their secondary school final examination, but other modes of admission include transfer from another degree or completion of fast track course depending on the specific requirements of the universities (Marriott et al., 2008; Pauline et al., 2004). There are significant number of international students throughout the Australian school of pharmacy who are admitted following their completion of secondary education from their country of origin (Marriott et al., 2008; Pauline et al., 2004).

New Zealand: In New Zealand, there are two schools of pharmacy, the University of Otago and the University of Auckland (Pauline et al., 2004). The School of Pharmacy at the University of Otago celebrated its 50th jubilee in 2013, a milestone representing 50 years of pharmacy education (Otago, 2013). Initially, pharmacy was located in the Department of Pharmacology and Pharmacy within the Faculty of Medicine (Otago, 2013). In 1970, pharmacy became an independent department after moving into the Faculty of Science. Admission into pharmacy at the University of Otago is competitive and is based on the student's grades obtained from their previous course (Pauline et al., 2004). Students from the Maori and Pacific communities are favorably selected due to their high health needs and shortages of pharmacists from these communities (Pauline et al., 2004). At the University of Auckland, the School of Pharmacy was established in the year 2000 and most students get entrance directly into the pharmacy after their completion of secondary school. The entry is limited and competitive, and is based on the academic merit and an interview. Both universities in the New Zealand offer the postgraduate programs to continue developing the knowledge and skills of pharmacy.

Community Pharmacy

The part of the health care system that people have the most regular contact and the easiest access are often the community pharmacies. Community pharmacies offer an accessible, safe, and efficient professional primary health care service nationwide (Pharmacy Guild of Australia, 2010). Community pharmacists are the health professionals most assessable to the public. As the first point of contact between the general public and the health care system, pharmacists provide early intervention, prevention, health promotion, and overall management of health. Conventionally, the main providers of medicines for the population of Australia have been pharmacists and pharmacies. In the community, pharmacy is increasingly becoming a vital source of comprehensive health care services. However, pharmacy in Australia and New Zealand are changing. Pharmacy practice in community settings not only covers medicines supply but also information and services delivery to support quality use of medicines. Although the main purpose of community pharmacy is still the supply of medicines, it has been extended to the provision of professional advice via involvement in the primary health care services in consultation with GPs and other health professionals (Pharmacy Guild of Australia, 2010).

Australia: In Australia, the National Health Act 1953 and the Australian Community Pharmacy Authority (ACPA), an independent statutory authority established under section 99J of the Act, regulate the community pharmacy practice. Regulation includes pharmacist registration, standard courses to become a pharmacist, and setting and ownership of pharmacies. There are more than 5300 pharmacies in Australia that are located throughout the remote, rural, metropolitan, and suburban region. Of all health care providers, community pharmacies are often the most frequently accessed; the average Australian visits a pharmacy 14 times a year; about 300 million individual patient visits each year (Community Pharmacy, 2014). Approximately 3.9 million Australians ask health-related advice with their pharmacist each year. Among these 79% reported that they were happy with the advice and that the advice met their needs fully (Australian Bureau of Statistics, 2009). Availability of a pharmacist to provide the service through a community pharmacy has helped achieve current government's objective to reduce the number of unnecessary visits to a GP and the subsequent costs involved (Community Pharmacy, 2014).

The Pharmacy Guild of Australia negotiates a funding agreement with the Commonwealth government every 5 years. The Guild is committed to supporting and maintain the community pharmacy model as the most appropriate and efficient system of delivering medicines, medication management, and related services to the Australian public (The Pharmacy Guild of Australia, 2017). The present agreement, the Sixth Community Pharmacy Agreement (6CPA) 2015–20, permits pharmacy to collect practice incentive payments in six major areas: (1) dose administration aids, (2) clinical interventions, (3) primary health care as well as screening, risk assessment, and some chronic condition follow-up, (4) working with at least two other nonpharmacist health care professional,

(5) community services support along with needle exchange and opioid substitution dispensing, and (6) staged supply of medications especially for benzodiazepines, analgesics, and antidepressants (Moles and Stehlik, 2015). The other services that are reimbursed through this agreement are MedsChecks, Home Medicines Reviews (HMR), and the Residential Medication Management Reviews (RMMR). The MedsChecks services emphasize on self-management and education that is conducted in pharmacy. It is an in-pharmacy, consumer-centered service that aims to improve quality use of medicines by educating patients about the use of medicines, interactions involved, and any difficulties experienced with their medicines. On the other hand, HMRs are conducted often in stages and take much more time. HMR is a comprehensive clinical review of patient's medicines in their home by an accredited pharmacist on referral from the patient's GP. Nonaccredited pharmacist can still conduct the review however; they are not paid by MBS but by patients directly out of their own pocket. The pharmacist interviews the patient and records into a comprehensive report. This report contains findings and recommendations for consideration by doctors, patient, and other health care professionals (Moles and Stehlik, 2015). Similarly, a RMMR is a service provided to permanent resident of an Australian Government-funded aged care facility to assist consumers and their carers to better manage their medicines (Community Pharmacy Agreement, 2015).

New Zealand: In New Zealand, the Medicines Act 1981 regulates medicines, related products, and medical devices. The District Health Boards (DHB) manages health services such as the operating of hospitals, community pharmacies, and providing other community services. Service agreements have been made between DHBs and community pharmacies in different regions known as Community Pharmacy Service Agreements (Remuneration and Regulation of Community Pharmacy, 2016). Within these agreements, community pharmacies get remunerated for dispensing pharmaceuticals listed in the pharmaceutical management agency's (PHARMAC) New Zealand Pharmaceutical Schedule. Of more than 3500 practicing pharmacist in New Zealand, about 75% work in community pharmacies. There are around 1000 community pharmacies providing a range of services with over 1.3 million patients visit each year (Pharmacy Action Plan, 2016).

Cognitive pharmacy services delivered by community pharmacies in New Zealand include the adherence support service, that is, "Medicines Use Review" and the medication review service, that is, "Medicines Therapy Assessment" that are provided by accredited pharmacists (Campbell et al., 2017). These services unfortunately have difficulty gaining consistent funding by individual DHBs. Services such as "Community Pharmacy Anticoagulation Management Service" that provides safe reliable anticoagulant care with a consistently high level of anticoagulant control is funded only in few DHB areas. However, a newer model of service in community pharmacy, "Pharmacy Long-Term Conditions Service," that helps identify and register eligible patients to encourage better medicine adherence has better funding via a monthly fee per registered service user (Campbell et al., 2017).

Hospital Pharmacy

Pharmacists play an integral role in delivering health care services in hospital settings (Mak et al., 2012). Hospital clinical pharmacy services is a specialty field of pharmacy that has extended further from the traditional roles of compounding and dispensing medications, to more cognitive clinical aspects focusing more on patient-centered care. Throughout the medication-management process, hospital pharmacists assist in optimizing medication-related outcomes for patients (Ng and Harrison, 2010). Hospital pharmacists make up 18% and 13% of the pharmacist workforce in Australia and New Zealand, respectively (Pauline et al., 2004; Pharmacy Action Plan, 2016). Every year in Australia, about 10% of pharmacy graduates obtain intern training in a hospital sector, whereas others are employed in hospital pharmacy after they get registered (Moles and Stehlik, 2015). In contrast to other countries, Australia had no defined residency training program for pharmacists who desire to work in hospital setting until 2016 (Moles and Stehlik, 2015). Recently in 2017, SHPA initiated the first and only structured, formalized, supported, and accredited national pharmacy residency program in Australia.

With the changing needs and demands of modern health care, the practice of clinical pharmacy continues to evolve. Expansion of pharmacists' roles was facilitated by better understanding of drug-related morbidity and mortality which could be prevented by pharmaceutical services. Clinical pharmacy services are provided in all hospitals in New Zealand and Australia where a pharmacist routinely participates in both multidisciplinary and specialty ward rounds, with the explicit aim of reviewing and optimizing medications (Ng and Harrison, 2010; Pauline et al., 2004). A hospital pharmacy survey conducted in Australia reported that pharmacists will usually spend almost half of their time offering clinical services, providing training and education, and drug information (O'leary and Allinson, 2009). Similarly, in manufacturing, acquiring, and dispensing medicines, pharmacists spent 38% of their time and 15% time in medicines management and implementing hospital-wide activities like institutional drug policy management. Pharmacists who are involved in clinical services activities like reviewing prescription, recommendations of therapy (initiation, substitution or cessation of treatments, dose changes) have been reported to increase efficacy of treatment, symptom control, and reducing adverse reactions (Tan et al., 2014). With continuing input of pharmacists, a few hospitals have established electronic prescribing or medicines reconciliation systems (Pauline et al., 2004). During hospital ward visits and at discharge from hospitals, various types of clinical interventions are carried out by pharmacists that are documented for monitoring purposes and to detect recurring issues.

In large public hospitals, the majority of pharmacist work in multidisciplinary team and some specialize in a particular clinical department such as surgery, mental health, oncology, geriatrics, and pediatrics, whereas in smaller hospitals, one pharmacist may be involved in several departments (Moles and Stehlik, 2015; Pauline et al., 2004). Few newer roles for pharmacy graduates in hospital setting are in antimicrobial stewardship, medical admission pairing, emergency department, and surgical preadmission clinics. This

versatile role of hospital pharmacists is, however, underutilized to its full potential. There are reports arguing that although hospital pharmacist work in a team to improve care, patient information is not always transmitted to other sectors in a timely manner (Mak et al., 2012). In addition, unlike promoted in social media and advertised elsewhere that pharmacy services would be available 24 h a day and 7 days a week, most hospitals are providing the services only during routine business hours and an overnight on-call service (Moles and Stehlik, 2015).

The Way Forward: Expanded and Extended Role for Pharmacists

Traditionally, the pharmacist's role in health care was focused more on dispensing medications in accordance with a prescription. Their role has expanded over time to include more coordinated, cost-effective, and direct patient care such as medication management, medication reconciliation, continued supply of medicines, patient education and counseling, and preventive care. The evolving health care setting provides opportunity for pharmacists to become a part of a coordinated team that provides health care to their local community to better utilize scope of health professionals to increase accessibility to health care. The World Health Organization (WHO) and the International Pharmaceutical Federation (FIP) have recognized an expanded role for pharmacists for the purpose of improving patient care and drug therapy outcomes. A small number of expanded roles of pharmacists are explained in below sections as examples.

Integrating Pharmacy into the Broader Health Care Environment

Optimizing health professional's skills and knowledge into a robust integrated health care team will address the health care needs and ensures equitable health outcomes for all (An Integrated Health Care Framework for Pharmacists and Doctors, 2016). In many countries, the pharmacy profession has expanded considerably in professional service delivery and is recognized as an essential profession in the multidisciplinary provision of health care. Australia lags behind other comparable countries in terms of pharmacy integration across the health system, and in addressing the need for a more coordinated and collaborative approach to patient care (Remuneration and Regulation of Community Pharmacy, 2016). The uptake of models of care, such as e-health approaches, transitional care arrangements, and collaborative care models, that assists integration of pharmacists into wider health care environments is slow.

There are several reasons behind the slow integration of pharmacy into the broader health care environment in Australia. First, health policy development and implementation have occurred in isolation, both within and across jurisdictions. The PBS and community pharmacy have been treated separately from the MBS, and other areas of health policy, including hospitals, population health, private health insurance, e-health, and broader workforce. Second, instead of focusing on overall patient health outcomes, the remuneration and delivery of primary health care services were focused on individual health providers and practitioners. Third, efforts to enrich the access, effectiveness and harmonization via the health service delivery interventions were seen as threats rather than opportunities to deliver more cost-effective health outcomes. Fourth, digital health enablement in relation to the development of collaborative tools and take-up of eHealth has been slow (Remuneration and Regulation of Community Pharmacy, 2016) However, an integrated approach to health service delivery has been adopted recently by government and health care providers with greater focus on transitional care and referral pathways. Hence, in order for pharmacist to reach its full potential as health care providers, integration with the broader health care environment is very essential.

New Zealand, however, has recognized an enhanced role of pharmacists and has developed new models of integrated, person-centered practice known as Integrated Health Care Framework, where pharmacists and doctors could work together as part of the wider health care team. This framework also addresses existing collaboration and integration in current practice across New Zealand, and includes methods for enhancing these (An Integrated Health Care Framework for Pharmacists and Doctors, 2016). The framework highlights the significance of connecting the pharmacist with all members of a person's care team, including doctors, nurses, and the nonmedical prescribers. This framework also focuses on the clinical partnership between pharmacists and doctors for achieving an enhanced patient medication journey. The successful implementation of this strategy of pharmacist and doctors working together in a collaborative health care environment would support the current governments "One Team" Health Strategy of Ministry of Health, New Zealand. "One Team" is a better integrated and cohesive system that positions people and their families at the center of care so that health and disability workforce are utilized in most effective and flexible way (An Integrated Health Care Framework for Pharmacists and Doctors, 2016).

Pharmacists in General Practice (the Practice Pharmacist)

Integrating pharmacists into a general practice multidisciplinary team was explored in Australia which has gained professional commendation from pharmacy and medical organizations (The Pharmaceutical Society of Australia, 2008; The Society of Hospital Pharmacists of Australia, 2008). They define practice pharmacist as "a pharmacist who delivers professional services from or within a general practice medical center with a coordinated, collaborative and integrated approach with an overall goal to improve the quality use of medicines of the practice population" (Freeman et al., 2014). The concept of the practice pharmacist is supported by PSA, the Consumers Health Forum of Australia and United General Practice Australia. PSA provides members with a total package of continuous professional development trainings, practice support tools, and relevant external resources to support those who wish to explore the career pathway as General Practice Pharmacist.

The major role of a practice pharmacist would be to support GPs to minimize the risks associated with medicines and optimize patient outcomes through the quality use of medicines. This role has been broadly classified into three different levels: *patient level* that includes activities such as comprehensive medication review, medication reconciliation, therapeutic drug monitoring, and adverse drug reaction review; *clinician level* that included activities such as drug information, education, training for students, and registrars; *practice level* that includes activities such as clinical prescribing review and feedback, public health initiatives, pharmacovigilance, and medication recall (Famiyeh and McCarthy, 2017).

Integrating pharmacists into general practice enables pharmacists to work closely with GPs and their patients in delivering quality patient care. It would reduce fragmentation of care and medication misadventure by utilizing pharmacist's complementary skills and distinctive knowledge within the practice (Famiyeh and McCarthy, 2017). The general practice pharmacist can advise GPs on medication selection, conduct medication reviews, and provide prescribing advice to minimize harms associated with medications. Working collaboratively with pharmacist within the practice, GPs would be able to better care for patients and minimize the health care costs associated with adverse drug events and medication noncompliance.

Pharmacist Prescribing

Pharmacists are advancing their skills and knowledge in evidence-based practice and patient care. Traditional role of pharmacists has rapidly evolved which is enabling them to undertake further roles with a focus on patient care. Pharmacist prescribing is one of these expanded roles which is recognized in many countries and across several care settings such as community, clinics, and hospitals (Famiyeh and McCarthy, 2017). The primary aims of prescribing pharmacist is to optimize pharmacists' skills to safely increase patient access to health care services, and facilitate a team-based approach to care (Famiyeh and McCarthy, 2017). There are different pharmacist prescribing models across countries and between jurisdictions within a country. Pharmacist in Australia, New Zealand, the United States, Canada, and the United Kingdom undertake prescribing that ranges from shared prescribing with GPs in collaborative environment, to prescribing from selected formularies (Bourne et al., 2016). Studies from Australia report that a collaborative doctor–pharmacist prescribing model had a positive outlook and a high satisfaction level with pharmacist prescriber consultations (Hale et al., 2013, 2016). Similar to the Allied Health Prescribing Training program that aims to introduce models of care featuring allied health prescribing, a part of Queensland Health initiative is launched at the Queensland University of Technology that includes pharmacist prescribing across a range of areas. Prescribing rights to pharmacist in the United Kingdom, the United States, and Canada are broadly classified into two categories: independent prescribing and dependent prescribing. In independent prescribing, a pharmacist can clinically assess patient and diagnose the condition prior to prescribing, without any supervision by other health care professional. On the other hand, in dependent prescribing, the authority to prescribe is delegated to a pharmacist by an independent prescriber, usually a medical practitioner (Famiyeh and McCarthy, 2017).

In Australia, a number of health professionals have prescribing rights within their scope of practice. These include dentists, optometrists, podiatrists, nurse practitioners, and midwives. Pharmacists can only prescribe a limited range of medications listed under Schedules 2 (S2) and 3 (S3) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (Hoti et al., 2011a). S2: *Pharmacy medicines* and S3: *Pharmacist-only medicines* are sometimes called "over-the-counter" medicines. These medications are used for the management of minor illnesses and for conditions that can be easily recognized by the consumer and do not require medical diagnosis or management (Hoti et al., 2011b). It has been reported that with appropriate training and support, pharmacists are in a position to prescribe medications and deliver comparable outcomes to usual medical care prescribing by doctors in Australia (Weeks et al., 2014). Patients also had a high satisfaction level with pharmacist prescriber consultations and were willing to engage in a collaborative doctor–pharmacist prescribing models (Hale et al., 2016). Despite evidences supporting an expanded prescribing role for pharmacist (Hale et al., 2016; Hanes and Bajorek, 2005; Hoti et al., 2011b; Weeks et al., 2014), the uptake in Australia is lagging behind compared to those in the United Kingdom, the United States, Canada, and New Zealand.

In New Zealand, a regulation was passed in 2013 that allows pharmacist with appropriate postgraduate qualifications and clinical experience to register as pharmacist prescribers. A pharmacist prescriber is defined as "a pharmacist who is registered with the Pharmacy Council of New Zealand and who has completed the prescribed qualification for registration in the Pharmacist Prescriber Scope of Practice and who works in a collaborative health team environment" (Pharmacy Action Plan, 2016). Pharmacist prescribers are involved in managing patient's medications working collaboratively with primary diagnostician. They prescribe within the limits of their professional expertise and competence and following ethical codes of practice. Pharmacist prescribers, as part of the collaborative health team, provide individualized medicines management services to people across a range of primary and secondary health care settings (Pharmacy Action Plan, 2016).

Pharmacist Vaccinating

Community pharmacist possess the ability and skills to enhance the health care system of a nation by offering an expanded range of health services and assisting the government to achieve cost-effective use of the health budget (Community Pharmacy, 2014). The pharmacist-expanded service has been demonstrated by a successful pharmacist vaccination pilot in Queensland—Australia's first ever pharmacist vaccination project (Nissen et al., 2015). The pilot started with vaccinations for influenza which were later expanded to include pertussis and measles vaccinations because of overwhelmingly positive response and uptake of this service in community pharmacies. The pilot demonstrated that an appropriately trained pharmacist can deliver immunizations safely and effectively in the

community setting (Nissen et al., 2015). This also shows that pharmacists are in a position to deliver vaccination services for many other diseases that currently have suboptimal immunization rates. Also, since vaccination falls within the scope of pharmacist practice as defined by the PBA, universities might aim to train their undergraduates with this skill and provide a pharmacist vaccination workforce in the near future (Nissen et al., 2015).

Conclusions

Pharmacists as the medicines experts are slowly being better utilized and integrated into different practice settings. This is a slow, but positive start to having this unique set of knowledge and skills recognized, accepted, and used to its potential. Nevertheless, there are still many more areas and practice settings where the skills of pharmacists could be better leveraged, which would reduce the burden of disease on society to generate savings in health care spending, and improve quality of life and health outcomes for patients. Ultimately, extended and expanded pharmacy practice will improve patient access to required health care services in a timely manner.

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Pharmacy Practice in China

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China

China is a large, geographically and culturally diverse nation comprising approximately 20% of the world's population. With a rapidly developing economy, China is moving quickly towards meeting international standards for pharmacy; however, given the diversity of the country there are enormous variations in the meaning and practice of pharmacy. In China, pharmacists have

traditionally been trained for work in manufacturing, production, and research. Recently, however, there has been more interest in developing pharmacists for clinical and patient-focused roles than in the past. Pharmacy practice in the country is quickly evolving. Pharmacy practice in China must also be respectful of the long-standing use of traditional, complementary and alternative medicines and healing systems that are used throughout the country. As a result it is difficult to represent all facets of pharmacy in China within a single article; here, we provide you with the highlights of current and emerging trends in diverse sectors of the profession as a way of supporting greater understanding of the evolution of pharmacy in the country.

Pharmacy Education

Pharmacy Education in China

With continuous development of the Chinese economy and society, and ongoing reforms in the medical and health system in China, the demand for pharmacy and pharmaceutical care services in China is increasing (Yu et al., 2016). Over the years, while there has been growth in the number of pharmacies and pharmacists, there have been concerns that the quality of care and services provided to the public may not be to the same level as in other countries, and that new graduates may not have sufficient capacity to practice what they have learned in a patient-focused, clinical manner (Xinhui et al., 2006). In part to address this need, new pharmacy "undergraduate talent training programs" have been developed. These programs were designed to produce high quality graduates with strong technical skills who can function at international standards for pharmacy practice, and who can help address the needs of a rapidly modernizing healthcare system in 21st century China (Lianrong, 2003).

Historically, pharmacy education in China has been focused on training individuals to work in research and drug manufacturing environments, rather than in clinical or healthcare settings. The role of a clinical pharmacist (one who advises, prescribers, educates patients, and monitors drug therapy to ensure it is safe and effective) in China is relatively new, while the role of industrial and research pharmacists is long established. This has started to change with the increasing recognition that pharmaceutical knowledge and skill that is relevant to the manufacturing industry can also be of service in a clinical, patient-centered setting as well. This shift is challenging, however; with few role models, mentors, or trained clinician-faculty members in China, it is difficult to reorient pharmacy education towards clinical practice in a rapid way. In order to meet the needs of the 21st century, China's healthcare and educational systems are both changing rapidly. As part of this change, there is increasing recognition of the need for strong experiential and practical teaching and training in the pharmacy program as a way of modeling for and mentoring young students into clinically oriented practitioners.

Reforming the Pharmacy Education System in China

Pharmacy education in China is evolving to meet the needs of a changing healthcare system, one that recognizes that the traditional pharmaceutical expertise and knowledge of pharmacists is necessary to ensure best possible care for patients. Currently, there is a significant lack of standardization in pharmacy education and programs across China; in fact it is challenging to even accurately count the number of "pharmacy" programs and "pharmacist" graduates given the lack of standardization in terminology or educational outcomes (Ming et al., 2010). To this end, the following key initiatives are being discussed in Chinese pharmacy education (Xiangkui et al., 2008; Ming et al., 2010):

1. Establish a new pharmacy education model (aligned with international standards and outcomes), one in which students are more better able to apply scientific and theoretical knowledge to real world clinical problems. Such education can also help develop critical thinking and lifelong learning skills, as well as build employment readiness. In most pharmacy education programs today, there is strong emphasis on the technical and scientific knowledge base, with less emphasis on clinical application and skills. As the curriculum evolves, a greater patient-care focus will build on this scientific base and allow for more effective clinical application of pharmaceutical knowledge (Xiangkui et al., 2008; Ming et al., 2010).
2. Create a scholarly campus, and build a university culture, similar to international standards. Situating pharmacy education as an academic and scientific discipline within a university will increase its quality and rigor. Pharmacy programs must be associated with high quality library and information centers to promote scientific literacy among graduates. In the past, training of pharmacists varied considerably within the country and was not necessarily linked to a high quality or accredited university campus (Xiangkui et al., 2008); going forward, ensuring that those who graduate as pharmacists are educated within a scholarly university campus environment will enhance the quality of the profession.
3. Strengthen the network of practical training placements off campus and within the school to provide students with greater options for specialization, accessibility to diverse role models and mentors, and to generate more of high quality career options (particularly clinical or patient-care focused pathways) for students to consider (Yong and Yi, 2012).
4. Establish rules and regulations for practical teaching to ensure some measure of standardization in the processes and outcomes across the country. Currently, there are too many diverse educational practices with few standard requirements; standardization and measurement of outcomes (similar to accreditation systems used in other countries) will help improve the quality of educational programs and their graduates (Ming et al., 2010; Yong and Yi, 2012; Ying et al., 2012).

There is much potential in the pharmacy education system in China. As interest grows in the potential role of pharmacists in patient-focused clinical settings, there will be a need to build upon the historic strengths of pharmacy education, and ensure they can

be applied to a clinical context. The profession's historic roots in manufacturing and research ensure a strong scientific foundation, but further work is required to ensure this translates into application in clinical settings. It will be essential to work towards standardization of the pharmacy curriculum, as has been done in many other countries. Clear standards and expectations, along with measurement, reporting, and accreditation, will ensure academic programs are rigorous and that graduates of these programs are ready for the important work they will do as pharmacists. While standardization of educational processes does not preclude specialization or concentration in certain fields, it does ensure that baseline competencies are the same for all graduates, regardless of place of graduation.

Pharmacovigilance

The Concept of Pharmacovigilance (PV)

Pharmacovigilance refers to the science and action associated with adverse event detection, monitoring, assessment, identification, prevention and treatment, or management of drug safety incidents (Lijuan et al., 2006). Given the size of China's population, the diverse array of prescription, non-prescription, traditional, and complementary/alternative medical products used in the country, pharmacovigilance is of enormous importance to healthcare system, and in particular the need to develop sentinel early-warning and detection systems when adverse events occur and threaten to spread nationwide (Xin and Rong, 2009; Liting et al., 2014). In particular there is an important potential role for pharmacists in pharmacovigilance work given their central role in all aspects of the medication life cycle, from research to production to distribution and post-marketing surveillance (Liting et al., 2014). In China, the term "pharmacovigilance" was first proposed in the symposium on "First Pharmacovigilance and Drug Epidemiology" held in Shanghai in September 2004 (Lijuan et al., 2006). Prior to this, pharmacovigilance work in China was carried out mainly in the form of ADR monitoring (Lijuan et al., 2006). China began formal ADR monitoring pilot work in 1988; in 1989, the Ministry of Health Adverse Drug Reaction Monitoring Center was established and in 1998, China joined the WHO International Drug Surveillance Cooperation Program. In 1999, the Ministry of Health Adverse Drug Reaction Monitoring Center was merged with the State Drug Administration and Evaluation Center and renamed as "National Adverse Drug Reaction Monitoring Center" (Lijuan et al., 2006). Since then, pharmacovigilance has been widely seen as central to ensuring the safety and reliability of the medication system in the country (Liting et al., 2014).

The Organizational System for Pharmacovigilance in China

At present, the Chinese pharmacovigilance administrative supervision system is divided into four administrative levels: national (countrywide), provincial, county, and municipal (local) (State Food and Drug Administration, 2016). At each level, Food and Drug Administrations exist; while their work at each level is not fully standardized or prescribed, within each provincial center, there is coordination to ensure national pharmacovigilance objectives are achieved.

The current strength of pharmacovigilance staff across all levels is nearly 3,000 people, more than 1,000 of whom are full-time staff (EB/OL, in press) (**Fig. 1**). Their academic qualifications/credentials may vary considerably based on geographical location, role, and responsibility (EB/OL, in press). A priority for pharmacovigilance in China has been to ensure that all parts of the country are covered; as the map highlights, every province, region, and major municipality in the country has personnel in place to monitor the medication system to ensure it is safe and reliable (Ya et al., 2016).

In the continuous improvement of the organizational system, the technical management of monitoring department has gradually become standardized, and the National Center and Beijing, Liaoning, Jiangsu, Sichuan, Hunan, Zhejiang along with other provincial centers have passed international ISO9001 quality management system certification. Such international quality accreditation is essential to ensure that Chinese pharmacovigilance systems are capable of providing robust monitoring and surveillance of medication safety across the country. It is anticipated that in the future more centers will achieve such accreditation, which would further strengthen the system (Ya et al., 2016).

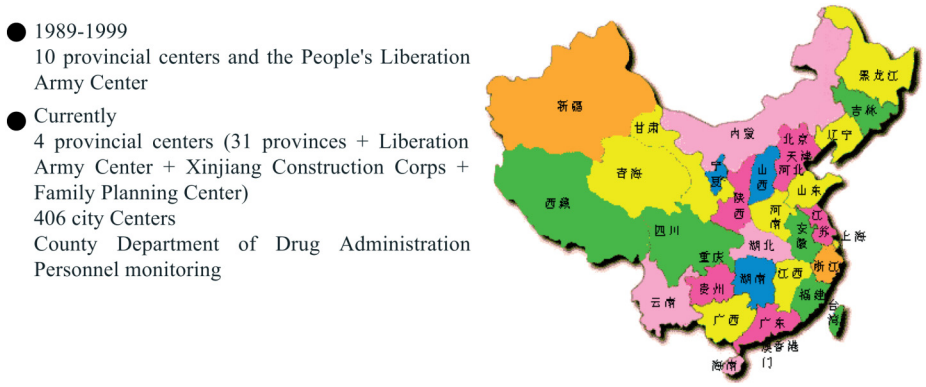

Figure 1 China Adverse Drug Reaction Monitoring Agency

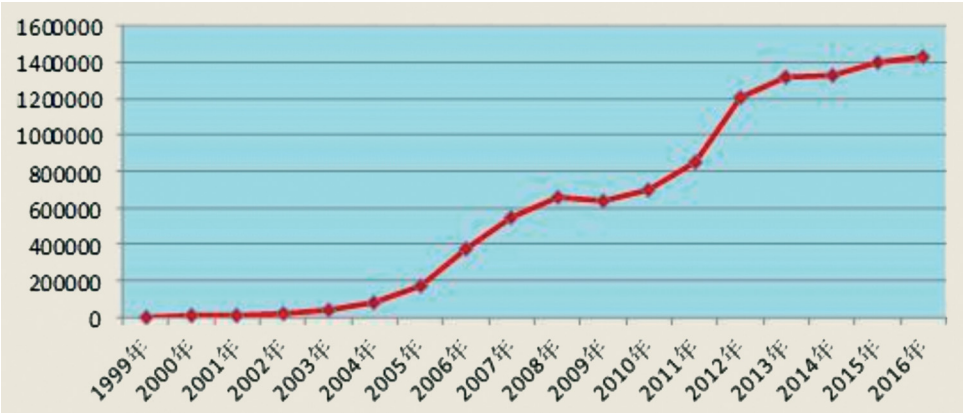

Figure 2 The growth trend of the national drug adverse reaction/events report in China from 1999 to 2016 (EB/OL, in press)

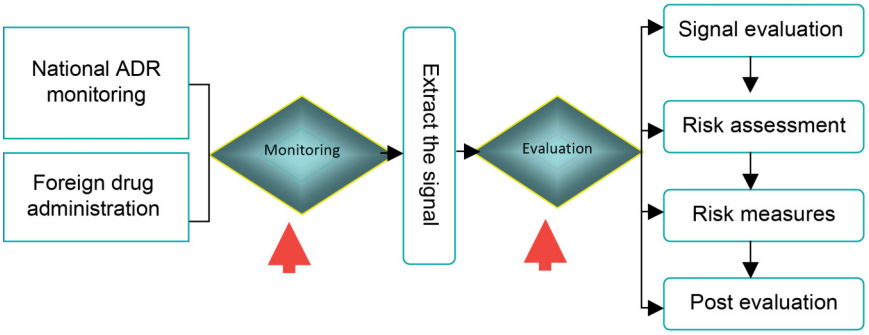

Figure 3 Signal mining and evaluation process

The Number of Reports Continues to Climb

From 1999 to 2016, the national ADR monitoring network received nearly 10.75 million reports of "adverse drug reactions / incident reports" (Fig. 4). In part, this increase may reflect better administrative structures to collect and analyze reports, as well as increased awareness about adverse drug reaction reporting amongst health care professionals (Liting et al., 2014). This increase in data is also important in helping China monitor its medication system more effectively. Yet, concerns persist that despite the increase, underreporting (particularly in some sectors such as manufacturing) continues to be a problem (Liting et al., 2014; EB/OL, in press). There exists significant opportunities for pharmacists (in industry, research, manufacturing, production and in clinical practice) to become better trained and more involved in reporting to reduce prevalence of under-reporting of adverse drug reactions (EB/OL, in press) (Fig. 2).

Risk Management Systems Continue to Improve

Signal mining and evaluation

At present, drug safety is established through daily monitoring of incident reports, weekly summaries, quarterly evaluations, and an annual evaluation. Through this process the National Adverse Drug Reaction System seeks to identify risk signals in China, while simultaneously monitoring other international pharmacovigilance data sources for comparison. While this monitoring system is aligned with international practices, it is important to note that the system is only as effective as the incident reports received; under-reporting, particularly by pharmacists, can undermine the quality of the system (EB/OL, in press). Further, there is a growing role for pharmacists who are trained to actually participate in the evaluation and risk assessment process, given their pharmaceutical knowledge and skills (Fig. 3).

Handling emergency events

With the goal of balancing harm reduction in as best as possible evidence-informed manner, mindful of time pressures and urgency, emergency events in drug safety may follow a different investigation and evaluation process than the traditional signal-mining approach. Given the large number of traditional, complementary, and alternative medications used in China, as well as the large number of pharmaceutical manufacturers involved in production of medications in the country, it is a challenge to identify emergency events in a timely manner without over-reacting. Pharmacovigilance staff must be careful in considering a

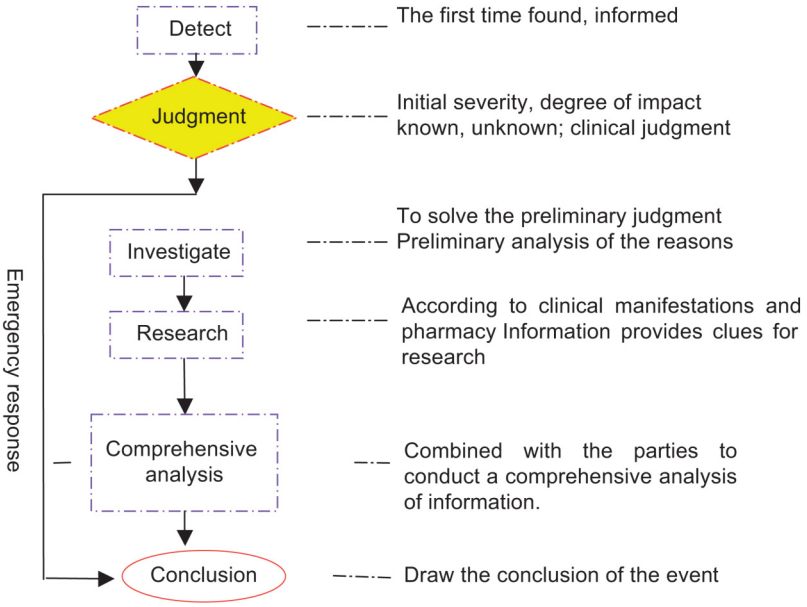

Figure 4 Emergency events treatment scheme

single or a few incidents of risk or harm; prematurely removing a product from the marketplace may cause greater harm than good in some cases, while conversely waiting too long for confirmation of risk/harm by additional cases can be problematic. To facilitate evidence informed decision-making, an emergency response treatment scheme has been developed to help support data analysis, interpretation, and decision-making. Again there is a growing opportunity for pharmacists to be involved, in both reporting and in evaluation and assessment (Fig. 4).

Risk warning

A national Early Warning Information Sharing Platform has been developed with the objective of providing support to decision-makers in flagging potential risks as problems that require immediate action. In a large and diverse country like China, there is always a challenge in balancing how information is transmitted and shared amongst stakeholders. Isolated or incomplete information about potential risk can lead to panic or stampede, while withholding of information can lead to gossip and innuendo. Developing a more systematic process for risk warning to different stakeholders, especially during emergency events, continues to be a work in progress. The current process is outlined in Fig. 5.

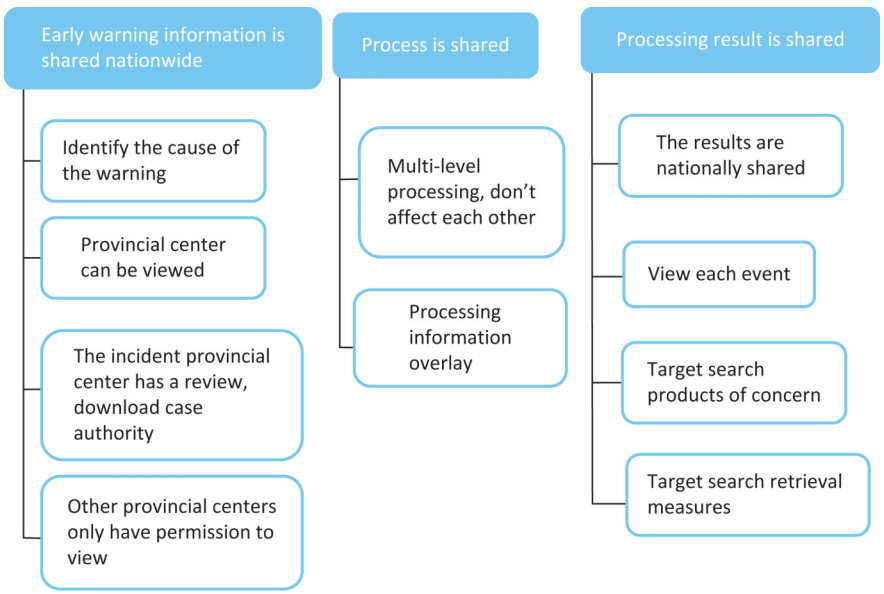

Figure 5 Early warning information sharing platform

Challenges and Opportunities for Pharmacovigilance in China

Reliability of the monitoring system needs to be strengthened

While the pharmacovigilance system in China is rapidly improving, several elements require strengthening (Liting et al., 2014; EB/OL, in press; Ya et al., 2016): (1) accountabilities and requirements of pharmaceutical production enterprises (manufacturers) must be clearer and legislated as currently there is likely significant underreporting by this group; (2) requirements for reporting of medication safety issues and risks by health professionals (including pharmacists) needs to be implemented; (3) systematic risk management systems in health institutions (including hospital pharmacy departments) need to be set up and developed; (4) pharmacovigilance monitoring institutions with qualified professionals (including pharmacists) must be expanded nationwide; and (5) penalties for non-performance in drug safety need to be established and enforced.

Case report quality to be improved

At present, the number of ADR reports in China is growing rapidly, but the quality of ADR reporting is uneven (Liting et al., 2014; Ya et al., 2016). Key issues to address include (Liting et al., 2014; Ya et al., 2016): (1) Participation of all parts of the country and the health system in reporting as currently reporting is generally limited to large urban centers; (2) all health professionals (especially pharmacists) must be trained in accurate reporting and documentation; (3) documentation standards regarding timeliness of reporting, quality, and authenticity need to be established; and (4) audit evaluations for quality need to be systematized and implemented.

At present, most ADR reports come from medical institutions such as hospitals; less than 7% of all reports come from the manufacturers, who currently have no regulated requirement to report. As a result, there is a likeliness of significant underreporting, which may undermine the entire pharmacovigilance system. Manufacturers need to be trained, incentivized, and ultimately held accountable to ensure they are working in accordance with laws and regulations to improve the overall reporting and monitoring system.

Risk Warning Capability Needs to be Strengthened

Early detection of risk is crucial to prevent harm. However, technical evaluation of risk to support evidence-informed decision-making requires further development. Currently, risk assessment and risk management standards can be somewhat non-specific, and this introduces potential of error or bias in decision-making (Yongfang et al., 2013). Prematurely withdrawing a medication due to early signal risks can, of course, produce other harms for patients who are now left without a medication that works for them. Conversely, waiting too long for additional evidence of harm may increase risk for patients. Technical guidance and decision support systems for risk warning need to be strengthened and better aligned with international standards to provide decision makers with confidence in their judgments. This is of course complicated in China due to the size of the country and population, and the diverse array of traditional, complementary and alternative medications used across each province and region (Yongfang et al., 2013; Ya et al., 2016). Further research and development in this area, customized to China's unique needs, is required.

The Future for Chinese Pharmacovigilance

Complete pharmacovigilance should include all aspects of drug safety and related factors, but at this stage China is still mainly focused on the post-marketing drug monitoring and ADR monitoring stages. In the long run, a comprehensive pharmacovigilance system needs to evolve, aligned with international standards, that begins with early stages of new drug development and continues to post-marketing surveillance along the entire life cycle of the drug (Lu et al., 2017). Further, pharmacovigilance activities need to extend to the traditional, complementary, and alternative medical products that are widely used across the country and that currently may not be reported as frequently as they should be.

Revise Laws and Regulations, and Strengthen the Duties of All Parties

Laws and regulations to enforce pharmacovigilance across the entire drug life cycle are required to reinforce the responsibilities of researchers, drug manufacturers, hospitals, health professionals, and ultimately patients to report on adverse drug reactions and other problems with medications. Currently, without laws and regulations, reporting by drug manufacturers is uneven and quite low; more robust reporting at the early stages of drug development and manufacturing would prevent problems at the post-marketing level from ever appearing. Legal requirements for individuals and institutions (including manufacturers) are an important way of strengthening the system.

Establish Inspection Mechanisms and Implement Corporate Responsibility

A major problem in the current system is the lack of consistency in accountability of pharmaceutical manufacturers. While some producers of drugs do take their reporting requirements seriously, many do not. Once laws and regulations on monitoring and reporting are in place, they must be supported by inspection and audit mechanisms by arms-length agencies, such as the National Adverse Drug Reaction Centre to reinforce corporate responsibilities. This is crucial to ensuring pharmacovigilance across the drug life cycle.

Promote Development of the Chinese Hospital Pharmacovigilance System (CHPS)

The Chinese Hospital Pharmacovigilance System (CHPS) is a potentially powerful information system for collecting and monitoring data related to medication use and safety in hospitals across the country. This system uses information technology to support and facilitate reporting by medical institutions, and to accelerate and improve monitoring of risks, signals, and trends. As of 2017, 62 hospitals had signed a cooperation agreement with CHPS, and 14 had implemented it (Lu et al., 2017). Though a very small number, it represents an important start on a technologically-enabled system for reporting and monitoring that could be a model for future developments in the country.

Strengthen Safety Education, Promote Information Feedback

In many countries, patients are encouraged to participate in ADR reporting, along with non-physician health professionals. Further work is currently underway to improve safety education for patients, and to provide mechanisms for non-physicians to report ADRs; in addition, there is a need to develop mechanisms to alert both patients and non-physician health professionals about the latest information on specific drug safety or risk issues. Within China, there is a particular interest in the role of journalists and media to eliminate rumors and panic regarding drug safety; further training of this group is needed, as are standards of practice, to ensure accurate and timely reporting of important public safety data (Lu et al., 2017).

Pharmacoeconomics in China

The size and complexity of the healthcare system in China means that the costs of medicines are substantial but difficult to actually calculate (Bae, 2015). Ensuring best possible value for pharmaceutical expenditures is crucial for the sustainability of the system (Reeder, 1995). Compared to other countries, the development of pharmacoeconomics in China has been slow, beginning only in 1990. However, since that time, there has been growing recognition of the importance of pharmacoeconomics within pharmacy and the healthcare system. Today, of the 100 more ISPOR (International Society for Pharmaceutical and Outcomes Research) regional chapters worldwide, seven are from China, highlighting its growing importance in the country (Walley and Haycox, 1997; Shi et al., 2014).

Guidelines for Pharmacoeconomic Evaluations in China

Although the development of pharmacoeconomics in China has been slow compared to developed countries, around 300 PE (pharmacoeconomic) articles from Chinese researchers are now published annually (Doherty et al., 2004). However, the research quality of the studies is uneven. Until recently, there was a lack of uniform standards in PE research across the country (Ramesh et al., 2014; Ma et al., 2016). To standardize research procedures and improve the quality of PE studies in China, the first edition of China Guidelines for Pharmacoeconomic Evaluations was published in 2011 (Hu, 2013). This guideline summarized essential items of PE studies, illustrated requirements and provided examples for each item. The guideline was updated in 2015 and a manual was added, which explained details on how to carry out PE studies by using specific examples (Ramesh et al., 2014). This updated guideline mainly included two sections: PE guidelines (introduction, instructions, executive summary, main texts, references, and appendix) and guidance manual. The PE guidelines were composed of 10 chapters, each corresponding to a step in the PE process itself: (1) Study question; (2) Study design; (3) Cost; (4) Health outcomes; (5) Evaluation techniques; (6) Modeling analysis; (7) Variability and uncertainty; (8) Equity; (9) Generalizability; (10) Budget impact analysis. **Table 1** highlights the Chinese approach to pharmacoeconomic evaluation, including criteria for study design, outcome indicators, evaluation techniques, and modeling methods used.

Potential Applications of Pharmacoeconomics in China

In general, pharmacoeconomics is not currently widely used in the public or private sector in China (Hu, 2013); it is most widely used by international pharmaceutical companies located in the country who sell their products to jurisdictions where PE is compulsory or more highly valued (Tian et al., 2012; International Society for Pharmacoeconomics and Outcomes Research, in press a; ISPOR, in press). Compared to international pharmaceutical companies, domestic pharmaceutical companies have a fewer pharmacoeconomic professionals, and they are not active in carrying out PE studies on their pharmaceutical products as the PE evidence is not currently a mandatory part of the drug approval or medicare reimbursement systems in China (International Society for Pharmacoeconomics and Outcomes Research, in press b; Ahmad et al., 2013).

The rate of health insurance coverage for Chinese populations has been rising in recent years (Letizia, 1995). The selection of drug lists for reimbursement is currently based mainly on clinical outcomes and benefit (Murray et al., 2000; Angevine and Berven, 2014); economic outcomes and budget impacts are not fully taken into consideration by decision makers. In China, pharmacoeconomics has not been used to guide selection of the hospital formulary. To promote rational use of medicine, reduce wastage of health resources, and to ensure a sustainable health system for the future pharmacoeconomics is now being discussed as a factor in developing hospital formularies, though practical implementation still is behind other countries (Hodgson, 1994; Shi et al., 2014).

Table 1 Ten chapters included in main texts of China Guidelines for Pharmacoeconomic Evaluations

Chapter	*Guideline*	*Recommended information*
1	Study question	1. Include study background (disease epidemiology and economic burden), interventions (conventional or standard treatment), perspective (society, payer, employer, healthcare provider, or patient), populations (inclusion and exclusion criteria), and objectives 2. Subgroup analysis to examine the stability of results
2	Study design	1. Select the study types (prospective, retrospective cohort, mix design, or secondary literature research) to determine data sources 2. Describe the rationale of study assumptions 3. Sample size and time horizon
3	Cost	1. Include cost identification, cost measurement, discounting, and uncertainty analysis 2. Cost identification should comply with the study perspective, including direct medical cost, direct non-medical cost, and indirect medical cost 3. Discounting rate for 0%–8% annually
4	Health outcomes	1. Include effectiveness, utility, and benefit 2. Final endpoints are preferred over intermediate endpoints 3. Generic utility values for healthy populations, and disease-specific utility values for patients 4. The recommended measurement of utility values: standard gamble, time trade-off, visual analogue scale, EuroQol-5 dimensions, short-form six-dimensions, health utilities index, and quality of well-being 5. The measurement of benefit outcomes: direct, indirect, and intangible benefits
5	Evaluation techniques	1. Decide the types of evaluations (cost analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis), while cost-effectiveness and cost-utility analyses are the preferred types 2. The incremental cost-effectiveness ratio (ICER) should be reported
6	Modeling analysis	1. Demonstrate the rationale of model structure, assumptions, and data sources in decision-analytic modeling (decision tree and/or Markov models) 2. Use econometric models to estimate medical cost and its influential factors, and internal estimates of ICER
7	Variability and uncertainty	1. Due to the uncertainty of variables, sensitivity analysis (one-way, multi-way, and probabilistic sensitivity analyses) and scenario analysis should be conducted 2. Due to the heterogeneity of patients, stratified analysis could be used for sub-group studies
8	Equity	Discuss the equity of study results for different age, gender, race, geographical, or social groups
9	Generalization	Describe the generalization or transferability of results for other regions, countries, or another medical environment
10	Budget impact analysis	Not compulsory analysis for pharmacoeconomic evaluation, but supplementary evidence for payers' decision making

In summary, while there is great and growing expertise in pharmacoeconomic models and methods in China, practical application and use of decision-making support has not been as widespread as in other countries (Jo, 2014; Sher and Punglia, 2014; Yee and Gary Chan, 2015; Nimdet et al., 2015). This is changing, and with new government standards in place (Academy of Managed Care Pharmacy, in press; National Institute for Health and Care Excellence, 2013; Rodrigues et al., 2014; Zhang et al., 2017; Zhao et al., 2017), pharmacoeconomic research is poised to grow significantly in the years ahead, beginning in the hospital sector (van Nooten et al., 2012; Jing et al., 2017) and spreading from there to the industry (Suh et al., 2002) and the private sector (Trask, 2011).

Social and Administrative Pharmacy In China, the terms "pharmaceutical administration" and "social and administrative pharmacy" are used; both are defined as the branches of pharmacy that use the theories and research methods of social science to study medication-related activities in diverse settings (Wengong et al., 2001).

The Development of Social and Administrative Pharmacy in China

In China, social and administrative pharmacy is focused on three main areas: commercial pharmacy, pharmaceutical administration, and social/societal aspects of pharmacy (Ying, 2006).

Commercial Pharmacy

Commercial (or "retail") pharmacy is a growing sector of the profession (Chao, 2011; Shimin, 2014). The economic, financial, and business aspects of commercial pharmacy are important to the viability and sustainability of the profession. Understanding how pharmacies work as commercial entities or businesses, and applying experiences from other business to improve the operations and success of pharmacies is a central part of this branch of social and administrative pharmacy. Social sciences disciplines ranging from economics to finance and accounting to information technology inform much of the work in this area, all aimed at understanding and improving the financial performance of the profession.

Pharmaceutical Administration

Pharmacies are complex entities and require sophisticated administration to ensure they function effectively. Whether in the commercial, hospital, or industrial sector, understanding of topics related to administrative laws, human resources management, legal and auditing practices, etc. are crucial for success (Ming et al., 2008a). Because pharmacies must work with specialty products–pharmaceuticals–additional standards and reporting requirements exist over traditional businesses, so pharmaceutical administration has emerged as a specialty area of social and administrative pharmacy in China. Given that some pharmacies employ hundreds of people, the importance of effective administration is clear. Social sciences such as marketing, psychology, sociology, management and law are all part of pharmaceutical administration and applied to the study of pharmacies in diverse settings.

Societal/Social Pharmacy

One of the fastest growing areas of research interest is societal/social pharmacy, which studies the ways in which medications, pharmacists, and pharmacies interact with and influence communities and societies (Ming et al., 2008b). Since the 1960s, with the development of clinical pharmacy, the societal role of the pharmacist has changed tremendously and redefined the pharmacist's interactions with patients, other healthcare professionals, and other stakeholders (Yu et al., 2010; Fang et al., 2013a). Social science disciplines such as sociology, psychology, and anthropology all are important in societal/social pharmacy, as are a diverse array of qualitative and quantitative research methods. Current issues explored in China include the pharmacists' role in preventing substance abuse, interprofessional collaboration, and the best way to encourage medication adherence (Yang et al., 2008; China Food and Drug Administration, 2015; Wiysonge et al., 2016).

Social and Administrative Pharmacy in China

The Development and Definition of the Discipline

In China, social and administrative pharmacy is a young discipline, and only became formally recognized in 2012 (Liu et al., 2011). In 1988, Professor Wu Peng in West China University of Medical Science first introduced the concept of pharmaceutical administration to China (State Council of People's Republic of China, 2015). In 1993, she published the first version of a reference text titled "Pharmaceutical Administration." In this version, she clearly defined the objective and research content of this discipline. Later, in 2002, Professor Yang Shimin in Xi'an Medical University also gave a formal definition of pharmaceutical administration. Professor Wu and Yang are regarded as the founders of this field in China (Chao, 2011).

Faculty

In 1988, during the early days of this discipline, there were only nine teachers in all colleges in the whole of China (Shimin, 2014). After years of development, the number of faculty in this area increased gradually. By 2007, there were 276 teachers in this discipline in 108 universities and colleges (Shimin, 2014). Some of these teachers were part-time professionals, as they came from hospitals, manufacturing units, and governmental organizations (for example, State Food and Drug Administrations) (Shimin, 2014). Compared with other disciplines, the number of teachers in pharmaceutical administration in China is still very small, and this has limited the growth and expansion of social and administrative pharmacy in the country (Ming et al., 2008a; Shimin, 2014).

Curriculum

Currently, pharmacy education in China is not quite standardized. Pharmacy students receive different levels of exposure to social administrative pharmacy theories, models, and methods depending upon the school they attend (Ming et al., 2008b; Shimin, 2014). In most programs, there is only one required social administrative pharmacy course: pharmaceutical administration and regulations, which highlights the laws and regulations governing the field (Shimin, 2014). Some programs have expanded curriculum offerings in areas such as management, economics, psychology, etc (Ming et al., 2008a; Shimin, 2014). As of 2007, the curriculum for pharmaceutical administration in China was classified into four categories : management, economics, laws and ethics, methodologies, and others (Ming et al., 2008a) (**Table 2**).

Unfortunately, the teaching of social and administrative pharmacy (both undergraduate and graduate) is quite unstandardized in China (Ming et al., 2008a; Shimin, 2014). In some cases pharmacists are not actually involved in teaching of the content (Ming et al., 2008a; Shimin, 2014). While the proliferation of different courses and programs may encourage innovation, the lack of standards in education has slowed down general progress in the field. As a result, social and administrative pharmacy education, research, and practice are still relatively immature in China compared to other parts of the world, though progress is being made, especially in graduate education.

PhD Graduate Student Education

The training of doctoral students began in year 2000 at Shenyang Pharmaceutical University. Since then several universities have established doctoral education programs in the hope of building capacity in China for pharmaceutical administration and social administrative pharmacy teaching and research (Ming et al., 2008a; Ming et al., 2008b; Shimin, 2014) (**Table 3**).

Table 2 Curriculum for pharmaceutical administration in China in 2007 (Ming et al., 2008a)

Category	*Topics covered*
Management	• Pharmaceutical management (including pharmaceutical administration, Chinese medicine administration) • Pharmaceutical administration and regulation • Hospital pharmacy management • Medical business administration • Medicine administration • Drug quality management practice
Economics	• Pharmaceutical marketing • Pharmacoeconomics • International pharmaceutical trade • Others (including medical economy, pharmaceutical e-commerce, medical market survey, and forecasting)
Laws and ethics	• Pharmaceutical laws and regulations • International drug regulations • Pharmaceutical intellectual property • Pharmacological ethics
Methodology and others	• Pharmaceutical administration research methods • Medical and pharmaceutical policy

Table 3 The number of PhD candidates and PhD graduates in the social and administrative pharmacy and pharmaceutical administration

	Number of PhD		*Number of PhD candidates*	
	Major of pharmaceutical administration	*Major of social and administrative pharmacy*	*Major of pharmaceutical administration*	*Major of social and administrative pharmacy*
2006	4	/	18	24
2007	8	3	29	27
2008	9		32	39
2009	7	15	32	47
2010	3	4	42	43

Professional Society

In July 1986, the 17th general council of the Chinese Pharmaceutical Society established the Pharmaceutical Administration Society. Since then, an annual academic conference has been held every year with focus on one specific topic. The topics discussed during the last 7 years are given in Table 4. More and more researchers, government officials, and professionals working in hospitals and pharmaceutical companies are involved in this conference. The participants increased from nearly 30 in the beginning to more than 200 in recent years, and the submissions also have seen a substantial increase in quantity and quality. All this points to an increasing role and influence of social and administrative pharmacy in China in the years to come.

Public Health Pharmacy in China

In China, the role of commercial (community or retail) pharmacies in providing healthcare services is growing (Yu et al., 2010). As in many other countries (Fang et al., 2013a), China's community pharmacies are private for-profit enterprise that historically have been

Table 4 Topics of the annual academic conferences of Pharmaceutical Administration Society in China from 2011 to 2017

Year	*Topic*
2011	Medical and pharmaceutical science development - new healthcare policy and medicine administration
2012	The development of 12th 5-year medical and pharmaceutical science
2013	The safety of medical and pharmaceutical products
2014	Strengthening the construction of pharmaceutical administration disciplines and promoting the healthy development of medicine
2015	Promoting legal system construction and administrating medicines according to law
2016	Focusing on the 13th 5-year plan and promoting healthy development of pharmaceutical administration
2017	Practicing the concept of healthy China and promoting the sustainable development of pharmaceutical administration

more focused on large-volume dispensing and sales rather than clinical services; by the end of 2015, there were over 450,000 community pharmacies nationwide (Wiysonge et al., 2016). As a result, there has been interest in the potential for public health pharmacy in China, despite the fact that currently most pharmacies are only involved in dispensing/drug distribution activities.

Legislation and National Policies

For public health pharmacy to flourish, it is essential that the pharmacy workforce is trained, competent, and meets professional standards for practice. To this end, new regulations and legislation are being developed in China to ensure all pharmacies have the human resource required to provide public health services.

Legal Requirement for Community Pharmacy

According to the Drug Administration Law (2015), a community pharmacy must: (1) be staffed with legally qualified pharmaceutical professionals, (2) meet specified standards for business operations, including, equipment, warehouses and hygienic environment required for drug distribution, etc., and (3) have systems in place to demonstrate quality control over the drugs to be dispensed (Wiysonge et al., 2016). According to the National 12th Five-Year Plan of Drug Safety (2012) issued by State Council of China (State Council of People's Republic of China, 2015), all newly opened community pharmacies must now be staffed by a licensed pharmacist. Further, all the owners or main administrators of community pharmacies must be certified and licensed pharmacists, and a licensed pharmacist must be on duty to supervise the rational use of medicines at community pharmacies during the operational hours (Yang et al., 2008; China Food and Drug Administration, 2015).

Standards to Ensure the Quality of Pharmacy Services

To enhance the quality of pharmacy services provided at community pharmacies, changes have been made to regulations and legislation (Liu et al., 2011; The State Council of People's Republic of China, 2012; State Council of People's Republic of China, 2015; National People's Congress, 2015). The Regulations for the Implementation of the Drug Administration Law (2016) of the People's Republic of China outlines the medication classification system in China (http://www.gov.cn/gongbao/content/2012/content_2068275.htm). Medicines are classified as prescription-only medicines (POMs) and over-the-counter medicines (OTCs); OTC medicines are further sub-categorized into two classes according to the safety level (http://www.gov.cn/gongbao/content/2012/content_2068275.htm).

In 2003, China Nonprescription Medicines Association (CNMA) developed the Chinese version of "Guidelines for Good Pharmacy Practice (GPP)" based on "GPP in Developing Countries" developed by the International Pharmaceutical Federation (FIP) (China Food and Drug Administration, 2016). This was further refined (http://www.sda.gov.cn/WS01/CL0053/159780.html) as "Guideline for licensed pharmacist practice" in 2015 (State Council, 2016). Recommended practices on several aspects, including prescription review, medication guidance, drug treatment management, and health education, are presented in detail in these guidelines (Yang, 2005; Fang et al., 2013b; http://www.cqlp.org/info/link.aspx?id=2557&page=1).

Emerging Roles of Pharmacists in "Healthy China"

In October 2016, China adopted "Healthy China 2030" plan as a national strategy for a healthy China in the next 15 years (Fang et al., 2013b; http://www.cqlp.org/info/link.aspx?id=2557&page=1). In this strategy, public health is given high priority (Top leadership of the Communist Party, 2016; Certification Center for Licensed Pharmacist of China Food and Drug Administration, 2017a). Strengthening health education has been highlighted as a key strategy (Badcott, 2011). It is planned that by 2030, all areas of China will have public health programs to support wellness, including: promoting balanced diets, tightening tobacco and alcoholic control, promoting smoking cessation, enhancing capacity to identify and intervene in common mental health disorders, and reducing unsafe sexual behavior and drug abuse/misuse (Carter and Slack, 2010).

In some developed countries, such as the United Kingdom and Australia, community pharmacists are already involved in delivery of such public health services (http://www.cqlp.org/info/link.aspx?id=2557&page=1; (Badcott, 2011; Top leadership of the Communist Party, 2016; Certification Center for Licensed Pharmacist of China Food and Drug Administration, 2017a). However, in China this is still only a "potential" rather than a reality. By August 2017, the number of licensed pharmacists practicing at community pharmacies in China had reached 343,402, accounting for 88% of total number of licensed pharmacists in the country (Carter and Slack, 2010). The variable quality of the workforce of licensed pharmacists in China has been identified by the Central Government as a key priority for meeting Healthy China 2030 objectives; in the years ahead, this may lead to greater training and support for pharmacists to implement the strategy (Deeks et al., 2014; Maher et al., 2015).

Education, Professional Qualification, Examination, and Training in Public Health

Higher education in pharmacy in China was initially and even currently is designed to train professionals for work in industry or research (Certification Center for Licensed Pharmacist of China Food and Drug Administration, 2017b). Clinical pharmacy education was introduced in China in recent years and is still at a nascent stage (Certification Center for Licensed Pharmacist of China Food and Drug Administration, 2017b). According to our best knowledge, public health courses seldom appear in the curriculum for pharmacy students, and public health knowledge is currently not included in the content of the National License Examination for pharmacists (http://www.gov.cn/zhengce/content/2016-03/11/content_5052267.htm). Public health has

emerged as a key priority for China in the years ahead, and as of 2017, the national Government has recognized that qualified pharmacists have a role to play in achieving the Healthy China 2030 objectives (http://www.gov.cn/zhengce/content/2016-03/11/content_5052267.htm; http://www.sph.umn.edu/academics/dual-joint-degrees/pharmacy/). Going forward, more work will be needed to train new pharmacists, upskill those currently in practice, and ensure community pharmacists are better integrated in the overall healthcare system (Ryan et al., 2008; Hu et al., 2014).

Future of Pharmacy

Throughout this chapter, we have highlighted the "potential" of pharmacy in China, and how recent recognition of the skills of pharmacists may, in the years ahead, lead to greater roles and responsibilities for pharmacists in different areas.

Hospital Pharmacy

As the complexity of care increases in China, there will be greater need for pharmacotherapy specialists to support cost-effective clinical practice (Xiang and Tan, 2016). This will result in a significant change in the function, organization, and structure of hospital pharmacies throughout China, as pharmacists become more prominent as medication experts. Traditionally, in a large general hospital of 1000 beds, pharmacy staff always accounted for about 8% of medical staff (= 45–50 persons) (Lee et al., 2013a). As the need for pharmacotherapy specialists increases, the staff will likely be subdivided into clinical pharmacists and dispensing pharmacists. The clinical pharmacist will mainly be responsible for clinical services (including therapeutic drug monitoring, adverse drug reaction monitoring, clinical recommendations and guidance to prescribers). The dispensing pharmacist group will mainly be responsible for the receipt and preparation of medicines, handling of drug accounts, prescription input and preparation of packaging materials. At the current time, the role of the regulated pharmacy technician (as it exists in other countries) has not been fully discussed in China.

Technology

As in other countries, automated dispensing systems are now being used in China to manage the labor- and time-intensive activities of drug distribution, thereby freeing pharmacists' time for more valuable clinical services. Hospital Information Systems (HIS) are being constructed now that will support robotic and automated dispensing systems (Lee et al., 2013a,b). This will also lead to better control over inventory, prevent drug loss, and ultimately save money in the healthcare system (Lv, 2016). This may also support greater research in pharmacovigilance and pharmacoeconomics to further improve the quality, safety, and effectiveness of the system.

Administrative Systems

Hospitals in China are currently moving towards establishment of a "master pharmacist" system, similar to the Chief Pharmacist in many other countries (Hammett et al., 2014). The master pharmacist will take responsibility for all aspects of the hospital's drug use process and has supervisory duties to ensure drug safety. This will require pharmacists to receive additional management education and training, and in some cases may lead to management specialization by some pharmacists and clinical specialization by others. Hospital pharmacists will therefore likely require additional training or credentials as they progress through their careers, and will have increasingly important roles to play in both departmental and hospital-wide administration.

Community Pharmacy

Community pharmacy will continue to evolve in China as pharmacists become more involved in medication management and public health activities.

Community Pharmacy in the Future

In the future, community pharmacies in China will likely conform to one of the following formats:

Standard pharmacy format: Similar to Japan's prescription drug dispensing pharmacy, the standard community pharmacy format will focus on providing high quality prescription and OTC pharmaceutical products, and basic but important education to patients about these products (Yang et al., 2015). The business model will be volume-focused with a strong emphasis on efficient, technologically sophisticated dispensing systems supervised by trained personnel.

Community convenience store format: This type of pharmacy will focus mainly on OTC (rather than prescription) products as well as a variety of day-to-day consumer items found in convenience stores. OTC product sales will likely account for less than 60% of all sales, and the business model will be volume-focused while providing some basic education and public health services (Wen et al., 2009).

Clinic pharmacy format: Such pharmacy clinics will have a doctor co-located with the pharmacy to ensure patients have immediate access to their medications and that prescribers have access to pharmacists to provide them with guidance and advice.

Clinical services such as medication management and medication review will be provided. In this format, medically complex patients with higher or chronic healthcare needs will be served; the business model is more patient-focused with the goal of minimizing drug therapy problems and optimizing healthcare (Min et al., 2009).

Online pharmacies: The main target customers of these pharmacies will be those patients who value speed, efficiency, and low cost, and who are comfortable with technology. Online pharmacies can also provide add-on services related to medication counseling, public health, or general health education, as the pharmacist's time will be freed up from technical dispensing activities due to technology though a pricing/economic model for this still needs to be developed.

Staffing and Management

The qualifications and professional skills of community pharmacists will gradually converge with hospital pharmacy staff, unlike the current situation where the two groups have major differences in academic qualifications (Xiao-ping, 2006). A minimum of an undergraduate degree will be required to be a pharmacist in any setting, and mobility between hospital and community sectors will start to increase. Graduate degrees and specializations (such as administrative pharmacy, or pharmacotherapy specialist) are also envisioned in the future as the pharmacist's role continues to expand.

Technology

More automated and robotics technologies will be introduced into community pharmacy, and this will free up the pharmacist's time to engage in public health and patient counseling activities. As logistics management of drug procurement, storage, and distribution becomes more automated, this will help to improve operational- and cost-effectiveness in community pharmacy. Technology will also facilitate group purchasing to further reduce costs of medication. A new specialty in community pharmacy logistics will evolve, similar to the administrative pharmacy role in hospital.

Summary

China is a large, diverse, and rapidly developing country. The profession and practice of pharmacy in China faces unique challenges due to the scale of the country, the plethora of traditional, complementary, alternative, and allopathic medications used, and (until recently) the lack of standardization in pharmacy education, community pharmacy practice, and understanding of the role and responsibility of pharmacists. As the country moves toward greater standardization in pharmacy practices based on international standards, there are many new opportunities for pharmacists, in areas such as pharmacovigilance, pharmacoeconomics, public health, and in social-administrative pharmacy research. A critical first step is to reform the Chinese pharmacy education system. Historically, pharmacy education has focused on research, manufacturing, production, and industrial pharmacy. The scientific foundations of the pharmacy curriculum are a useful starting point for evolution toward a more clinical, patient-focused curriculum, one that includes more social, administrative, and clinical components. As the curriculum evolves, more graduates with diverse and important skills will be produced, and these individuals will help shape the future of the profession in China.

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Pharmacy Practice in India

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Introduction

In India, "Pharmacy Practice" is defined as a subdiscipline of "Pharmacy" that involves the development of the professional roles of the pharmacists (Whalley et al., 2008). Across the world, the primary function and the purpose of pharmacy is to ensure timely access to the medicines to the individuals in society. This purpose is continuously evolving with the advancements in the health care system, and must adapt to changing societal needs (Brodie, 1981). Aligned with international standards, the pharmacists of India are expected to provide an array of professional services along with the traditional role of dispensing. The substantial variations in pharmacy practice existing across the length and breadth of the country are a result of India's diversity in cultures, languages, rural versus urban health care settings, disease burdens, policies, and local regulations. A consistent and standardized delivery of pharmaceutical care services across the country is therefore a significant ongoing challenge.

Realizing the need to adopt international pharmacy practice standards, pharmacy educators in India have introduced new degree programs such as the Masters in Pharmacy Practice and Pharm D which primarily focuses on training the pharmacists in patient care rather than pharmaceutical analysis or formulation. These programs introduced has produced only few hundreds of graduates specialized in the field of pharmacy practice. As a result, there is scant limited evidence of successful outcomes of pharmaceutical care services in India, though this will evolve in the years ahead as more graduates are produced and pharmaceutical care becomes more prevalent across the country.

Health Status of India

Incredible India

India, comprising about 2.4% of the Earth's land area is ranked as the second most populated country, accounting for more than 16% of the world's population (http://factsanddetails.com/india/Nature_Science_Animals/sub7_9a/entry-4264.html). There are 29 states and 7 union territories in India with 22 major languages, 13 written scripts, and over 720 dialects. On an average, every 1000 km distance in India results in a new/different language and culture across the country. Genetically, India has two divergent populations, the Ancestral North Indians (ANI) and Ancestral South Indians (ASI). The former population is genetically related to

Central Asians, Middle Easterners, Caucasians and Europeans and the second group, the ASI are not closely related to any other ethnic groups outside the subcontinent.

Key Indicators of Health

Life expectancy at birth and infant mortality rate have improved considerably over time in India, but are still lower than that of many developing countries. The comprehensive report on "Disease Burden Trends in the States of India 1990 to 2016" revealed that the estimated life expectancy at birth in 1990 of 59.7 years and 58.3 years for males and females respectively has significantly increased to 70.3 years and 66.9 years in 2016 (ICMR, 2017). However, this indicator showed huge variation among the individual states ranging from 66.8 to 78.7 years for females and 63.6–73.8 years for males. According to the official sources of the Indian government (http://niti.gov.in/content/infant-mortality-rate-imr-1000-live-births) the infant mortality was reduced by 50% from 2000 to 2016 with the figures of 68–34 per 1000 live births. But there is a disparity between the rural and urban areas with the figures of 38 and 23 per live births respectively. Such statistics highlight the need for a strong health care system—one that includes pharmacists as experts in medication use and management.

Disease Burden and Epidemiological Transition

In the last three decades, India has undergone a major epidemiological transition as the disease patterns and mortality have shifted from communicable, maternal, neonatal, and nutritional diseases (CMNNDs) to noncommunicable diseases (NCDs) and injuries. India reported 33% of the total DALYs (Disability Adjusted Life Years) from CMNNDs, 55% from NCDs, and 12% from injuries in 2016, those were 61%, 30%, and 9% of DALYs, respectively in 1990 (ICMR, 2017).

The epidemiological transition ratio (ETR) is defined as the ratio of DALYs caused by CMNNDs to NCDs and injuries. A ratio of greater than one indicates a higher burden of CMNNDs than NCDs and injuries and vise versa. Most of the Indian states had epidemiological transition ratio (ETR) of more than one in 1990 and all the states scored ETR of less than one in 2016 which is another indicator which reveals the paradigm shift in the disease pattern in the country. But, once again, there is a wide variation of ETR among individual states, ranging from 0.16 in Kerala to 0.74 in Bihar (ICMR, 2017).

Similarly, the proportion of all deaths in India due to CMNNDs reduced from 53.6% to 27.5% between 1990 and 2016, those due to NCDs increased from 37.9% to 61.8%, and those due to injuries changed from 8.5% to 10.7% in the same period, showing an alarming death rate due to NCDs that was over two times that of CMNNDs in 2016. The categories of CMNNDs caused the highest proportion of death were diarrhea, lower respiratory infections, and other common infectious diseases including HIV/AIDS and tuberculosis and neonatal disorders. Among NCDs, cardiovascular diseases were the leading cause of death, followed by chronic respiratory diseases, cancers, diabetes, and urogenital disorders (ICMR, 2017).

Ischemic heart disease (IHD) was the leading cause of YLL (Years of Life Lost) in the all the states across India except in the North–East states where stroke was the leading cause of YLLs. Across all the states, IHD caused a much greater proportion of total YLL among males than females, accounting for 14% of premature mortality in males compared to 10% in females. Road injuries also caused a higher proportion of YLL among males than females. Diarrheal diseases and lower respiratory infections were responsible for a higher proportion of YLL in females. The years lived with disability (YLD) had also increased in India from 17% to 33% between 1990 and 2016 (ICMR, 2017).

Thus, all these indices viz. DALYs, ETR ratio, death rate, YLL, and YLD have revealed the striking health status and inequalities between the states of India, rural and urban population and genders. This unique health profile in India warrants customized health care strategies, policies and guidelines for different states, geographical regions and populations of the country. It also highlights the importance of a well trained cadre of pharmacists to support better health outcomes and the need for a national pharmaceutical care system/infrastructure to improve the health of all Indians.

The Health Care System in India

The Health Survey and Development Committee (Bhore Committee) Report, 1946, is one of the landmark reports in India, from which the current health policy and systems have evolved (Ma and Sood, 2008). This report recommended a three tiered health-care system for providing preventive and curative health care in rural and urban areas in order to ensure that access to primary care is independent of individual socioeconomic conditions. But, over the period of postindependence, the lack of capacity of public health systems to provide access to quality care resulted in the simultaneous evolution of the private health-care system (Peters et al., 2003). Though the first national population program was announced in 1951, it took almost three decades for the release of the first National Health Policy of India (NHP) in 1983, which had a focus on providing primary health care to all by 2000. Twenty years later, NHP 2002 included an objective of decentralizing health services to the general public through the private sector and increasing public expenditure on overall health care, and also emphasized the use of nonallopathic form of medicines (Chokshi et al., 2016).

In the federalized system, the governance and operations of the health system in India have been shared by both the union and state governments where the national health programs are implemented by the former and adopted by the later. Further, the federal ministry provides technical assistance to the state governments in preventing and controlling the spread of seasonal disease

outbreaks and epidemics (Chokshi et al., 2016). However, the Indian Constitution identifies health care (including public health, hospitals, and sanitation services) as a state (rather than federal) responsibility. Areas such as family welfare, population control, medical education, prevention of food adulteration and quality control in manufacture of drugs are governed jointly by both federal and the state governments.

India has mixed health-care system including both public and private health-care service providers (Sheikh et al., 2015). Private health care is mostly established in the more prosperous urban regions while the rural areas are supported mostly by the public health-care system. However, the public–private dichotomy in health care services is skewed toward the urban population who constitute about 28% but have access to 66% of total hospital beds in the country while the rest of the 72% population in the rural areas are left only with 34% of beds (Ghosh, 2014).

Public Health Care System

The public health care system in India has three-tiers viz. subcenter (SC), primary health center (PHC), and community health center (CHC) established based on the population size of 5000, 30,000 and 120,000. respectively (Chokshi et al., 2016). SC is the connecting point between the PHC and the community. Each SC is required to be staffed by at least one male or female auxiliary nurse midwife (ANM)/health worker. These SCs are assigned with the tasks to bring about behavioral changes and provide services with respect to maternal and child health, family welfare, nutrition, immunization, diarrhea control, and control of communicable diseases. PHC are committed to provide integrated curative and preventive health care and maintained by the state Governments. PHCs also act as a referral unit for 5–6 SCs in the surrounding area and have 4–6 beds for inpatients. CHCs are also established and maintained by the state Government with about 30 beds apart from an operating theater, X-ray, labor room, and laboratory facilities which serve as a referral center for PHCs within the region. In 2016, there were about 722 district hospitals, 4833 CHCs, 24,049 PHCs, and 148,366 SCs in the country (Ma and Sood, 2008). An existing health care facility such as a district hospital, subdivisional hospital or CHC shall be declared a fully operational "first referral unit" (FRU), if it is equipped to provide 24 × 7 services for emergency obstetric and newborn care, apart from all other emergency care services and a blood storage facility.

Private Health Care System

Private health care is chiefly concentrated in urban India and is oriented only toward curative care. According to the WHO, health care expenditure in India averages $75 per capita and mostly comes from the private spending of households; out-of-pocket expenses (private spending) cover about 75% of costs and the remaining 25% is covered by public system spending (http://www.who.int/whosis/whostat/EN_WHS09_Table7.pdf).

The average cost for hospitalization in private health care was about four times greater (INR 5636 vs. INR 21,726 for rural population) than the expenditure at the country's public health care set up, according to a report published in 2016 (http://mospi.nic.in/sites/default/files/publication_reports/nss_rep574.pdf). About 72% and 79% of ailments were treated in the private sector in rural and urban areas respectively (http://mospi.nic.in/sites/default/files/publication_reports/nss_rep574.pdf). The report also revealed that in the treatment of in-patients at both rural and urban areas, the private institutions dominated with the share of 58% and 68% respectively. About 72% and 68% of total medical expenditure was spent by the rural and urban population for purchasing "medicines" for nonhospitalized treatment. It was also reported that about 86% and 82% of population from rural and urban areas were not covered by any health insurance schemes (http://mospi.nic.in/sites/default/files/publication_reports/nss_rep574.pdf).

The government through its health protection scheme cover only about 12% and 13% urban and rural population respectively, mostly for the people of unorganized sectors, Employee's State Insurance (ESI) Corporation for organized sectors, Central Government Health Scheme (CGHS) for government employees and other state insurance plans. In spite of creating awareness and marketing of private health insurance schemes, only 12% of the urban population had any level of arrangement for medical insurance from private insurance players, and the share of private insurance for all others is negligible (http://mospi.nic.in/sites/default/files/publication_reports/nss_rep574.pdf).

Inequality in Access to Health Care Systems

There are three important determinants of inequities responsible for persistent and widening differences in health outcomes across India; historical inequities, socio-economic inequities, and inequities in provision and access to health services (Baru et al., 2010). Availability, accessibility, and affordability of health services are the key factors influencing equity in health care services in India. Though there has been an expansion in both public and private health care sectors during the postindependence period, by and large such expansion has been inadequate and unable to ensure universal access to quality health care throughout the country. The inequities pertaining to distribution of public facilities and human resources between rural and urban and inter states are well documented (Duggal, 2005). Differences in infrastructure, human resources, supplies, and spatial distribution lead to uneven availability of preventive and curative interventions by public health services across the states of India. The evidence shows that people who are socially marginalized have limited access to preventive and curative health services (Govender and Kekana, 2007; Gupta and Dasgupta, 2007; Hart, 2000; Mahal et al., 2002; Peters et al., 2002).

Medication Use Problems

The disparities observed in the health status and health care systems are associated with various medication use problems in India. The factors that contribute to medication use include but are not limited to are:; multiple health care systems, illiteracy, poverty, limited access to independent, unbiased drug information, irrational fixed dose combinations, and the sale of prescription drugs without prescription by community pharmacies (Parthasarathi et al., 2002). However, few initiatives have been implemented at central, state, and local levels to address these issues. The Delhi Society for Promoting Rational Use of Drugs (DSPURD), and the Tamil Nadu Medical Services Corporation Limited (TNMSC), were the two earliest initiatives in the country toward ensuring access to quality medicines (DSPRUD, In press; Mohanta and Manna, 2015). TNMSC revolutionized the procurement procedure as the pooled procurement of medicinal products required for the state's health care facilities directly from the manufacturers, establishing the warehouses at every district with ICT enabled management and modern storage facilities including cold storage.

The central government has taken initiatives by developing guidelines, policies, procedures, and regulations for combating microbial resistance to antibiotics, medicinal product's price control, and establishment of community pharmacies exclusively to sell generic medicines (Mohanta and Manna, 2015). Recently, about 343 fixed dose combinations (FDCs) have been recommended for prohibition of sale by the subcommittee of the Drugs Technical Advisory Board (DTAB) as these combinations are deemed to be irrational (https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/panel-recommends-ban-on-343-fixed-dose-combination-medicines/articleshow/65142395.cms). The decisions of the central government on compulsory licensing for anticancer medicines made those formulations as affordable ones (Mohanta and Manna, 2015). However, the rapid emergence of technology driven online pharmacies may in the future contribute to new medication related problems and their safety as central government control and oversight of such practices may be difficult.

The safe use of medicines is advocated by the Pharmacovigilance Program of India (PvPI) functioning under the National Coordination Centre (NCC) of Indian Pharmacopoeia Commission (IPC). There are about 250 adverse drug reactions (ADRs) monitoring centers across the country reporting ADRs to national center. NCC has also adopted various strategies for enhancing the patient safety which includes, capacity building for ADR monitoring, surveillance, and collaborations with other national health programs to enhance ADRs reporting and to ensure PvPI as a vital knowledge database for the regulators of India (Kalaiselvan et al., 2016).

A very few drug and poison information centers established by various educational institutions and professional associations are functioning in the country. As per the literature (Malik, 2010), not more than 25 such centers are providing information to the health care professionals of the institution where the center is established and to the general public. Though a few centers facilitated the access to their service by toll free numbers, mobile applications, compared to the number of health care setups and the massive population requiring these services, the existing numbers of drugs and poison information centers are significantly less. The country needs many more such centers and professionals as full time drug information specialists offering unbiased, evidence based information for better patient care.

The Pharmacy Profession in India

Pharmacy, the third largest health care profession in India, has a workforce of about one million registered pharmacists in India distributed in four major domains; 55% in community pharmacy, 20% in hospitals, 10% in industry and regulatory roles, and about 2% in academia (Sahu et al., 2016).

Industry

The Indian pharmaceutical industry which was almost nonexistent in the early 1970s has grown today to be one of the largest in the world, with the approximate value of about US$ 8 billion (Shah, 2012). Globally, the Indian pharmaceutical industry ranks 4th in terms of volume and 13th in terms of value and ensures the availability of essential drugs to the majority of the Indian population at affordable prices (Shah, 2012). The highest numbers of USFDA approved manufacturing plants outside US are in India and about 85% of the formulations manufactured are sold within the country (Shah, 2012). From the mere volume of INR 100 million during independence in the year 1947, the Indian pharmaceutical market had a value of INR 10 billion in March 2018 (https://www.springer.com/cda/content/document/cda_downloaddocument/9783790828757-c2.pdf?SGWID=0-0-45-1353130-p174515562; http://pharmabiz.com/NewsDetails.aspx?aid=108358&sid=1). As per the white paper report (http://ficci.in/spdocument/22944/india-pharma-2018-ficci.pdf) published by the Federation of Indian Chambers of Commerce and Industry (FICCI) in February 2018, the Indian pharmaceutical industry not only contributes to the local market but holds a significant share of the global market as well. 50%–60% of vaccine demand is supplied by Indian pharmaceutical industries; about 40% and 20% of the generics dispensed at US and UK respectively are from India. 60% of global ARV drugs and 30% of annual UNICEF requirements are supplied by Indian pharmaceutical market players. It is also projected that India will become one of the top three pharma markets by 2030.

Table 1 Various pharmacy programs offered in India

Sl. No.	*Name of the program*	*Number of years*	*Number of colleges*[a]	*Number of approved intake**
1.	D.Pharm.	2	1194	70,541
2.	B.Pharm.	4	1272	97,494
3.	M.Pharm. (12 specializations approved)	2	733	23,126
4.	Pharm.D.	6	237	7,110
5.	Pharm.D. (post baccalaureate)	3	111	1,110
6.	B.Pharm. (Practice)	2	24	960

[a]As on June 2018, according to the official website of PCI (http://www.pci.nic.in/home.html)

Education

Pharmaceutical Sciences

The first pharmacy college in Asia was started at Goa, India in the year 1842 by the Portuguese (http://www.ipapharma.org/news/career%20booklet.pdf). An institute for training compounders in pharmacy was established at Madras (now Chennai) in 1899 followed by the commencement of a similar program by the state medical faculty of Bengal in 1928. These were considered the earliest pharmacy institutes in the country and in the Asian continent (Tharappel et al., 2014). However, the department/college of pharmacy established in 1932 at Banaras Hindu University (BHU) by Professor. M.L. Schrof, fondly known as "Father of Pharmacy Education in India" offered a formal undergraduate degree program, Bachelor of Science (B.Sc.) in Pharmaceutical Chemistry This created the momentum in structured pharmacy education and paved the way for introducing a 3 year Bachelor of Pharmacy (B. Pharm.) program in 1937 at BHU (Basak and Sath, 2008) and the other Universities. Andhra University (1937), Madras University (1938), Bombay University (1943), Punjab University (1944), and L.M. College (1947) continued the legacy of university-based pharmacy education.

In 1948, the Pharmacy Act was enacted to regulate the pharmacy profession in the country (The Pharmacy Act, 1948). The Pharmacy Council of India (PCI), the body which regulates pharmacy education and the profession was established in 1949 and the first Education Regulations (ER) were framed in 1953, which was further amended in 1972, 1981, and 1991 (Sachan et al., 2012). All these four ERs refer to Diploma in Pharmacy (D.Pharm.) program. At present the regulations, curriculum for the other pharmacy programs, B Pharm, M Pharm, Pharm D are made available by PCI and are common to every institution imparting pharmacy education in the country.

Pharmacy programs are offered at three-tiers in India: D. Pharm., B.Pharm., Doctor of Pharmacy (Pharm.D.). The details of programs approved by PCI are summarized in **Table 1** and the scope, salient features of all such programs are discussed here.

- *D.Pharm.:* D.Pharm. is the minimum qualification to become a "Registered Pharmacist" in India. This program comprised of 1500 h of teaching with a share of 57% and 43% of didactic teaching and laboratory work spread over 2 years followed by 500 h of onsite training in dispensing of drugs. The curriculum is introductory in nature and thus trains pharmacists for dispensing and the sale of medicines either in hospital or in community pharmacies rather than providing any professional or pharmaceutical care services. D.Pharm. qualified pharmacists constitute the majority of the workforce among registered pharmacists in the country.
- *B.Pharm.:* The curriculum of B.Pharm. program in India is traditionally focused on the industrial aspects of the pharmacy profession rather than clinical practice concepts. The B.Pharm. graduates are groomed as the work force for pharmaceutical industry in the areas of pharmaceutical sales and marketing, manufacturing, quality control. B.Pharm graduates play a very small role in community pharmacy practice.
- *M.Pharm.:* This 2 years postgraduate program after B.Pharm enables the aspirants to choose their study in 12 specializations approved by PCI. The program is structured to have 1 year of education and training with theory and practical 1 year dedicated for research work leading to submission of a dissertation. It is noteworthy that among these 12 specializations, all except "Pharmacy Practice" are industry focused.

Thus, from inception the higher education in pharmacy both at undergraduate and post graduate levels in India focused on the needs of industry rather than pharmacy practice (i.e., pharmaceutical care or patient care). This structure therefore has limited the potential impact of pharmacists on the real and growing health care needs of the Indian population.

Pharmacy Practice Education

- *Pharm.D.:* The Pharm.D. program in India typically consist of two phases; theory and practical courses in the first 5 years (Phase I) followed by a 6th year internship (Phase II) consisting of "Introductory Pharmacy Practice Experiences" (IPPE) and "Advanced Pharmacy Practice Experiences" (APPE). The subjects included in phase I are logically sequenced and advance year on year with basic biomedical, pharmaceutical sciences and administrative pharmacy subjects in the first 3 years to build the foundation followed by intensive teaching of pharmacy practice subjects in the last 2 years. The 5th year also comprises a clerkship training in hospital wards and community pharmacy for a minimum period of 500 h (20 h per week dedicated for a minimum of 25 weeks in

an academic year) and 6 months' research work done in a group with not more than 4 students, leading to submission of a dissertation. The overall hours of teaching and training in Pharm.D. program have 29% didactic teaching, 16% practical in laboratories, and 55% of clinical and community pharmacy training.

- *Pharm.D. (PB).* : This is a 3 year program after B.Pharm. in which the students join directly the 4th year of the Pharm.D. program and pursue the same program along with the regular Pharm.D. students.
- *B.Pharm. (Practice).*: The curriculum of this 2 year bridging program for practicing pharmacists with D.Pharm. qualification includes the subjects of pharmacy practice to equip them to provide professional pharmaceutical care services. The practicing pharmacists pursue this program as a week-end (part-time) course with at least 10 contact hours per week.

More details about these programs are available from the respective regulations available from the official website of Pharmacy Council of India (http://www.pci.nic.in/home.html).

Evolution of Pharmacy Practice Education

The evolution of pharmacy practice education and inception of the Pharm.D. program were not knee-jerk reactions by the regulators or ill-conceived ones as criticized by a few professionals (http://www.pharmabiz.com/NewsDetails.aspx?aid=75997&sid=1), but rather a well-planned response with the vision of matching global standards of pharmacy education. This argument is substantiated by comparing the historical perspective of pharmacy practice and Pharm.D. to international standards. For example, in 1992, the Pharm.D. degree was approved as a professional degree in Pharmacy by the American Association of Colleges of Pharmacy (AACP) (Buttaro, 1992) and in 1997 the Accreditation Council for Pharmacy Education (ACPE) mandated all colleges of pharmacy to convert their degree programs to Pharm.D. by refusing accreditation for Bachelor of Science programs effective from the year 2000 (Carter, 2016). In the same decade, parallel processes occurred in Indian pharmacy education with the introduction of the first specialization in "Pharmacy Practice" at Masters degree (M.Pharm.) level in 1997 at JSS Colleges of Pharmacy Mysore and Ooty through a joint Indo–Australian program of cooperation (Nyfort-Hansen and May, 1998). This program was associated with the introduction of clinical pharmacy services at a private teaching tertiary hospital and a district headquarters secondary care public hospital respectively.

This was achieved through the planning and efforts initiated in the year 1992 by the JSS Colleges of Pharmacy, Mysuru and Ooty with the assistance of Frank May and his colleagues at Repatriation General Hospital (RGH), in Adelaide, Australia. Under a Memorandum of Understanding (MoU) in 1995, four faculty members of JSS Colleges of Pharmacy including the first author of this chapter, were trained in Australia and acquired a graduate diploma in clinical pharmacy from the University of South Australia (Berg, 2001). Thus, the M. Pharm program in the specialty of "Pharmacy Practice" started by these two colleges with trained faculty members, supported by clinical pharmacists from RGH, served as a reference and model sites for the entire country to offer similar educational programs and training (Nyfort-Hansen and May, 1998).

The "Mysore Declaration on Clinical Pharmacy Practice and Education in India" presented in a national meeting on "Hospital and Clinical Pharmacy" held at Mysore in the late 1999 was another milestone in the journey of pharmacy practice education in India. This declaration discussed the standards for the practice of clinical pharmacy in India including but not limited to: Training and facilities, Syllabus, Patient-focused teaching, Hospital infrastructure requirements, Resources, Interested and committed management, Inspection and approval of institutions (Berg, 2001). Two decades later in 2018, about 60 pharmacy colleges are offering M. Pharm program in Pharmacy Practice/Clinical Pharmacy/Hospital and Clinical Pharmacy specializations (http://www.pci.nic.in/home.html). The shifting of pharmacy education away from the traditional industry-focused stream to new postgraduate options in pharmacy practice can be seen as a pivotal development for the pharmacy profession in India.

After gaining experience for about a decade in the education and training requirements of the pharmacy practice curriculum, the Indian pharmacy fraternity decided to introduce the Pharm.D. degree, a 6-year professional doctorate program to train the professionals specialized in pharmacy practice and clinical pharmacy services. PCI introduced this new program:

1. Abolishing the existing B.Pharm. program and introducing a new Pharm.D. program
2. Upgrading the existing B.Pharm. program with additional years of study on clinical pharmacy curriculum
3. Introducing Pharm.D. program in parallel to B.Pharm. program and recognizing both as registrable qualifications for practicing the profession in the country

The decision of choosing the third option is well supported by data indicating that the Indian pharmaceuticals market has increased from US$ 6 billion in 2005 to US$ 36.7 billion in 2016, with a compound annual growth rate (CAGR) of 17.90% between the period 2005–16 (Parthasarathi et al., 2002). It is also forecasted that by the year 2020, on the basis of incremental growth, India is likely to be the top three pharmaceutical markets by incremental growth and sixth largest market in absolute size in the world (Parthasarathi et al., 2002). It is estimated that India's cost of production in the pharmaceutical sector is up to 60% lower than that of US and almost 50% compared to Europe, which gives India a competitive edge in pricing pharmaceuticals for the global market (https://www.ibef.org/download/Pharmaceutical-January-2017-D.PDF) These statistics reveal the growth of the Indian pharmaceutical industry and also the professional scope for B.Pharm. graduates with high demands for B. Pharm graduates trained in industrial perspectives.

On the other hand, the growth of the health care industry has also been massive, representing one of the largest sectors in India in terms of both revenue and employment in the period between 2008 and 2020. The total size of the Indian health care industry which

was about US$ 100 billion in 2015 will touch almost the three times the figure of US$ 280 billion by 2020 with CAGR of 16.5%, reports revealed (http://www.india-opportunities.es/archivos/publicaciones/Healthcare-January-2016.pdf). The majority of the secondary, tertiary and quaternary health care institutions are established by the private sector especially in urban centers and is poised to grow to US$ 280 billion by 2020 (http://www.india-opportunities.es/archivos/publicaciones/Healthcare-January-2016.pdf). Further, it is estimated that from 2009 to 2015, about 3043 clinical trials were carried out in India which also opened a huge market for employment for Pharm.D. graduates with about 1000 companies in the specialized sector of the industry known as Contract Research and Manufacturing Services (CRAMS)(http://www.india-opportunities.es/archivos/publicaciones/Healthcare-January-2016.pdf). Thus the decision of policy makers to introduce the Pharm.D. in India in parallel to the B.Pharm. program has served India well.

There has been debate about abolishing the Diploma in Pharmacy (D.Pharm.) as a registration qualification, and to mandate B. Pharm. as the minimum qualification for practicing the profession of pharmacy in India (http://www.pharmabiz.com/ArticleDetails.aspx?aid=109315&sid=1). This has proven controversial for two reasons: firstly, the proportion of B.Pharm. graduates choosing community pharmacy as their career is negligible and even if it is chosen, they are limited only to urban areas but not in rural. Secondly, upgrading the qualification of practicing D.Pharm. qualified pharmacists to degree would be time-consuming as they constitute about 75% of all pharmacists, with the community and hospital sectors sharing 55% and 20%, respectively (https://www.fip.org/files/fip/HR/final%20report/Part1.pdf). Further, such a major step toward shifting the professional standards of a country like India requires strong policy decisions and enormous resources by both central and state Governments.

However, PCI has introduced a bridging program called B. Pharm (Practice) through its regulation, "Bachelor of Pharmacy (Practice) Regulations, 2014" (**Table 1**; http://www.pci.nic.in/home.html). Pharmacists from community and hospital settings with a minimum of 4 years' professional practice experience can join this program to upgrade their qualification to degree which will be registered as an additional qualification. The success of this effort by the PCI should be assessed in due course as it would be premature at this time to make an assessment of outcomes. However, until professional benefits and career advancement with increased remuneration are realized, motivating D.Pharm. qualified pharmacists to pursue B.Pharm. (Practice) is likely to be a big challenge.

Having introduced the B.Pharm. (Practice) program to equip the practicing community and hospital pharmacists to provide pharmaceutical care services, PCI also redefined the roles of pharmacists in the country through its "Pharmacy Practice Regulations, 2015" (http://www.pci.nic.in/home.html) which is another milestone in the professional practice standards of pharmacy in India. Now practicing pharmacists with any qualification in either community or hospital who desire to offer any of the professional pharmaceutical care services listed in the regulation are encouraged to pursue B.Pharm. (Practice) to attain the required knowledge and skills. This regulation also paved the way for the pharmacists with degree qualification, both B.Pharm./Pharm.D. to focus their career either in community settings or in hospitals.

Thus, it is evident that the pharmacy profession and practice standards in India is evolving and progressing very systematically at a slow and steady pace. It is anticipated that by 2030, the professional practice standards shall reach international bench marks.

Practice

Historically the patient care role of the pharmacy profession in India was not developed to the same extent as roles in industry. The primary focus of pharmacy education toward industrial aspects for more than 70 years is one of the prime reasons for this. In addition, the pharmacists registered and licensed to practice in both community and hospital pharmacies were dominated by D. Pharm. holders who lacked the knowledge and skills needed to provide pharmaceutical care services on par with international standards.

Community Pharmacy Practice

As per the regulations of India governing the sales and distributions of drugs, each community pharmacy must have a registered pharmacist with a minimum qualification of D.Pharm. However, a significant number of community pharmacies are owned by nonpharmacists, in which registered pharmacists are employees and this sometimes leads to handling and sale of drugs by unqualified personnel. Though the minimum space requirement for establishing a community pharmacy is 10 m^2, the majority have about 20 m^2 but rarely more than 50 m^2 (Berg, 2001). In general, these retail outlets are open for about 13 h daily between 9.00 am and 10 pm and a few in urban areas are open 24 × 7 (http://www.pci.nic.in/home.html). As there are no regulations curtailing the number of pharmacies or the minimum distance between two pharmacies, community pharmacies are often concentrated in areas close to hospitals, market areas and bus stations, and urban regions. It is also common for many hospitals to have their own dispensaries through which drugs are sold to ambulatory patients and others. By default, about 99% of community pharmacies stock the formulations distributed by pharmaceutical industries either directly or through wholesalers and dispense them to the end users rather than making any extemporaneous preparations (http://www.pci.nic.in/home.html). These pharmacies stock a wide variety of products including prescription drugs, nonprescription medicines, food products such as health drinks, cosmetic products, surgical supplies, and certain medical devices, etc. depending on the location, market trends, and product demand.

Community pharmacists are paid only for the medication costs and receive no payment for pharmaceutical care services even if provided, and so there is a lack of incentive and motivation to provide professional services. The majority of patients meet their own health care expenses including purchase of drugs, unlike in the western world where many are covered by national health systems or private health insurance companies. However, the pharmacy practice regulations, 2015 of India has given provision to charge

patients for professional services if patients are willing to pay for these. The interaction between community pharmacists and prescribers are often limited to prescription clarification and permission to change brands of drugs during prescription filling.

Community pharmacists, known as retail pharmacists in India, are traditionally perceived by the public and physicians as traders of medicines rather than as professionals with the potential to provide professional services (Basak and Sathyanarayana, 2009). However, the efforts of the PCI and professional associations in the country including the Indian Pharmaceutical Association (IPA) in training them to offer pharmaceutical care services have had positive outcomes in certain areas. A distinctive example is the publication of "Good Pharmacy Practice Training Manual" by the collaborative efforts between the Drug Controller General of India (DCGI), IPA and WHO. This is used by IPA as a manual to conduct training programs for community pharmacists on various professional roles and activities (GPP, 2005). As the majority of the community pharmacy outlets are owned by individuals rather than companies, bringing these pharmacists in for training programs is a great challenge as every individual needs to be motivated toward this. Apart from the professional bodies/associations, the pharmacy colleges with pharmacy practice departments and or Pharm.D. programs also use their workforce, the faculty and students to conduct continuing pharmacy education (CPE) programs to update and upgrade the knowledge and skills of community pharmacists toward providing pharmaceutical care services.

A success story of a community pharmacy in the southern part of the country is motivational for new graduates to take up community pharmacy as their career choice. Two M.Pharm. (Pharmacy Practice) graduates established a community pharmacy in the year 2001 with many innovations at that time viz. larger premises, fully air conditioned, an exclusive space marked for patient counseling, along with pharmaceutical care/ health screening services such as measuring BP, blood sugar, BMI, medication counseling, all provided at free or subsidized cost. This novel practice attracted a huge number of patients to the community outlet, and due to this over-whelming response from patients, and their strategic plan, today the pharmacy stands as a private limited company having about 59 retail outlets across 18 cities in the state of Tamil Nadu with more than 700,000 customers registered in their database (http://thulasipharmacy.com/about.php). This reveals the potential benefits of professional services being offered at community pharmacies, and a role for these pharmacists to contribute to improving the health of the Indian population.

Pharmacists partnering with National TB Program

India accounts for about 20% of the global incidence of TB and has the highest burden in the world, adding nearly 2 million new cases annually. The indirect cost to society toward tuberculosis control is about US$ 3 billion. The Indian government has introduced the Revised National Tuberculosis Control Program (RNTCP) that includes the Directly Observed Treatment, Short Course (DOTS). Under this scheme, the full course of anti-TB drugs is given to patients. The community pharmacists in Mumbai were involved for the first time in the TB Fact Card Project, which was focused on creating awareness of TB and monitoring of medication adherence. The success of this project encouraged the stakeholders to involve about 350 community pharmacists in Mumbai and other parts of Maharashtra in the DOTS TB Pharmacists project in which the community pharmacists act as DOT providers (Nyfort-Hansen and May, 1998). The success of the Maharashtra model has led to a scale-up of this project to the entire country and it is reported that nearly 75,000 pharmacies across 4 states and 12 districts are engaged as DOTS providers to the patients near to their home (https://www.fip.org/files/fip/news/DOTS_TB_projectIndia.pdf).

Mission of combating HIV/AIDS in India

According to the UNAIDS gap report 2016, about 2.1 million people live with HIV and nearly about 86,000 were infected in the year 2015; of those about 43% were on antiretroviral drugs (UNAIDS, 2016). By recognizing the significant role of pharmacists in medication adherence and management, WHO and International Pharmaceutical Federation (FIP) jointly made a declaration on the role of pharmacists in combating HIV/AIDS pandemic (FIP and WHO, 1997). Consequently, as part of the countrywide initiative, IPA released a guiding principles document that was used for training the trainers and in-service pharmacists with the objectives of:

- Motivating pharmacists to disseminate information to the community on protection against HIV/AIDS;
- Explaining the safe use of disposable needles and condoms;
- Informing the HIV/AIDS patients about proper usage of drugs, diet, and lifestyle changes;
- Encouraging and counseling the kith and kin of the AIDS patients;
- Offering moral support to the HIV/AIDS patients to lead a normal life.

The contents of the training included pathophysiology, mode of transmission and therapeutics of AIDS, role of pharmacists in prevention of HIV/AIDS, safe use of blood and blood products, diagnostic screening tests and hazards of injectable drug use. Accordingly, about 400 pharmacists in New Delhi, 250 from Mysore and 25 from Kolkata were trained through this scheme in the year 2004 and IPA included the same in its regular training module as well (ICIUM, 2004).

Other initiatives by educational institutions in community pharmacy

Apart from these two nationwide initiatives to use the community pharmacy workforce for health care schemes, the other initiatives were limited to institutions and resulted in a few publications. Many of these studies were student projects, dissertations of M. Pharm., and or Pharm.D. programs. Few of such studies carried out were impact of patient counseling/education by community pharmacists on the quality of life of hypertensive patients (Carvalho and Nagavi, 2007), diabetes patients (Adepu et al., 2007; Kumar

et al., 2006), management of asthma (Van Sickle, 2006), self-medication (Manju et al., 2016), management of anticoagulants (Lakshmi et al., 2013), etc.

As the above case studies indicate, there is significant unmet potential for clinical pharmacists in the community to help address health care needs and disparities in India. The findings of these pilot studies should be extended to a larger section of community pharmacists in order to create a nationwide impact, but unfortunately in the majority of instances, after the study is completed, the community pharmacists do not show any interest to continue such services. Many times, the research in community pharmacy is limited to assessing the knowledge, attitude and perception (KAP) of community pharmacists on various professional activities and or assessing the KAP of patients/consumers on various services of community pharmacists. There is considerable scope for community pharmacists to extend professional services as they remain as the first contact point for the patients.

Hospital and Clinical Pharmacy Practice

Hospital pharmacy practice

The pharmacy practice standards in hospitals vary depending on the type of hospital viz. public vs. private/corporate, primary, secondary, tertiary care, and super specialty. The spectrum of drugs used also differs between the different types of hospitals.

Public Hospitals: As the drugs are dispensed free of cost at public hospitals, the generic formulations are made available rather than the branded ones. The procurement of these drugs and other surgical supplies are done through a centralized purchase procedure against a public tender, often for the entire state. The list of drugs to be procured are decided based on the essential drug list of WHO by the physician group who are in the administrative arm of government and thus the involvement of pharmacists in the process of centralized purchase procedure is very minimal.

The drugs purchased centrally are then sent to warehouses at district levels in which the pharmacists are in-charge of stock storage including cold storage and distribution to other health care facilities of the district. Once these stocks are received from the warehouse by the hospitals they are stored in the central store of the hospital from where they are distributed to the ambulatory pharmacy commonly known as the outpatient pharmacy in India. Once again here the central stores and ambulatory pharmacies are manned by registered pharmacists. In case of a PHC, the drugs received from the warehouse are stored directly in the ambulatory pharmacy of the PHC by the pharmacist. Interestingly, drug distribution into the wards for inpatients is not done by pharmacists but depends on nursing staff raising orders as per the medication orders written in the patients' case record. Thus, in the public health care system, the pharmacists are maintaining the stock of medications, inventory management and distributing them to various end-users rather than participating in the decision making process of drug procurement or in clinical medication management services.

Private Hospitals: Unlike the public hospitals, private hospitals tend to stock both branded and generic medications and depending on the size of the hospital, the responsibilities of the pharmacists vary. The number of pharmacists appointed also varies depending on the type of private health care system, viz. nursing home, small hospital, and large hospital. But, even in private settings, the hospital pharmacists do not have any role in dispensing drugs to inpatients. It is not a common practice to have a hospital formulary in India, and so the procurement of drugs in private hospitals is done based on demand and supply.

Thus, in both public and private health care settings, hospital pharmacists are involved only in drug procurement, inventory management and distribution. There is unrealized potential for pharmacists to be involved in pharmaceutical care and medication management services to improve patient health care outcomes.

Clinical pharmacy practice

The advent of the Pharm.D. program in the country has resulted in many remarkable changes with respect to the standards of pharmacy practice especially in the area of clinical pharmacy services, but only in selected private health care organizations. The large hospitals managed by corporations are very much concerned about the quality of health care services provided to their patients, who are ultimately customers. During this process, they strive to get the national and international accreditations for the quality aspects of various services offered by them. The quality standards of these accreditation procedures have a component of clinical pharmacy services with a set of quality indicators such as medication errors, drug-related problems, adverse drug reactions etc. In order to achieve the quality standards, hospitals aspiring to get accreditation establish a clinical pharmacy department, appoint clinical pharmacists and entrust the responsibilities on them.

Pharm.D. and M.Pharm. (Pharmacy Practice) graduates find placements in such hospitals, often with the responsibility to establish the clinical pharmacy department for the first time and become the chief of such clinical pharmacy divisions. In the hospitals where the clinical pharmacy department is established and clinical pharmacists are appointed, the quality use of medicines is achieved by various clinical pharmacy services viz.

- Constitution of a Pharmacy and Therapeutics Committee
- Establishment of drugs and poison information services
- Medication reconciliation
- Patient chart review
- Addressing drug-related problems
- Unit dose dispensing system
- Dose division for pediatrics

- Intravenous admixture services
- Educational services to Medical Doctors, Nurses, and other paramedical staff
- Therapeutic drug monitoring services
- Drug utilization evaluation (DUE)
- Preparing standard treatment guidelines for the institution, region
- Antibiotic stewardship programs
- ADR monitoring and reporting
- Chemotherapy preparations
- Total parenteral nutrition
- Patient education and counseling

As per the needs of the hospital, any of the services mentioned above are provided by the clinical pharmacist or a team of clinical pharmacists. These clinical pharmacists also act as student preceptors if it is a teaching hospital or providing internship training to Pharm.D. students.

Pharmacy practice and industry

A contract research organization (CRO) supports the development of pharmaceutical or biological products and medical devices on a contractual basis. The services include but are not limited to drug development, product development, process development, bio-analytical method development, preclinical studies, any phase of clinical trials apart from clinical trial management and pharmacovigilance services. India is emerging as a leading destination for CROs for various reasons such as the acceptance of intellectual property rights and international guidelines, presence of a huge population with diverse disease conditions, availability of larger hospitals with a huge patient load, educated and accessible human resources, and low operational costs.

It is estimated that the Indian CRO market will reach the heights of US$ 1973.82 million in 2023 from US$ 1000 million in 2016, at a CAGR of ~12.00%. Further, the market share by end users in the year 2017 was found to be about 22% by clinical trials and 18% by post marketing surveillance (India CRO, In Press). These two areas in which the Pharmacy Practice/Pharm.D. graduates have career opportunities constitutes about 40% of the CRO's market and is expected to expand further in future. Thus, the Pharmacy Practice/Pharm.D. graduates do not need to confine their career options to hospitals or community practice as they have wider employment opportunities in the industrial sector as well. Currently CROs absorb a higher proportion of Pharm.D. graduates than the hospital sector (India CRO, In Press).

Pharmacy practice research

Pharmacy practice research has a low profile compared to pharmaceutical sciences research, which may reflect funding limitations from research grants. Pharmacy practice research examines the impact of pharmacy practice services on patient and health care system outcomes. Though it has a wide scope to include clinical, economical, humanistic, and behavioral changes as study outcomes, in practice there is a paucity of evidence on the quality of services delivered by pharmacists, patient outcomes, and cost-effectiveness. This lack of evidence is due to the fact that by and large pharmacy practice research is carried out as part of the academic requirement to acquire a post graduate or Ph.D. degree rather than multicenter or nationwide studies to develop pharmacy practice services in a more systematic way. Carrying out such large scale studies is both an opportunity and challenge for researchers in the pharmacy practice area. Therefore, development of a professional evidence base and strategically integrating the same with practice is the first priority and will require the profession to build up research capacity in pharmacy practice.

Future Directions

Pharmacy education and practice continue to evolve in India, albeit at a slow pace due to the size, complexity, diversity, and economic realities of the country. Several key priorities have emerged:

Education

- Though the curriculum of Pharm.D. and M.Pharm. (Pharmacy Practice) are the same throughout the country, the quality of education and training provided by institutions has disparity in many aspects. Robust quality assurance mechanisms through national or international accreditation processes will help to minimize this difference if implemented in the future. Introducing a national licensure examination is a good idea to bring in uniformity in training the students.
- The pharmacy colleges need to adopt more student centric learning experiences so as to improve not only the clinical skills of the graduating students but also their soft skills to render a holistic development of the graduates.
- Novel pedagogies and assessment tools, such as OSCE/OSPE should be introduced throughout the country which is currently available only in a couple of institutions.
- As more graduates join hospitals/community settings, there is a growing opportunity for them to act as independent preceptors for future students.

Practice

- After a few years, pharmacists with higher qualifications may choose community pharmacy as their career choice as there is scope for practicing the profession and providing pharmaceutical care services.
- If the health expenditure pattern shifts from out-of-pocket to third party insurance, the possibilities of "professional services reimbursement" may improve that will further encourage many pharmacists to choose community pharmacy as their career.
- Similarly, if accreditation procedures are mandated for all large hospitals including public hospitals to ensure the quality of services provided, appointments of clinical pharmacists in those organizations will open up more and more opportunities for pharmacists.
- The ever increasing scope for CROs in India is promising for future pharmacy practice graduates including Pharm.D.

Research

- Generating robust evidence for successful implementation of pharmacy practice services is needed to obtain more funding from different agencies, and above all to convince the regulators to implement new regulations and guidelines pertaining to the profession of pharmacy.
- Apart from academic research, independent research by universities, professional bodies and associations is needed to generate reliable high quality data in pharmacy practice that can guide policy making and decision making.

Summary

Though pharmacy education and a regulated pharmacy profession have existed in India for more than 75 years, pharmacy practice education and professional/clinical practice are relatively young. In response to a paradigm shift across the globe with respect to the focus of pharmacy education and training, India strategically approached this change and took a balanced decision of retaining the B.Pharm. program to cater for the needs of the pharmaceutical industry while also introducing the Pharm.D. to strengthen pharmacy practice in the country. The experiences gained from the M.Pharm. (Pharmacy Practice) program helped institutions to more adopt the Pharm.D. program. Pharm.D. graduates are able to find jobs in CROs, academia and hospitals, as well as a small number who pursue higher studies. At present the community pharmacy and hospital pharmacy environment is not in a position to welcome revolutionary changes in practice standards as the majority of the workforce are D. Pharm qualified pharmacists who were not trained to provide professional services. However, PCI has already taken steps to bridge the gap in the knowledge and training of D.Pharm. holders through the introduction of B.Pharm. (Practice) program, and encouraged incumbents (through the pharmacy practice regulations 2015) to offer various pharmaceutical care clinical services for a professional fee, if the patient agrees. Pharmacy practice research needs to be carried out nationwide to create strong evidence in order to support policy changes by government and regulators.

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Further Readings

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Pharmacy Practice in the Gulf States

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Introduction

For nearly a decade, we sat on the admission committee of a pharmacy training degree program in a Gulf State country. Applicants' country of origin peppered the map of the wider Middle East and North Africa region: Egypt, Jordan, Palestine, Yemen, Sudan, Somalia, Eritrea, Tunisia to name a few. When asked to describe their motivations for joining the pharmacy program, many applicants offered candid revelations in their written personal statements:

> My father experienced a major drug-drug interaction that nearly took his life. Thankfully, he recovered but he suffered and his hospital stay was prolonged.
>
> My main purpose for entering pharmacy major is to prevent medication errors because I have lost one of my best friends due to a medication error.
>
> I come from a place in the world where having a proper healthcare service is an advantage that is not available to all. Considering the suffering experiences in my community, I applied to study pharmacy with the objective of making healthcare more accessible to patients.
>
> Seeing people with amputated limbs because of suboptimal diabetes care and treatment raised a crucial question in my mind, "who is responsible for these patients?"

Shortcomings in medication-related health care exerted a profound and deeply personal toll on these young individuals, so much so that each made career decisions to address and defeat them. The World Health Organization (WHO) continues to endorse a prominent position for pharmacists in health-care systems. Outlined roles include those of *decision-makers*, *communicators*, *leaders*, *managers*, *life-long learners*, and *teachers*. First and foremost, however, is the duty as a *caregiver*, described as the provision of clinical, analytical, technological, or regulatory services that must be of the highest quality. These students determined that their families, their friends, their communities deserved better care and to contribute by becoming a pharmacist.

This chapter outlines the pharmacy practice landscape into which such young pioneers enter and where they and other colleagues will continue to lead in the future.

A Geographic and Cultural Orientation to the Gulf States

The "Gulf States" are considered to represent the seven Arab countries bordering the Persian Gulf, namely, Bahrain, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates (UAE).

The estimated regional population is 90 million and ranges from 1.4 million in Bahrain (also the smallest country in square kilometers) to 36.5 million in Iraq. Historically, low population density has been accounted for by geography (extreme aridity and limited freshwater supplies); however, in recent modern times, rapid economic growth in oil and gas sectors has led to widespread migration to develop and support local infrastructures. Indeed, significant proportions of enumerated residents are expatriate workers who inevitably contribute to cultural diversification at their destination. Meanwhile, the local population structure is generally young (just over half is under 25 years of age) and technologically savvy. Such demographic elements assuredly converge to impact health-care delivery and consumption in these settings.

With the exception of Iraq, all are members of a separate group of nations, the Gulf Cooperation Council (the GCC, formed in 1981) and are governed by monarchies (constitutional or otherwise). However, this formation of contemporary states has not annulled their shared history and traditions or common languages, beliefs, and values.

Defining a culture is a complex and nuanced enterprise. One of the most notable frameworks for characterizing national values is Hofstede's cultural dimensions model (Hofstede, 2003). Through comprehensive workplace study in over 60 countries, he arrived at six features, whereby a country's collective society exhibit different behaviors or preferences along these values: *power distance*, *individualism vs collectivism*, *masculinity vs femininity*, *uncertainty avoidance*, *long-term vs short-term normative orientations*, and *indulgence vs restraint*.

Cultural dimension profiles among the Gulf State countries are largely consistent. For example, society members accept and expect unequal distribution of power (high *power distance*); interdependency exists among members (low *individualism*); tolerance for ambiguity is low (high *uncertainty avoidance*); and focus tends to be on present and past over preparation for the future (*short-term orientation*).

Other models exist for characterizing cultures but most cover similar or overlapping concepts. It is important to recognize that a national (or even regional) cultural profile cannot represent the predisposition of every individual member. This is especially true for countries with heterogeneous resident populations, such as those of the Gulf State nations. Despite such caveats, these frameworks are useful guides to understanding how governments and professionals approach health-care regulation and delivery and in turn, how it may be received by patients and families and therefore have resulting implications on health care and pharmacy practice in the region.

Pharmacy Practice in the Gulf States

Health care in Gulf State countries is available through both private and public systems. Public medical services are often free or significantly subsidized. Pharmacy practice within the Gulf States is typically governed by a national Ministry of Health (MOH) or equivalent. In addition to health-care infrastructures and delivery in their country, these bodies and its subdepartments are responsible for the regulation of drug pricing, medication access, safety monitoring, pharmacy ownership, and pharmacist licensure.

Saudi Arabia has the largest domestic drug market and purchases approximately two-thirds of all medications sold elsewhere in the region (Almemman and Aljedai, 2016). Patented drug brands dominate the supply and generic substitution by community pharmacists is uncommon, due in part to regulations, but also patient rejection of perceived inferior product. Many therapies that might require prescriptions in other jurisdictions may be self-selected by patient for purchase at community pharmacies. Most countries more strictly regulate pharmacist dispensing of antibiotics, opioids, and controlled drugs. The patient safety threats of counterfeit medication in these developing countries are also recognized and a number have outlined strategies to combat infiltration into their jurisdictions.

Electronic health records are typically only available within inpatient care settings (for example, hospitals and not in community pharmacies), but variability exists. This poses difficulties for continuity of care across public and private settings and is confounded by both residents and expatriates importing medication for personal use from other countries.

Technical medication preparation functions such as compounding and prescription assembly are also still largely conducted by pharmacists. In community settings, in particular, it may be difficult for patients to differentiate between pharmacist and non-pharmacist staff.

Expanding scopes of outpatient pharmacy practice in Gulf State countries face additional hurdles. While over 75 pharmacy degree training programs now exist, the region still relies heavily on expatriate professionals and will continue to do so for the foreseeable future (Kheir et al., 2008). As an example, Saudi Arabia annually graduates the most pharmacists (~1000), but at a rate projected to take to 2035 to completely "nationalize" its pharmacy workforce (Almemman and Aljedai, 2016). As such, uniform knowledge and skill-set remains elusive. It is additionally difficult to attract and retain pharmacists to outpatient practices in the region (particularly community pharmacy or nongovernmental operations) as competitive pay and professional atmosphere are generally lacking. Indeed, the pervading public attitude toward pharmacists' roles is as "dispensers" or "businessmen," impressions which may be reinforced when motivated pharmacists chose other workplace settings. Most Gulf State countries do have pharmaceutical societies who strive to engage pharmacists and promote their roles to society.

Despite the extrinsic and intrinsic challenges to contemporary patient care in these landscapes, the past decade has in fact marked an important period of pharmacy practice advancement in Gulf State countries, which will undoubtedly continue, fueled by the vision and commitment of its young leaders.

Bahrain

Bahrain is the smallest among the Gulf State nations and may also be considered the most developing in its pharmacy practice. In 2015, Bahrain became the last country in the region to offer pharmacy degree training domestically (a 4-year Bachelor of Science in Pharmacy at the University of Bahrain). The total pharmacist workforce is currently an estimated 550 (as many as 65% in noninpatient settings), and practice development is supported by the Bahraini Pharmacist Society, established in 1996 ("Bahrain Pharmacists Society," www.baphso.org).

The public health-care service for the 1.425 million population is based upon a series of over 25 health centers and 6 government hospitals. The largest is Salmaniya Medical Complex that hosts a number of specialized outpatient clinics and is the main center for acute care. This complement of public institutions does not include at least an additional 16 private hospitals and health units (WHO, 2007, 2017). Community pharmacies (chain or otherwise) are pervasive (145 were registered in 2014) and many are open to provide services 24 h a day (Otoom et al., 2010).

Iraq

Iraq is located in the North of the Arabian Peninsula with a population of 38 million distributed across 18 governates (World Population Prospects 2017). Health-care services are provided without charge through public hospitals and primary clinics controlled by the MOH. However, years of conflict and imposed embargoes have left many facilities deficient in medications and medical supplies and lacking in information technology. Personnel staffing is also problematic, as health professionals have also left the country during this extended time period resulting in profound workforce shortages. For example, as per 2009 data, there were just over 5300 pharmacists practicing in the public sector (Ibrahim and Wayyes, 2016). As a result, pharmacy service hours are typically truncated (7 h, from 0800 to 1500 h) and functions are largely distribution in nature. Pharmacists in the public sector may work as managers in hospital pharmacies dispensing medications to ambulatory patients or as internal hospital personnel responsible for distributing drugs to the wards. There are reports of small number of pharmacists performing direct patient care on wards of major public hospitals (Al-Jumaili et al., 2013).

In contrast, the private health system in Iraq has been expanding to account for public sector shortcomings includes 96 private hospitals, 12,000 physician clinics and 6140 community pharmacies distributed throughout the country (Ibrahim and Wayyes, 2016). However, the private sector requires cash (out-of-pocket) payment as no private health insurance exists in the country.

Iraq has a long tradition in pharmacy services. The first apothecary in history is believed to have been established in Baghdad in 754 AD (Hamarneh, 1962; Ibrahim and Wayyes, 2016). Community pharmacies are privately owned by licensed pharmacists, but there are no chain pharmacies in the country. The MOH is responsible for community pharmacy regulation and monitoring. Pharmacist presence at the pharmacy is mandatory, and consequently, operating hours depend on the pharmacist's license. Part-time license is usually given to pharmacists working in the public sector meaning the community pharmacy may open after 1600 hours. Full-time license is issued to pharmacists who are retired or resigned from the public sector (Al-Jumaili et al., 2013). The majority of medications are designated as over-the-counter (OTC) and may be self-selected by patients. Unlike other countries in the region, community pharmacists in Iraq can make generic substitution to prescribed brand name medications; however, this practice is discouraged by physicians concerned with product integrity (Ibrahim and Wayyes, 2016). Medication shortages and absent quality control in pharmaceutical industry have undoubtedly left the country vulnerable to the counterfeit drug market influencing generic and brand therapy alike. Community pharmacists in few settings offer weight, blood glucose, and blood pressure monitoring services in addition to medication- and disease-related advice (Ibrahim and Wayyes, 2016). Such scope of pharmacist practice is in part associated with the political and economic situations preventing patients from visiting their physicians when community pharmacies meanwhile are easily accessible and are freely available (Basheti et al., 2014).

In terms of formal pharmacy education, the first college of pharmacy was opened at Baghdad University in 1936. Nearly 20 now exist in the country offering 5-year Bachelor of Pharmacy degree and some Masters and Doctoral programs. Unfortunately, many qualified academics have left the country, and colleges have consequently begun recruiting its own novice alumni (Kheir et al., 2008; Ibrahim and Wayyes, 2016). Doctor of Pharmacy degree training is not available (Al-lela et al., 2012). However, The Iraqi Council for Medical Specialties approved a professional degree in 2011 under the name of the "Iraqi Board in Clinical Pharmacy," permitting pharmacists a chance to provide advance patient care activities (Basheti et al., 2014).

Kuwait

The health care for Kuwait's population (~4 million) is predominantly provided by the public sector through primary, secondary, and tertiary care facilities. Primary care is delivered by over 70 health centers distributed in the country's six governates each of which also possess a general hospital (Awad et al., 2006; "Annual Health Report 2013", https://www.moh.gov.kw/en/Ministry-Statistics).

Medication is dispensed freely to Kuwaiti nationals and expatriate residents when obtained from pharmacies in public hospitals and clinics if prescribed by a hospital physician. However, certain therapies (typically high cost drugs) are no longer provided freely to expatriates, but they may be accessed if the individual wishes to pay out-of-pocket for the prescription. The MOH regulates the standards of private care where many hospitals and clinics also have their own pharmacies (WHO, 2006, 2012).

Almost two-thirds of pharmacists in Kuwait work in the government (public) sector. Only Kuwaiti nationals are granted pharmacy license for ownership and operation from the MOH (Szadkowska and Sochacki, 2015). Community pharmacists are acknowledged as the most accessible primary care provider in the country, but study indicates the public trusts medication-related information from physicians foremost. Less than one-quarter surveyed thought pharmacists had a suitable balance between dual health-care provider and business owner roles (Awad et al., 2017). Perhaps ironically, Kuwaiti law restricts a pharmacist to ownership of a single pharmacy (Szadkowska and Sochacki, 2015). Patient attitudes toward community pharmacies are more akin to a supermarket where product is purchased (Awad et al., 2017). However, only pharmacists or medical factories are

permitted to "warehouse" medicines for resale and so in fact medication is actually not available in supermarkets or shops, unlike in countries elsewhere.

Most drugs are available from community pharmacies as OTC and may be self-selected resulting in little routine interaction between the pharmacist and the patient. Prescriptions are however necessary for antimicrobials, corticosteroids, opioids, and certain psychoactive drugs. The law mandates labeling for all medications dispensed in both private and public sectors, but workplace conditions (patient volume, patient willingness to wait) may preclude routine adherence. Community pharmacies are not obligated by law to maintain patient medication records and most therefore do not (Matowe et al., 2003).

Clinical pharmacy services have not yet take root in most public and private hospitals in Kuwait (Kheir et al., 2013). In these settings, pharmacists fulfill mainly technical functions with minimal ward-based direct patient care. However, pharmacists in at least one large governmental hospital report participation in multidisciplinary rounds, development of pharmaceutical care plans, as well as committee work on guideline development and medication safety protocols (Lemay et al., 2018). While most inpatients will have first prescription of discharge medication filled directly at hospital pharmacies, opportunities for pharmacist interaction are unfortunately limited due to workload and environment (crowding of small available space) (Katoue et al., 2014).

Domestic pharmacist training is available at the national higher education institution, Kuwait University where approximately 60 students (male and female) are annually admitted (Kheir et al., 2008). Survey has found these gradates more likely to initiate clinical services in hospitals than pharmacists from overseas programs (Lemay et al., 2018). The Kuwait Pharmaceutical Society was established in 1974 representing one of the oldest professional associations in the Gulf State region. While continuing education is not a current requirement for pharmacist licensure, the government has outlined in its Kuwait Vision 2035 intention to enhance competencies and improve the performance of the country's health-care workers with training programs, in addition to expansion in health services and infrastructure ("New Kuwait" www.newkuwait.gov.kw.en),

Oman

The Sultanate of Oman has a population of almost 2.5 million and is administratively divided into 11 Governorates ("WHO 2010," www.who.int). The current status of health care stands in sharp contrast to the state of affairs up to 1970, when only two hospitals existed in the country. In keeping with decentralization policy, the Omani MOH was tasked with the delivery of comprehensive health care through a network of hospitals, health centers, and mobile units. Three public hospitals are now joined by over 1000 private clinics and 13 private hospitals and health centers. In the 1990s, the first computerized drug information service and a national poison center were established. In 2000, the MOH established the Directorate of Rational Drug Use, a body dedicated to overseeing rational prescribing and use of medications.

Two governmental bodies under the MOH regulate and oversee pharmacy practice and services in Oman. These are the Directorate General of Medical Supplies (DGMS) and the Directorate General of Pharmaceutical Affairs and Drug Control (DGPA & DC). Together they are responsible for drug registration, pricing, and quality assurance, as well as the country's Pharmacovigilance and Drug Information Department. The DGMS oversees the procurement, storage, and distribution of medicines, surgical, and laboratory consumables to all hospitals under the MOH and provides technical supervision of pharmacy services, including standardization of hospital pharmacy practices, continuing education, and training of pharmacy personnel. The DGPA & DC is the MOH's arm for licensing community pharmacies, pharmacists, and assistant pharmacists/pharmacy technicians. Approximately 2500 pharmacists and 2200 pharmacy technicians and assistants are working in Oman ("Directorate General of Pharmaceutical Affairs and Drug Control", https://www.moh.gov.om).

The country has approximately 674 community pharmacies. Community pharmacies in Oman sell both OTC and prescription medicines in addition to other health and lifestyle products. Except for few medications classified as prescription medicines (such as antibiotics, drugs acting on the central nervous system, drug-containing hormones), most of the medicines in the country require no prescription stocked and are dispensed or self-selected as OTC products. Several large chain pharmacies own the majority of the private pharmacy business in the country, and most of these also function as agents of giant pharmaceutical drug companies ("Ministry of Health, Sultanate of Oman," https://www.moh.gov.om/en/web/statistics/annual-reports)

Pharmacy practice governance is well organized in terms of laws outlining the physical requirements of community pharmacies, licensure of pharmacists, sale and documentation of controlled drugs, and other such aspects. However, like in other neighboring countries, there are virtually no regulations governing the "advanced practice." In the absence of regulations allowing provision of any cognitive services (such as medication review and pharmaceutical care services), community pharmacists perform basic pharmacy tasks of dispensing. For example, there are very little routine patient-centered services, such as medication counseling or simple patient assessment. When a cross-section of the Omani public was surveyed, over half considered pharmacists as "venders" or "dispensers" and did not expect them to have abilities to treat minor ailments (Jose et al., 2015). Community pharmacists in Oman, also like in other countries in the region, neither keep patient medication records in the pharmacy nor do they utilize computer-based programs to thoroughly review prescriptions for drug interactions (Paravattil et al, 2017). The minority of community pharmacies are web-enabled for seeking drug-related information (Al-Farsi et al., 2014). All of these short-comings mean that an opportunity to utilize a large network of accessible pharmacies and pharmacists is lost.

An estimated one-third of the pharmacy workforce has been "nationalized" and is much higher in government than in the private sector ("Oman Health Vision 2050," www.moh.gov.om/en/healthvision2050/). Replacing expatriates with Omani pharmacists in the community pharmacy sector is a huge undertaking considering some of the realities of practice. Remuneration of pharmacists working in the private sector had traditionally been significantly lower than those in the public. As a result, Omani pharmacy

graduates express greater interest in joining large government hospitals where they have more chance to provide advanced pharmacy services for which they have been trained therefore slowing of pharmacy practice development in ambulatory and private sectors. Meanwhile, the private sector remains primarily profit-oriented market and very few cognitive pharmacy services have emerged.

Unsurprisingly, there is a progressive scope of clinical pharmacy practice in the major tertiary hospitals where young and motivated Omanis seek employment ("Sultanate of Oman Ministry of Health," www.moh.gov.om/documents/). Clinical pharmacists are increasingly accepted members of the medical team and specialized clinical care (e.g., anticoagulation, cystic fibrosis clinics) are being formed. The government sponsors Omani nationals' education in overseas baccalaureate, masters, and doctoral degree training programs and are the pharmacists performing the majority of such advanced practice roles.

In 2014, the MOH released a long-term plan for the country's health-care sector focusing on disease prevention, strengthening primary health care, and initiating health promotion activities (Al-Riyami, 2012). Health Vision 2050 also aims at increasing specialized services, emphasizing principles of patient-centered care, equity in health-care provision, accessibility to services, and information sharing.

Qatar

The State of Qatar has a population of approximately 2.7 million people. The development of oil and gas reserves and parallel infrastructure and modernization projects have led to an influx of workers posing pressure on existing health-care services; approximately 80% of the country is made up of expatriates ("Ministry of Development and Planning," www.mdps.gov.qa/en/statistics1).

The Ministry of Public Health (MOPH) is the central government authority responsible for health laws, policies, standards, as well as facility and practitioner registration, certification, accreditation (Bener and Mazroei, 2010). The main public health-care provider is Hamad Medical Corporation, a MOPH-run organization encompassing a number of national public-sector hospitals, associated-pharmacies, and medication warehouses (Kheir, 2016). Government hospitals provide free (for Qataris) and subsidized (for non-Qataris) health care and pharmaceutical services and products. The country launched its first version of a National Health Strategy in 2011 outlining a comprehensive program of reforms to advance patient-centered health services throughout its facilities aligned with the Qatar National Vision 2030 ("National Health Strategy Qatar," www.nhsq.info).

Community pharmacy services are featured in this strategy that advocates a pharmacy network supported by appropriate policy and processes for enhanced efficiency and access in order to decrease patient reliance on hospitals for filling prescriptions.

Over 500 private community pharmacies are licensed in Qatar including 19 "chain" pharmacy groups (pharmacies in these bodies number from as few as 3 to as many as 50). According to Qatar law, community pharmacies must be owned by Qatar nationals, but may be managed and run by registered pharmacists (usually expatriate pharmacists). Pharmacies sell OTC and prescription medication, as well as cosmetics, mother-and-baby products, patient-support items, and diagnostic tests. Except for a few classes of medications requiring prescription (antibiotics, steroids, hormones, and drugs acting on the central nervous system), all other medications are available as OTC (Kheir, 2016).

Services provided by community pharmacies are still largely "traditional" without extended roles or cognitive services. Notable of the many contributing factors is the absence of regulations mandating maintenance of patient records within community pharmacies to ensure the provision of seamless care across repeated patient visits. Community pharmacy in the country has not yet made the necessary strides to position itself as a prominent source for public health and primary health care. The limited role is reflected in pharmacists' high levels of professional dissatisfaction (El Hajj et al., 2011). However, it is expected the next iteration of the country's health plan (Public Health Strategy 2017–2022) will help redefine the scope of community pharmacy practice in the country through new requirements for pharmacist continuing professional development and supporting roles of pharmacy technicians, automation, and information-technology systems (Kheir and Fahey, 2011). These initiatives will also encompass practice of over 160 pharmacists who are employed at two dozen public primary health-care centers who dispense prescriptions, provide patient counseling, and education. Conversely, pharmacy services delivered from government-run hospitals include traditional roles (medication dispensing), as well as advanced practice whereby ward-based pharmacists provide care and assume responsibilities in specialized clinics (such as heart failure and anticoagulation). Similar expanded roles of de-centralized pharmacist care in private hospital settings are lacking (Kheir et al., 2013).

Several initiatives are slowly driving the practice change in Qatar. While there is no autonomous association or society representing pharmacists, the country's only College of Pharmacy assumes promotional roles for the profession and has been one of the few providers of continuing professional development nationally (Kheir et al., 2011; Wilbur, 2010). Government health-care facilities have increasingly directed new staff recruitment from this Canadian-accredited program and pharmacists with advanced degrees in clinical pharmacy from elsewhere. As of 2016, all health-care providers in Qatar (including pharmacists and pharmacy technicians) must participate in a point-based and accredited continuing professional development system for registration and licensure renewal. Best practices are also being fostered within health-care facilities whereby international accreditation is underway throughout the country. The MOPH additionally plans modernization of the national pharmacy regulatory framework through eventual creation of a national drug information unit and a pharmacovigilance center.

In June 2017, a coalition of Middle East countries abruptly imposed widespread sanctions against Qatar. The country's inability to conduct trade with a major partner such as Saudi Arabia has depleted reserves and restricted regional import of many commercial goods and medical supplies, including drugs (Tharoor, 2017). Qatar has been compelled to accelerate development and diversification of its domestic supply chains, but the long-term effects of the dispute on health delivery, research, and pharmacy practice initiatives requiring GCC-wide coordination are unknown.

Saudi Arabia

Patient care delivery in the Kingdom of Saudi Arabia is distributed across facilities under the Ministry of Health (MOH) and other government sectors, such as the Ministry of Interior, the Ministry of Defense & Aviation, or the Saudi Arabian Oil Company (Alrasheedy et al., 2017). As of 2014, there were 270 public hospitals and 2251 primary health-care clinics in the country. While the majority of care is provided free through government services, the private health-care industry is also robust (141 private hospitals and 2412 polyclinics in operation), and patients may access services at private facilities paying out-of-pocket or through insurance. Tens of thousands of pharmacists (primarily expatriate or "non-Saudi national") are employed throughout the country, mostly working in the government settings (Almemman and Aljedai, 2016; Alrasheedy et al., 2017). Established in 1988, the Saudi Pharmaceutical Society is the primary group representing pharmacists in Saudi Arabia.

There are over 7300 community pharmacies in Saudi Arabia staffed by an estimated 12,500 pharmacists (Alaqeel and Abanmy, 2015). These include independent and chain stores located throughout communities, some of which may be linked with private health-care clinics. All community pharmacies are privately owned by a Saudi-licensed pharmacist (as dictated by law) and regulated by the MOH. Government requirements include the division of inventory within the pharmacy (OTC products, prescription medications, pharmaceutical preparations, cosmetics) and special permission to stock and dispense-controlled substances (and fulfillment of the associated security requirements).

All professional operations in a community pharmacy must be performed by a licensed pharmacist. Unless designated as an OTC, therapy must not be dispensed without a prescription. However, unlike in countries such as the United States, United Kingdom, or Australia, nearly every drug is considered an OTC (Khan, 2014). Medications obtained from a community pharmacy must be dispensed in their original packages and include the package insert/patient information leaflet. The intact outer package must show the medication name, manufacturer, active ingredients, dosage form, strength, storage condition, and price. Unfortunately, there are unintended implications of such laws that adversely affect the consumer. For example, patients with strength or dexterity issues would not be able to receive therapy in a modified container. Patients with cognitive impairments or multiple medications could not receive blister-packaging of their drug regimen. Powder-based treatments (such as antibiotics) are not reconstituted by the pharmacists prior to dispensing leading to high risk for preparation and dosing error by patients at home.

Other patient safety-related aspects of community practice draw attention from authorities. In Saudi Arabia, it is common for prescription-only medication to be supplied by community pharmacies without the necessary prescription. Examples include antibiotics, oral contraception, and therapy for chronic disease (such as drugs used to treat cardiovascular conditions or diabetes). Community pharmacists may then serve as the only point of contact for patients before initiating prescription drug therapy. While wide patient access to such a public health resource can be beneficial, there may be pharmacist skill or contextual factors that prevent adequate counseling. For example, the patient themselves may not the one presenting to the pharmacy for the prescription (this may be a driver or other member of the household). When studies are conducted to understand this phenomenon, pharmacists identify influencing patient factors such as age, emotional state, and financial means. They may feel unwilling or uncomfortable to challenge patients asking for the drug by name. Self-confidence in diagnosing and selecting the appropriate medication, especially antimicrobial therapy, are also cited as reasons to dispense treatments without the necessary prescription (Bahnassi, 2016a; Bahnassi, 2016b; Kashour et al., 2016; Al-Rukban et al., 2012). Many pharmacists do not find this practice problematic, but regulators conversely have concerns that perceived abilities may not match objectively documented knowledge of skills. Yet another cited reason is unintentional violation of the law; pharmacists are not always familiar with the medication prescription status. Others accurately concede that "if we don't sell it, someone else will" (Al-Mohamadi et al., 2013). Government resources to monitor and enforce legislation are lacking and are believed to have exacerbated these practices. In the capital of Riyadh, as an example, less than a dozen health directorate inspectors are responsible for thousands of community pharmacies.

Current conditions for pharmacy practice and advanced pharmacist roles are generally considered superior in in-patient settings (Al-jedai et al., 2016). Pharmacists are permitted to make medication changes and dosage adjustments in a number of institutions. Specialized pharmacy services are established in a number of the tertiary- and secondary-care hospitals, including pharmacist-run clinics for cardiology, anticoagulation, oncology, pain, and solid-organ transplant. As these care models are new to the country, the MOH is proceeding conservatively and often in collaboration with external international agencies and societies to guide planning and execution. Such clinics are also often staffed by "consultant clinical pharmacists" who have completed their education and postgraduate training abroad (e.g., Europe or the United States).

Indeed, Saudi Arabia visibly invests in advanced and international training of its pharmacists. Saudi-national pharmacy graduates are often supported to continue professional development overseas and return to the country to assume leadership positions in patient-care settings, government, and academia. Many such pharmacists are responsible for devising and implementing the 2010–2020 strategic plan for the MOH National Pharmacy Practice Programs. Eighty projects are intended to advance the MOH mandate to "*provide the best pharmaceutical and clinical care [using] high quality, modern technology, [at] the most reasonably-priced cost for patients*" and covers more than 7000 community pharmacies, 2200 primary care centers, and 400 hospital pharmacies across both public and private sectors (Alomi, 2015).

United Arab Emirates

The United Arab Emirates consists of seven emirates: Abu Dhabi (the capital), Dubai, Fujairah, Umm Al-Quwain, Ras Al-Khaimah, Ajman, and Sharjah. An affluent country of over 9 million, approximately 3.6% of its Gross Domestic Product (GDP) is allocated to

health-care spending (Blair and Sharif, 2012). Health-care services are offered free of charge to UAE citizens. For expatriates, health insurance is mandatory but usually provided by the employer. The MOH regulates and monitors health-care and pharmacy services in concert with the Health Authority of Abu Dhabi (HAAD) and the Dubai Health Authority (DHA) in these respective emirates. The MOH alone monitors services in the other parts of the country. Service quality is generally felt to have improved with the advent of the two additional semi-decentralized regulatory bodies, but is also coupled with some shortcomings in functions and task delegation among them (Hassan et al., 2017; Rayes et al., 2015; Sadek et al., 2016).

There are an estimated 1500 community pharmacies in the UAE (independent and chains) and all are privately owned. Nonpharmacists are permitted to own community pharmacies, but they must be operated by pharmacists. Pharmacies are open throughout the week for an average of 13 hours daily. Inventories include cosmetics and baby products in addition to medications and medical supplies (Rayes et al., 2015). The majority of medications in UAE community pharmacies are OTC and can be sold without a prescription. Exceptions include narcotics, psychotropic therapies (including antipsychotics, antidepressants, and benzodiazepines), and other substances considered "controlled," such as isotretinoin, misoprostol, dextromethorphan, octreotide, pimecrolimus, hormone therapy (Yeboah and Yeboah, 2014). The UAE has an expanding pharmaceutical industry regulated by the MOH (Hassan et al., 2017). The HAAD is in particular support of the local generic drug market and has developed policy for generic-only prescribing. While physicians persist in prescribing brand name products, in this emirate, pharmacists have the right substitute with generic alternatives (Hassan et al., 2017; Rayes et al., 2015).

Although many community pharmacies are staffed by two or more pharmacists, over two-thirds of pharmacies dispense less than 100 prescriptions at day (Hasan et al., 2012; Rayes et al., 2015; Sadek et al., 2016). Community pharmacists are additionally responsible for monitoring controlled substances, maintaining inventories, and interacting with insurance companies for medication approvals (Dameh, 2009). Professional roles are often limited to drug dispensing and basic counseling (drug dosing and administration). While it is expected that community pharmacists would offer patient counseling and advice regarding appropriate and rational use of medications, several barriers hinder provision of advanced pharmacy services in the UAE, including the lack of access to information resources and electronic medical records at community pharmacies, physician trust in the pharmacist skills, patient demand for these services, and the business image of the pharmacists in the country (Hasan et al., 2012). High pharmacist turnover associated with excessive workload, long hours, and professional dissatisfaction serves to exacerbate these circumstances (Hasan et al., 2012).

Conditions and scope of practice in the hospital sector may be considered more favorable to pharmacists. Pharmacists review medication orders, fill prescriptions, and provide basic counseling to patients at in-patient or outpatient pharmacies inside government or private hospitals. However, some institutions possess "smart pharmacies," where medications are dispensed by a robot and therefore freeing pharmacist time to interact with patients. Clinical pharmacists provide pharmaceutical care in direct patient-care settings at several hospitals and a few have developed one-year Pharmacy Practice Residency (PGY-1) accredited programs.

Domestic pharmacy training in the UAE was first provided to female students in 1992 by the Dubai Women's College. Seven colleges now offer undergraduate pharmacy education with some offering a Masters or PharmD degrees. Despite the presence of these colleges, the majority of licensed pharmacists are expatriates who obtained their degrees elsewhere (e.g., Egypt, India, Jordan, Philippines) (Rayes et al., 2015). Pharmacist licensure issued by MOH (or if applicable, HAAD or DHA) is required for practice in UAE. In certain emirates, evidence of continuing education is mandatory for renewal. The "Emirates Pharmacy Society" is a national association promoting the profession and providing continuing education opportunities (Rayes et al., 2015).

Increasing immigration to the UAE has placed added demand on its health-care system. As a result, the government has increased services and pledged health-care excellence in its 2021 Vision by achieving public and private hospital international accreditation. Additional public health and safety initiatives by the MOH include establishing national pharmacovigilance centers for monitoring of drug products and adverse drug reactions as well as medication error reporting from clinics, hospitals, and community pharmacies (Hassan et al., 2017).

Conclusion

Pharmacy practice in the Gulf States is a true study in contrast. The region is home to what is widely considered the "cradle of civilization" (modern day Iraq) and the source of some of the earliest documented records of pharmacists and formularies. Unfortunately, continued evolution from the long tradition in pharmacy here is stagnant, in part due to enduring political and national instability. Conversely, the governments of younger and newly oil-and-gas affluent states are investing heavily in health-care infrastructure and its professional workforce. Considering both ends of this spectrum (and in between), the region still faces challenges to reach and maintain standards of contemporary pharmacy practice, not least of which include: few available competency-based pharmacy educational opportunities and the reliance on expatriate pharmacists with heterogeneous and product-centered training; low public expectations of basic pharmacist roles; restrictive policies and resistance to expanded scopes of community practice; and preferred professional atmosphere of inpatient settings by new graduates.

Such clear and consistent accounts of barriers to advancing pharmacy practice in Gulf State nations offer ideal insight on directed approaches to move the profession forward. Momentum from emerging successes in the delivery of pharmacist care for specific populations (e.g., perinatal care, diabetes, and cardiovascular disease) within primary care settings can be further exploited as a strategy to extend nondispensing pharmaceutical services to other outpatient settings, perhaps initially at a small number of

"concept" or "model" community pharmacies where trained pharmacy technicians could instead assume most product-oriented tasks. Increased visibility of pharmacists engaged in health and therapeutic-oriented dialogue with patients (e.g., medication counseling and monitoring, OTC self-selection) over time is necessary to iteratively shift public opinion of pharmacy roles and expectations for their services. Ongoing development and quality assurance of domestic education programs and health-care environments (e.g., international accreditation initiatives) and government sponsorship for advanced professional development opportunities overseas will continue to build capacity of those exposed to contemporary pharmacy paradigms and their execution. Subsequent support for these advanced trained locals to assume positions of influence in government and policy decision making will be critical to implementing the changes required to facilitate the fundamentals of pharmaceutical care and patient safety. These include a commitment to web-enabling community pharmacies and mandating a shared electronic health and medication profile accessible across public and private and inpatient and outpatient settings, as well as review of community pharmacist reimbursement schemes. Similarly advocating for pharmacist members as stakeholders in the design plan and implementation of health-care infrastructure projects and national health programming initiatives would enable incorporation of perspectives that could have wide and long-term impact on how pharmaceutical care is delivered.

The future of pharmacy practice in the Gulf State will rely on these and other young motivated pharmacists, longstanding residents, and nationals alike, to push for change, innovate, and capitalize on new opportunities afforded by national expansion projects to contribute to enhancing cultures of patient-centered care and prominence of pharmacist roles there within.

Glossary

ASHP American Society of Health-System Pharmacists
DC Directorate General of Pharmaceutical Affairs and Drug Control
DGMS Directorate General of Medical Supplies
DHA Dubai Health Authority
GCC Gulf Cooperation Council
GDP Gross Domestic Product
HAAD Health Authority of Abu Dhabi
KSA Kingdom of Saudi Arabia
MOH Ministry of Health
MOPH Ministry of Public Health
NHS National Health Strategy
OTC Over-the-Counter
UAE United Arab Emirates
WHO World Health Organization

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Pharmacy: A Business, A Profession, Both, or Neither?

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Pharmacy, like many health care providers, has undergone significant change over time. Some of these changes, such as the ability to provide immunizations, have been quickly adopted (Baroy et al., 2016). While other changes, such as completing medication reviews and medication therapy management (MTM), have been more slowly integrated (Stafford et al., 2017). These changes, and whether or not they have been taken into pharmacy practice, have prompted much discussion, and soul searching, amongst pharmacists and pharmacy educators. For some this soul searching has been geared toward understanding systemic reasons behind pharmacists' lack of change (Roberts et al., 2006, 2008). Others have focused on pharmacists as being the barrier to change (Rosenthal et al., 2010, 2016). Still others have focused on pharmacists' lack of integration into the health care system (Harding, 1997). Some have also pointed out the lack of professionalism of students as future pharmacists (Brown and Ferrill, 2009). While still others have pointed out that within pharmacy practice there is no consensus on how pharmacy defines professionalism (Wilson et al., 2010).

These final two points bring to light a long-standing debate within pharmacy that can be ultimately related back to the first three observations. In particular, this debate focuses on whether or not pharmacy can be considered to be a profession in the same way that medicine or law have been. Some have suggested that there is a disconnect between the true mission of the "profession" of pharmacy, and seemingly contrary images of pharmacy as a "business." *As such, the primary objective of this article is to examine the following question: Is pharmacy a profession, a business, both, or neither?* To begin to address this question, a brief recap of the history of pharmacy will be provided. Then a review of past sociological literature defining and describing professions will be outlined. This will be followed by a discussion of the threats to pharmacy being considered a profession, and conclude with a discussion of the future of pharmacy.

Please note that the following discussion may be uncomfortable. This article will revisit discussions of pharmacy that many people feel are better left in the past. However, ignoring this past and its influence on how members of the group have been, and continuing to be socialized, impacts how the practice of pharmacy does, or does not, move forward. Therefore, *the secondary objective of this article is to build a case for why carefully considering the possible answers to the question posed in the primary objective is important for pharmacy and its future.*

A Brief History of Pharmacy

Since ancient times people from various civilizations have utilized "remedies" from the natural world to address human illness. While understandings around the origins of illness, and the abilities of plants, animals, and minerals to treat it have changed over time, there have always been men and women tasked with returning health (Please note that the following overview of the history of

pharmacy is meant to be cursory, if the reader is interested in getting more detailed information please see Kremer and Urdang's History of Pharmacy (1976) (Sonnerdecker, 1976).). Examining the texts and histories left by various civilizations, it is often difficult to draw firm distinctions between those who would now be considered physicians and pharmacists (Sonnerdecker, 1976). In fact, in many rural areas, the physician and the pharmacist was often the same person (Sonnerdecker, 1976). It was not until the 11th or 12th century, depending on which European country is being considered, that pharmacy as a practice distinct from medicine began to flourish (Sonnerdecker, 1976).

However, this separation did not eliminate all of the problems for pharmacists. While physicians and pharmacists continued to vie for influence, a battle also began between the druggists, chemists, apothecaries, who would later be more formally known as pharmacists, and the "spicers" (Sonnerdecker, 1976). Spicers (épicier) were importers and wholesalers of bulk spices and drug products from the orient, but lacked formal training in the preparation of medications (Sonnerdecker, 1976). Eventually, pharmacists were able to gain formal control of the creation, and distribution of medicines as prescribed by a physician, through the delegation of the authority to inspect and regulate the quality of drug products (Sonnerdecker, 1976). However, this authority is a relatively recent development, not being granted in Britain until the 1930s. (Sonnerdecker, 1976)

As time passed, the position of pharmacists was further codified through the development of associations, societies, and colleges and schools of pharmacy. In the United Kingdom, the Royal Pharmaceutical Society was founded in 1842. In the United States, the American Pharmacists Association (APhA) became the country's first national pharmaceutical organization in 1852. The development of these associations took place alongside that of the legal regulation of pharmacy (Sonnerdecker, 1976). This licensure process began in the Territory of New Orleans in 1808, and spread to the rest of the country thereafter (Sonnerdecker, 1976).

As technological and manufacturing abilities advanced in the 20th century, pharmacists transitioned from being the makers and distributors of drug products to primarily the distributors (McCormack, 1956). This role was further cemented in the United States through the code of ethics promoted by the APhA from 1922–69, and the 1951 Durham-Humphrey amendment to the Food, Drug, and Cosmetic Act (Hepler and Linda, 1990). As such, pharmacists began to stake out a greater place in the provision of health care directly to the population. The Nuffield Report from the UK proposed and led to the extension of pharmacists' role to include, "advice to patients on minor ailments, keeping patient medication records, offering domiciliary services, advice to general practitioners and providing diagnostic testing, such as measurements of blood pressure, blood glucose and cholesterol levels" (Harding, 1997, p. 549). This shift from the creation of medicines to dispensing them marks the initial questioning of whether or not pharmacy could be considered a profession as group members sought to legitimize their role in patient care.

Definitions of Professions

Sociological Definitions

Much of the discussion about pharmacy as a profession began in sociology, which during the early 1950s was particularly interested in characterizing occupations to understand power differences between them (Newton and Paulshock, 1982). In particular, these early scholars were looking to answer very grand questions about human nature, and understand how people could have justified participation in the atrocities of the Second World War. While the following discussion should not be considered an exhaustive examination of the sociology of professions, it does provide guidance to meet the objectives of this article (see Further Reading).

According to some scholars there were two main schools of thought on the nature of professions, the "Harvard School" and the "Chicago School" (Newton and Paulshock, 1982). To the Harvard School, a professional occupation was characterized by a high degree of social importance, a complex knowledge base requiring extensive training, and a high degree of uncertainty, responsibility, and resultant stress (Newton and Paulshock, 1982). The "Chicago School," saw professions as a "semi-mythic construct"(Newton and Paulshock, 1982). In practice, this meant that members of the profession actively persuaded society to accept their "professional" status, as a means of obtaining social and economic advantages, by keeping aspects of their practices secret from the general population (Newton and Paulshock, 1982).

Using the example of physicians, it is possible to see their professional status from both the Harvard School (HS) and Chicago School (CS) perspectives. Physicians possess a great deal of social importance as is evidenced by their continued placement at the top of lists of most prestigious and/or trusted professions each year (HS/CS) (McCarthy, 2016, Butterfield, 2017). Furthermore, becoming a physician requires tremendous and lengthy training (an estimated average of 14 years post high school; Emanuel and Fuchs, 2012) (HS), and failing to apply this knowledge appropriately can result in injury or even death, leading to a high degree of stress (HS) (Rabatin et al., 2015). Physician groups have also self-advocated and amassed a great deal of power in the process. For example, during the development of Canada's single payer medical system, the Canadian Medical Association fought vigorously to maintain their previously independent status, and to this day work as state contractors not employees (CS) (Simpson, 2012).

Following the HS perspective, the first definition of professions suggests that they are occupations with specific training that provide a skilled service or advice for a definite fee (Denzin and Mettlin, 1968). The authors of this definition also state occupations that transform into professions, " . . . develop special codes of ethics, engage in formalized recruitment patterns, establish formal institutions to transmit . . . [and] develop social organizations to insure the perpetuation of the profession . . . " (Denzin and Mettlin, 1968;p. 376). Through this process occupations gain control over a particular, "social object" (Denzin and Mettlin, 1968). For example, the social object of medicine is generally considered to be the process of identifying and treating the causes of illness. The authors also state that occupations are professions if they, " . . . claim a mandate to define what is proper conduct of others toward the matters concerned with their work" (Denzin and Mettlin, 1968, p. 380). One example of this kind of mandate is medical

associations' objections to independent pharmacist prescribing (Pojskic et al., 2014). As a part of physicians' social object, the treatment of illness through the prescription of particular medications is being co-opted by pharmacists.

A second definition of professions outlines five characteristics, four of which could also be interpreted as being part of the Harvard school's perspective. The first characteristics is that a profession, "has an exclusive technical expertise based on systematic knowledge", which can only be obtained through formal training (Ladinsky, 1971, p. 25). Second, a profession has exclusive and publicly recognized control over its field of work, or social object (Ladinsky, 1971). Third, a profession has strict training standards and a code of ethics (Ladinsky, 1971). Fourth, a profession is characterized by the service idea meaning that, "technically competent work is exercised with devotion to clients' interests more than to personal or commercial interests" (Ladinsky, 1971, p. 25).

The fifth characteristic of this second definition deviates from the Harvard school into the Chicago school, as it advocates for a profession having self-control, meaning that it has the latitude to make decisions about how it approaches its work (Ladinsky, 1971). This self-control is also mentioned in the first definition through the statement, " . . . finally [professions] take on the characteristics of self-governing, autonomous institutions" (Denzin and Mettlin, 1968, p. 376). Self-determination affords the profession the ability to advocate for itself by determining how much of its knowledge is shared with the public and in so doing amass greater influence.

A third definition of professions also offers five characteristics that are similar to the previous definitions. More specifically, according to these authors, professions possess a systematic body of knowledge and theory, they have authority recognized by their clients and broad community sanction for this authority, they have a regulative code of ethics, and a professional culture sustained by associations (Anderson, 1977). These characteristics are further enshrined, and expanded upon, through definitions of professionalism applied to pharmacy students:

> "Traits of a professional include: knowledge and skills; a commitment to self-improvement and life-long learning; a service-minded orientation; pride in the profession and a dedication to advance its value to society; create a conventional relationship with those served; alertness, creativity, initiative, and innovation; conscientiousness, integrity, and trustworthiness; flexibility and punctuality; accountability for his/her performance; ethically sound decision making and moral behavior; leadership" (Popovich et al., 2011, p. 2).

Reading across these definitions, professions are characterized in the following ways: They have control over exclusive knowledge; requiring specific training, they develop a code of ethics and professional organizations to enforce that code; they obtain the social authority to provide this knowledge to both potential members of the profession and the public; and they recruit professional members who possess altruistic motivations. While some would argue that pharmacy meets these criteria, others have argued that pharmacy fails to meet the "ideal type" of this criteria (Anderson, 1977). In fact, some have argued that the only claim that can be made with respect to pharmacy is that it is an incomplete or "quasi-profession" (Denzin and Mettlin, 1968).

Threats to the "Pharmacy Profession"

Arguments for why pharmacy does not meet the ideal-type criteria often focus on "threats" to professional status. An examination of these threats suggests three themes, those that come from within pharmacy (internal threats), those that come simultaneously from within and outside of pharmacy (intermediate threats), and those that come from outside of pharmacy (external threats).

Internal Threats

Internal threats are those that stem from how pharmacy self-organizes and come from four primary areas: recruitment, training, fragmentation within the profession, and perspectives on the product of pharmacy.

Recruitment

As a profession develops, recruitment is key in how that profession distinguishes itself from all other occupational groups. Consider the "spicers" of France, who once functioned as parallel importers of drug products to pharmacists (Sonnerdecker, 1976). As pharmacists received the designated training, and consequent authority by governments, they supplanted spicers as the sole providers of prescribed medications (Sonnerdecker, 1976). This was accomplished by pharmacists advocating for legal changes making it unlawful for any other group to import and distribute drugs (Sonnerdecker, 1976). Therefore, to be called a pharmacist one needed not only the legal status, but also special training that distinguished them from mere importers.

Recruitment is also integral to the maintenance of the professional status. If a medical student was asked, "Why have you chosen to pursue a medical degree?" It would come as no surprise to receive a clichéd reply such as, "I really just want to help people." Medicine has reinforced its authority over the social objective of identifying and treating the causes of illness through the recruitment of *only* those people expressly interested in selflessly returning the public to health. However, it has been argued that pharmacy recruits future members who lack commitment to such, " . . . humanitarian and people-oriented endeavors" (Denzin and Mettlin, 1968).

For example, in a speech delivered in 1976, the speaker pointed to a number of "regrettable surveys," showing that students saw pharmacy as more of a business than a science or a profession (Anderson, 1977). That is, students from this time saw pharmacy as an entrepreneurial pathway, rather than a calling. While emphasis on the business aspect of pharmacy has waned since that time, more recent surveys of pharmacy students continue to suggest that many of them have entered the profession with little idea of what it

means to be a pharmacist (Noble et al., 2014). Some authors have posited that part of the reason for pharmacy's inability to recruit truly committed and altruistic candidates is that, unlike medicine where the social object is clear, pharmacy has failed to identify its core values (Denzin and Mettlin, 1968, Anderson, 1977).

Furthermore, each year it is possible for faculty at schools of pharmacy to identify a handful of students leaving for programs such as medicine or dentistry. In fact, the pull of medicine is so powerful that even completely trained pharmacists have left established practices to pursue medical degrees (Austin et al., 2007). An examination of the experiences of some of these pharmacists turned doctors revealed that pharmacy imposed too many limitations, such as having to defer to others to make final decisions about patient care (Austin et al., 2007)— limitations that were not present in medicine (Austin et al., 2007). While it could be argued that these few people chose poorly in coming to pharmacy in the first place, the perception of the power differential around these health care fields becomes obvious when imagining a reverse flow of students. How would a medical student leaving their program to attend pharmacy school be looked upon by fellow students and faculty?

Training

Another internal barrier of pharmacy is pharmacists' training. Early commentaries on this topic focused on the impact of courses like math, chemistry, and biology, which " . . . project a model of the pharmacist as a disinterested scientist, a man who understands, 'the principles upon which the methods of pharmacy depend'" (McCormack, 1956, p. 309). These authors go on to argue that if students trained in this way are provided opportunities to employ this scientific aptitude they, " . . . may find it satisfying enough to dismiss the publics' attitude" (McCormack, 1956, p. 309). That is, this training may generate good scientists but not good patient care providers. Along the same lines, other authors have suggested that the additional training in physical sciences, " . . . is usually at the level of such complexity . . . that it would only benefit, in a practical sense, the future graduate student" (Shaw, 1971, p. 540).

This focus in pharmacy training is an artifact of a time when pharmacists compounded of prescribed medications (Sonnerdecker, 1976). As this is no longer the case, the focus of pharmacist training has shifted to more clinically oriented services (Anon, 2015). It may be argued that this shift was accelerated by the advent of the "pharmaceutical care model" (Hepler and Linda, 1990). Pharmaceutical care is defined as, "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Linda, 1990, p. 539). Furthermore, it is intended to be patient centered in nature (Hepler and Linda, 1990).

Although the transition to this model of education is largely complete, it has fallen short. A paper published shortly after the proposal of the pharmaceutical care model found that most pharmacist respondents were not engaged in the active provision of clinical care (Schommer and Cable, 1996). Rather these respondents were engaged in information gathering and acting as a drug information resources (Schommer and Cable, 1996). More recently, reports suggest that pharmacists continue to miss opportunities to provide MTM services to patients who qualify (AmerisourceBergen, 2016, Stafford et al., 2017). This lack of uptake is compounded by traditional models of community pharmacy practice wherein, " . . . a pharmacist may spend a long period of time explaining the difference between several products [to a patient]", but neglect to charge a fee for that knowledge (Shaw, 1971, p. 540). In so doing, the patient is left with the perception that the pharmacist's consultation, and knowledge, is only relevant to the product or products under investigation, rather than to the patient's health more generally.

As such, students, especially in the community pharmacy setting are not exposed to examples of these clinical services in practice. Consequently, newly graduated pharmacists are left disillusioned. One study asking pharmacists to define their role found that in as little as 6 months' postgraduate new pharmacists said that pharmaceutical care was not a reality for their practice settings (Rosenthal et al., 2011). This lack of example may also contribute to students relatively lower rate of anticipated initiative in providing MTM services upon graduation (Urmie et al., 2007).

The reasons for this stalling out of the implementation of pharmaceutical care are complicated. As one commentator lamented the people at fault include, " . . . some educators who have failed to instill the professional ethic, chain executives and independent pharmacy owners who have degraded the profession, and employee pharmacists . . . who have allowed themselves to become professionally subservient" (Provost, 1979, p. 147). Today, pharmacy students are graduating with more clinical knowledge than ever before, but do they have what is needed to integrate that knowledge into a system that is not prepared for these new modes of practice? Perhaps, the next evolution of pharmacy training needs to be a focus on how to integrate the training students receive in pharmaceutical care into their practices. Or how to work effectively on large and diverse health care teams. Moreover, this new approach to the training of pharmacists may also impact pharmacy student recruitment. Over time, as these "new" kinds of pharmacists get into practice, the publics' interaction with and perception of pharmacists would also change attracting different kinds of applicants to the profession.

Fragmentation

The third internal barrier is fragmentation. It might be argued that the process of fragmentation started with, " . . . the new growth and professionalization of hospital pharmacy, the creation of clinical pharmacy programs, and the desire by the medical establishment for more of these" (Ladinsky, 1971, p. 29). As a result, a distinction grew between hospital/ambulatory care pharmacists and community pharmacists, or clinical and nonclinical pharmacy practices. Looking at the online resources for pharmacy students trying to decide which kind of practice to pursue, hospital pharmacy is often described as the practice wherein one would have the greatest opportunity to apply the extensive clinical knowledge they obtained in school (Hassan, 2013, Phelps, 2016). However, community pharmacy practices, particularly in the United States, often lack access to patient medical records and the resources needed to engage effectively in more complex patient care activities (Phelps, 2016, Hassan, 2013). Further distinctions are also made

within hospital pharmacy as some staff pharmacists' primary practice is reviewing and verifying orders, while clinical pharmacists' primary practice is outside of the dispensary interacting more directly with other clinicians and potentially patients (Phelps, 2016).

At one point in time, it was argued that a "monolithic community pharmacy orientation" focused on business aspects of pharmacy practice dominated pharmacy school curricula (Anderson, 1977), however, this is no longer the case. Moreover, there have been increasing efforts to further solidify pharmacists' clinical status through the expansion of both entry level doctor of pharmacy (PharmD) programs around the world, and increased emphasis on completing residency training to qualify for direct patient care roles (Murphy et al., 2006, Popovich et al., 2011, Anon, 2011). Even jurisdictions like Alberta, Canada, where legislation was passed granting independent prescribing authority without additional training have opted to transition to an entry PharmD program (Yuksel et al., 2008). As a result, it is a growing perception that there is a substantive difference between those pharmacists who graduated with bachelor's degrees and those who obtained PharmDs, as well as between those who did or did not complete a residency.

Some have argued that hospital pharmacists, and perhaps by extension clinical pharmacists, " . . . have demonstrated a personal and collective 'sense of mission' that is essential to a professional psyche" (Anderson, 1977). In particular, authors have stated that these pharmacists have honed in on the talents and abilities they bring to patient care that other members of the hospital care team do not possess or provide (Anderson, 1977). As such, hospital and community pharmacy practices are treated as distinct entities. Does this distinction make the development of a coherent vision around what constitutes pharmacy as a profession more difficult?

Perspective on the Product of Pharmacy

The final internal barrier is pharmacists' perspective on what constitutes the product, or social object, of pharmacy. According to some commentators' pharmacists in the community setting view, " . . . the drug as a product to be sold rather than as an object to direct a service toward" (Denzin and Mettlin, 1968, p. 378). By making the social object of pharmacy a physical product that can be seen and touched pharmacists are forced to advertise for a "profit" rather than a "fee" (Denzin and Mettlin, 1968). As one commentator describes: "We are paid not for our knowledge and service but for the products we dispense" (Anderson, 1977). The consequence of this perspective is that, " . . . pharmacists [compete] with each other, not on the basis of training and knowledge but on the basis of marketing" (Denzin and Mettlin, 1968, p. 378).

One possible solution to pharmacy's problem of identifying the incorrect social object would be to disconnect pharmacists from the physical drug. Efforts in this direction may be observed in pharmacist-run academic detailing programs, wherein pharmacists become drug knowledge repositories used to help improve drug decision-making (China et al., 2017). The popularity of this approach evidenced in the proliferation of these programs across Canada, as well as a growing set of research suggesting these programs yield improvements in evidence-based decision-making. (Jin et al., 2012)

Others have chosen to maintain the direct connection between pharmacists and the physical drugs, but have reimagined the social object of pharmacy as being the, " . . . symbolic transformation of a drug into a medicine" (Harding, 1997, p. 554). According to the authors this symbolic transformation has a long history of being under the purview of pharmacists who once created the physical "medicines" (Harding, 1997). Despite no longer being responsible for the physical creation of medicines, these authors maintain that a symbolic change is still taking place as the drug passes from the hands of the pharmacist to the patient (Harding, 1997). These authors go on to suggest that pharmacists' success in reprofessionalization depends upon their ability to promote, "... their knowledge and skills as mystical to the public they serve" (Harding, 1997, p. 555). An approach to professionalization also advocated for by the Chicago School. (Newton and Paulshock, 1982).

These are just three of the many differing perspectives on the social object of pharmacy. Similar to the fragmentation discussed, these multiple perspectives further complicate not only how pharmacists see themselves, but also how they are seen by nonmembers (Schommer and Gaither, 2014). As is often touted by pharmacists and pharmacy educators, pharmacists are medication experts, but a question remains as to which definition of this term impacts current and future pharmacists' practice?

Intermediate Threats

Intermediate level threats stem from what has been described as the commercialization of community pharmacy. It has always been the case for some commentators that pharmacy could not be considered a profession because of the conflicting goals of businesses and the altruistic treatment of patients by true professionals (McCormack, 1956). More specifically, how could a business owner, interested in staying in business, be trusted not to sell an unneeded product or service to a patient. In fact, one study suggested that pharmacy owners were much more likely to recommend a patient purchase a product (Harding, 1997). This concern may have been accelerated by the move away from single owner, relatively small operations to large corporations, which now employ the majority of community pharmacists (Ladinsky, 1971). Herein, the pharmacist serves two masters: the patients who need medical aid and the owners and shareholders of the corporations, who are primarily interested in profits (Ladinsky, 1971). In fact, there have been a number of recent examples of when this relationship has tipped too far in the direction of profits from instances of pharmacies supporting "pill mills" and helping to precipitate the opioid epidemic, to others accepting kickbacks from drug wholesalers to stock their drugs versus others (Anon 2017a, Sochoka, 2015, Bisgood, 2017, McLean, 2016).

Unlike physicians who have established business models wherein they act as independent contractors and the exchange of money is kept out of the public eye(Simpson, 2012), community pharmacy practice's connection to commercial endeavors is much more obvious. As one author suggested, "Even in the most exclusive prescription pharmacies, the pharmacist still uses a cash register" (Denzin and Mettlin, 1968, p. 380). Some jurisdictions, especially European countries, have addressed the concern of

nonpharmacists influencing pharmacy by limiting ownership of pharmacies to pharmacists (Gross and Volmer, 2016). However, in other countries, such as the United Kingdom, the United States, and Canada, few such restrictions exist (Gross and Volmer, 2016).

Interestingly, some research has suggested that the pressure on nonpharmacy owners may not be as great as once suspected. One study, which surveyed 646 pharmacy managers from across Canada, found that while pharmacist respondents were oriented toward their professional role, managers working in chain pharmacy settings were less oriented toward their business role than managers working in independent pharmacy settings (Perepelkin and Dobson, 2010). These findings were also supported by a study examining pharmacists clinical intervention in patients requesting assistance with OTC products, wherein nonowner pharmacists were less likely to recommend a product when their clinical judgment suggested that it was not needed (Kennedy and Moody, 2000). As such, it would seem that pharmacists who are not owners are freer from business constraints, and may be more able to focus purely on the care of patients. While more research into these findings is needed before firm conclusions can be drawn, this correlation may represent an unacknowledged opportunity for the advancement of pharmacy practice toward more clinical service provision.

External Threats

External threats are those that emanate from outside of pharmacy. The literature suggests these threats come from two main areas. The first are those attempting to curtail the role of pharmacy within health care. The second are those that act and make decisions with little understanding of the potential role of pharmacists in health care. In the following sections, players attempting to curtail the role of pharmacists in patient care will be exemplified by physician groups, and those acting with little knowledge of pharmacists' role will be exemplified by both patients and policy makers.

Physicians

At this point it is likely no surprise that medicine represents an external threat, especially given that the definition of "professions" was predicated on observations made of medicine. Medicine is the archetypal profession in health care. While an extensive discussion on how medicine was able to obtain this status is beyond the scope of this work, populations around the world have always placed high value on "healers," with insights into the human body, to decode illnesses and return health (Sonnerdecker, 1976). So physicians have been afforded broad social support in their role, as outlined by the Harvard School's definition of professions (Newton and Paulshock, 1982). However, physicians have also been careful to maintain a degree of mystery around their work, as outlined by the Chicago School's definition (Newton and Paulshock, 1982). Pharmacy, and many other health care professionals, exist in the long shadow cast by medicine (Ladinsky, 1971). Therefore, any attempt by groups, like pharmacy, to claim part of physicians' social object is a serious threat to their power.

As pharmacy has taken on a greater, more recognized, role in patient care, its understanding of itself has also changed. Arguably, this started with pharmacists increasing involvement in the detection and remedying of medication errors, which became more prominent as medication prescribing increased (Stewart and Cluff, 1972). More specifically, academic pharmacists began staking a new role by showing pharmacists' review of prescriptions could decrease medication errors (Folli et al., 1987). While this role was initially resisted by physicians, over time it became appreciated (Ranelli and Biss, 2000). However, with each "new" pharmacist role, they have had to start over with physicians showing their value to patient care. For example, in a study examining pharmacists' integration onto family medicine teams, physicians appeared to initially underestimate the contributions of pharmacists, but changed their minds as the study continued (Farrell et al., 2010).

Even as the body of evidence demonstrating pharmacists value in the active management of patients with chronic health conditions has increased, pharmacists continue to face resistance (Wubben and Vivian, 2008, Morgado et al., 2011). One relatively recent, and highly contentious, example is granting pharmacists the ability to prescribe medications. As far back as 1971, a report from the Commission on Pharmaceutical Services suggested that ultimately pharmacists should be given the ability to, and responsibility for, prescribing medications and monitoring patient outcomes (Yuksel et al., 2008). However, each time a change is proposed, or made, to legislation around pharmacist prescribing organizations like the American Medical Association (AMA), it comes out with resolutions like the one from 2012 opposing these changes (Pullen, 2012). Statements like these are particularly important because organizations like the AMA in the United States represent important and powerful government lobbies. For instance, a report from Kaiser Health News found that in 2010 the AMA spent more than $22 million supporting laws important to their members, which was more than another health lobby that year (Vaida, 2011). As such, physicians have the ability to seriously slow down, if not curtail, the expansion of pharmacists' scopes of practice.

Patients

Listing patients as an external threat may seem surprising given that pharmacists are often ranked by the public as being amongst the most trusted health care providers (Riffkin, 2014). However, there is some indication that patients' perceptions of pharmacists have shifted over time. In studies conducted in the mid to late 1970s, patients stated that they most often received drug information from friends or neighbors (Anderson, 1977). In fact, when asked to order their top sources of health information pharmacists were listed last after physicians and the media (Anderson, 1977).

It is also unclear if the current positive perception of pharmacists is based on patients' evaluations of the care they are provided or some other factor. As one commentator said when considering the proliferation of chain pharmacies, "Independents have watched with envy as the chains, recognizing that *convenience* is primary in consumer choice of pharmacy, secure the best urban shopping

center locations" (emphasis added) (Provost, 1979). This sentiment was reinforced in a study developing a pharmacy rating system wherein patient participants stated their choice of pharmacy depended on convenience, accessibility, and getting prescriptions filled quickly (Warholak et al., 2017). While patients pointed to instances wherein pharmacists had identified things like potential drug–drug interactions, they did not seem to equate this to part of pharmacists regular duties (Warholak et al., 2017). Rather, patients spoke as if the pharmacists had gone out of their way in identifying the problem (Warholak et al., 2017).

Another study wherein groups of pharmacists and patients were identified and compared over time found a mismatch between the conceptualization of pharmacists' role in the two groups (Schommer and Gaither, 2014). Pharmacists perceived great time pressures, which meant that they often neglected to provide medication advice, despite believing it to be an important part of their role (Schommer and Gaither, 2014). Consequently, patients did not seek medication advice from pharmacists, and rather relied on physicians to fill this role (Schommer and Gaither, 2014). The authors suggest that this results in a reenforcing cycle wherein pharmacists do not provide advice, so patients do not seek advice and vice versa (Schommer and Gaither, 2014).

Others have speculated that patients' misperceptions may stem from the nature of community pharmacy practice and the relationship it fosters between patients and the pharmacy. For example, even if your doctor's office houses several doctors, you will likely have your own "personal physician" who you will see every time you visit (Shaw, 1971). However, this is not generally the case in community pharmacy, where anyone on duty can be substituted in, and the personal relationship between patients and pharmacists is largely absent (Shaw, 1971). Moreover, the commercialization of pharmacy practice, with its resultant drive for efficiency and interchangability, may further compound this lack of relationship between pharmacists and patients (Provost, 1979). As such, patients are driven further away from seeing pharmacists as resources for medication information and chronic disease management assistance.

At the same time as the nature of community pharmacy practice is teaching patients to see a very narrow version of the care that pharmacists can provide, patients themselves are also changing. Some have referred to this as the "revolt of the patient," which has been driven by both media messages encouraging patients to demand their rights and an increase in patient knowledge and access to information (Traulsen and Bissel, 2004). Part of this shift is related to the availability of information online, and through democratization of internet access (Ahmed et al., 2006).

Another part of this shift, in places like the United States and New Zealand, has been the direct-to-consumer advertising of health products such as drugs (Guessous and Dash, 2015). The underlying assumption of these advertisements is that health care providers are no longer able to keep up with new medical developments, so patients must also keep abreast of medical research developments pertinent to them. Research suggests this advertising has resulted in increased prescribing, although it is difficult to determine whether or not this increase has rectified medication underuse, or resulted in medication over or misuse (Guessous and Dash, 2015). Even though direct-to-consumer advertising is illegal in most other jurisdictions, patients from around the world are exposed to them through the globalization of media products. As a consequence, it has been argued that patients today are fundamentally different from those in the past, regardless of whether or not this "revolt" has taken complete hold of the population (Traulsen and Bissel, 2004). If it is indeed the case that the patients do not completely understand the role and skills of pharmacists, this new attitude may make "reeducating" patients even more difficult.

Policy and Policy Makers

The final external threat to the perception of pharmacy as a profession comes from policy and policy makers. On the one hand, pharmacists' scope of practice has benefited greatly from policy changes (Gray et al., 2007, Yuksel et al., 2008, Richardson and Pollock, 2010). In the United States, this started with the expansion of Medicare Part D, which not only extended medication coverage to elderly patients under Medicare, but also introduced pharmacists' medication therapy management for eligible patients as a reimbursed service (Touchette et al., 2006, Gray et al., 2007). There is also growing momentum in the United States to get pharmacists provider status, which will enable them to seek reimbursement for patient care from the Centers for Medicare and Medicaid Services (Menigham, 2017). In the United Kingdom and parts of Canada, policy makers have developed legislation to enable pharmacists to independently prescribe medication to patients (Yuksel et al., 2008, Baqir et al., 2012). On the other hand, it is important to consider just how long some of these changes took, or are taking. For example, the process of developing pharmacist prescribing in Alberta, Canada started in 2001, before it was finally rolled out in 2008 (Yuksel et al., 2008). Pharmacist provider status has been a topic of discussion for many years in the United States and has only very recently risen again to the attention of federal policy makers (Harper, 2015).

There are numerous reasons for these delays. As outlined in a previous section, more powerful groups like physicians may present objections to perceived encroachments on their social object (Pullen, 2012). Depending upon the situation, the group of objectors, and their reach, legislators may have no choice but to reject policy changes. As one commentator stated, " . . . technically sound does not equal politically viable" (Harper, 2015). Politicians' primary objective is to remain in a position for long enough to do what they think is the most good for their constituents. This can mean sacrificing good and sound legislation in the interest of passing something less good, and less sound that also has a better chance of success, and keeping them in office. (Harper, 2015)

As such it is important to consider the constraints under which policy makers are working in their particular political environment. While Canada, the United States, and the United Kingdom have dramatically different health care systems, they all struggle with the cost of providing health care to their populations. Consequently, governments in each of these countries are looking for ways to reduce health care expenditures. Like many other groups, pharmacists have taken advantage of the need to reduce costs through demonstration projects showing the cost-effectiveness of pharmaceutical care in comparison to more traditional physician-provided care (Vegter et al., 2014, Truong et al., 2015).

However, it is also possible for occupational groups traditionally considered to be less powerful than pharmacy to make similar efforts. For example, there is an increasing body of evidence promoting an expanded scope of practice for pharmacy technicians (Elliot et al., 2014, Markovic et al., 2017). Tasks that are considered low status for pharmacy, such as taking medication histories, represent upskilling for pharmacy technicians (Traulsen and Bissel, 2004). Moreover, pharmacy technicians also seem to be interested in taking on more of these types of roles from pharmacists (Boughen et al., 2017). Importantly, from the perspective of policy makers, pharmacy technicians also cost the health care system less money. Therefore, it is possible, with a concerted effort and the right political moment, for pharmacy technicians to usurp many traditional pharmacy roles. The question remains as to whether or not pharmacists will be prepared to move into new and rising practice opportunities if this happens.

What Does This All Mean?

Using the sociologically derived definitions of professions and previous analyses of pharmacy as a profession a number of threats were identified. These threats are internal (i.e., recruitment, training, fragmentation, perception of the product of pharmacy), intermediate (i.e., influence of business), and external (i.e., physicians, patients, and policy and policy makers) to pharmacy. Each of these threats also plays some part in the kinds of people who become pharmacists (recruitment), how they understand and practice pharmacy (training, fragmentation, and perception of product), their primary focus as community pharmacists (business vs. health care), and how those outside of pharmacy see and influence it (physicians, patients, and policy makers). Taken together, it might seem obvious to conclude that pharmacy is not a true profession, and that perhaps community pharmacy, in particular, is a business. However, taking such a stance overlooks important details about the broader discussion of professions.

Unlike pharmacy, medicine has been discussed as having a singular and agreed upon social object, recruiting only those who purport altruistic intentions for becoming a physician, and not advertising for a profit (Denzin and Mettlin, 1968, Ladinsky, 1971, Anderson, 1977). But there is also another side of medicine that is rarely discussed. As one author laments the "medical-industrial complex" in the United States, encourages overuse, fragmentation, overemphasis on technology, and cherry picking of the healthiest, and therefore cheapest, patient populations (Relman, 1980). While few health care systems are as profit driven as that in the United States, this discussion brings into relief physicians' interest in being well compensated for their work.

Fascinatingly, there has been little questioning of physicians' potential business aspirations, despite the fact that physicians make most of the decisions about the medical needs of patients (Relman, 1980). Therefore, is it reasonable to assume that all recommended care is always, and solely, in the patient's best medical interest? Evidence examining the traditional fee-for-service funding model for physicians suggests that it is a major driver of increased health care costs and may incentivize increasing the volume services whether appropriate or not (Schroeder and Frist, 2013). It is also important to note that this is not a discussion that is unique to one country, place, or time. Physicians in Canada have also struggled against integration into the larger single payer system in the country (Simpson, 2012) and resisted tax reforms that may impact their revenues (Reddekopp and Hansen, 2017).

Moreover, the bureaucratization of health care to address costs has led others to question whether or not medicine can still be considered a profession, as they can make fewer and fewer decisions completely unencumbered (Abbasi, 2009, Galton, 2016). However, at no point have these discussions invalidated physicians' continued claim to professional status. As such, perhaps the question should no longer be whether or not pharmacy is a profession, business, both, or neither? Formally "clear" distinctions between professions and nonprofessions are permeable, and definitions are more complicated. As such, the more important question is how can pharmacy be a profession and a business, while placing patient needs at its center?

Rethinking the Mix: Can You Have Your Cake and Eat It Too?

One possible approach for pharmacy to be both a profession and a successful business might be through the combination of relationship marketing with patient-centered care and through the establishment of fiduciary relationships. Relationship marketing is most easily understood as the, "activities aimed at developing long-term, cost-effective links between an organization and its customers for the mutual benefit of both parties" (Bentley and Rosenthal, 2016, p. 417). To accomplish this long-term and mutually beneficial relationship, organizations must demonstrate four values. The first value is having a holistic approach to marketing, wherein the entire organization understands the importance of the customer in its success (Bentley and Rosenthal, 2016). The second value is recognizing and fostering long-term collaborations with not only customers, but also suppliers and other health care providers (Bentley and Rosenthal, 2016). The third value is fostering a culture wherein all collaborators are actively involved in the success of the collaboration (Bentley and Rosenthal, 2016). The fourth value is reinforcing the second and third values by focusing on relationships and service rather than rigid adherence to policy (Bentley and Rosenthal, 2016).

These values fit well with the underlying principles of patient-centered care. At its most basic level, patient-centered care accounts for the specific health needs and desired outcomes of each individual patient (Anon 2017b). It accomplishes this objective through the development of a relationship with the patient wherein their needs and concerns are sought out to understand their world view, so that common ground can be established to enhance health and maintain the relationship into the future (Stewart, 2001). Through patient-centered relationships all health care providers have a shared understanding of that patient's needs and desires. Therefore, developing a truly collaborative approach for helping patients to successfully manage their conditions is more straightforward and mutually beneficial for the health care team.

Both relationship marketing and patient-centered care are predicated on the idea of a fiducial obligation between the pharmacist and the patient. As was outlined in each of the definitions of professions, professionals possess a knowledge that the average person does not. The average person must, therefore, have faith that the professional will apply that knowledge fairly and honestly, as they lack the ability to assess whether they received the best health care (Zlatic, 2014). Taken together, these ideas demand a different underlying assumption to be made about the nature of business profits. Rather than thinking about maximizing profits solely through sales, at the expense of relationship development, the focus is on creating a sustained customer base through relationship building. For example, the previously described practice of pharmacy owners/managers recommending patients' purchase products they may not require would be replaced by that of staff pharmacists erring on the side of not selling the product in the interest of generating and maintaining patient trust.

Research suggests this approach has significant benefits to patients who avoid the stress and anxiety of finding new providers, and will in turn reward pharmacies with their continued business (Bentley and Rosenthal, 2016). Furthermore, there is a growing sense that patients will continue to rethink their relationship with health providers like pharmacists. Millennials are now the largest living generation in the United States according to the census bureau (Fry, 2016). This is important because literature from the business world suggests that this group, perhaps more than in generations past, is particularly interested in doing good within their communities, not just the bottom line (Case, 2014). Millennials are also interested in engaging with companies that exude a sense of authenticity and allow them to align and participate with the company (Jubenville, 2016). Relationship marketing, patient-centered care, and the fiduciary relationships, when well practiced align with the demands of not just patients falling into the Millennial generation, but arguably others as well.

Next Steps

Like most such proposals, successfully reworking the current practice of pharmacy to not only address pharmacists' own self-perceptions, as well as that of outsiders, but also developing a new business model is totally overwhelming, and seems unrealistic. As was outlined in the beginning of this article, pharmacy has a long history, struggling greatly with how it defines itself. Furthermore, while it has made many great strides in clarifying its role in patient care, as the overview of the threats to pharmacy suggested, there remain a number of outstanding issues, crossing the spectrum from internal to external, that need to be addressed. Practicing pharmacists, pharmacy educators, current and future pharmacy students, and patients must come together to decide how to best overcome these threats. Once potential approaches to overcoming these threats have been developed, carefully constructed and theoretically driven implementation programs are needed to test whether or not these programs are practical. Implementation science, or knowledge translation, offers a number of theoretical models that might be utilized in this capacity (Nilsen, 2015).

Conclusion

We began this article with two objectives:

1. To examine the following question: Is pharmacy a profession, a business, both, or neither?
2. To build a case for why carefully considering the possible answers to the question posed in the primary objective is important for pharmacy and its future.

While we were unable to wrap up this discussion with a neat and clean conclusion, the process of examining the components of the first objective have reinforced the case for the second. Pharmacy does not need to define itself as a profession to the exclusion of also seeing itself as a business. There is a way that it can be both of those things. If pharmacy chooses to move in this direction then the next steps it takes are crucial. What does a sustainable and scalable patient-centered, relationship marketing driven, business model look like? How do we train future pharmacists to meet the needs of this new model? And how can we help current pharmacists rethink their roles to take advantage of these news opportunities?

Glossary

1. Spicers were a group of spice importers that competed for status with pharmacists in the 13th century France.
2. *Social objects* are ideas, or objects, that gain additional meanings when they are integrated into self-perception of professions.

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Pharmacy Practice in the Philippines

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Health Scenario in the Philippines

The Philippines is located in Southeast Asia with the land area of approximately 300,000 square kilometers (Philippine Statistical Authority, 2017). As of 2017, the population of the Philippines was 104,921,600 with the density of 337 persons per square km, (Philippine Statistical Authority, 2017; Philippine Statistical Authority, 2016) which is projected to reach 142 million by 2045. With rapidly changing demographics, the population aged 65 years and over may quadruple in size to 16 million by 2045 (Philippine Statistics Authority, 2016). The country witnessed economic growth of 6.7% GDP in 2017 and an annual average growth rate of 6% over the past 5 years (Bangko Sentral ng Pilipinas, 2017). The projected average life expectancy at birth will increase from 70.38 years (male: 67.61; female: 73.14) from 2010 to 2015 to 75.68 years (male: 73.01; female: 78.34) from 2035 to 2040 (Philippine Statistical Authority, 2017; Department of Health, 2012). Furthermore, there is a steady decline in the total fertility rate of three births per woman as of 2017 (Department of Health, 2012; Philippine Statistics Authority and ICF, 2018a). The maternal mortality rate has also decreased to 114 per 10,000 live births in 2010 (Pinlac et al., 2015) due to the improved quality of maternity healthcare services by healthcare professionals (93%) and the symbiotic public–private partnership (Philippine Statistics Authority, 2018a; The Philippine Star, 2018) for healthcare services.

In 2016, 6 out of 10 leading causes of death were NCD in etiology. Most of the NCD mortality cases, such as ischemic heart disease, cancer, diabetes, and others shown in **Table 1**, are considered to be lifestyle-related (Philippine Statistics Authority, 2018b). Alarmingly, an increasing prevalence of obesity among children and adolescents are risk factors for NCDs. Behavioral risk factors, such as an unhealthy diet, smoking, alcohol consumption and a sedentary lifestyle also promote NCDs (Department of Health, 2012; Pinlac et al., 2015). The increased consumption of items such as saturated oils, fast food and sugar coupled with a decreased intake of carbohydrates, fruits and vegetables also contribute to the development of NCDs (Ulep et al., 2013). **Table 1** also highlights infectious diseases as one of the leading causes of morbidity (Philippine Statistics Authority, 2018b). Despite campaigning by the Department of Health (DOH) and funding agencies, tuberculosis still remains a leading cause of mortality and morbidity in the country (Department of Health, 2012). Though HIV cases are less than 1% (Department of Health, 2012), cumulative data from 1984 to 2017 implies that there were 60,207 confirmed HIV cases (94% male; 6% female) reported to HARP. There is an average of 32 people who have been newly diagnosed with HIV per day from January to October 2018 alone (Department of Health Epidemiology Bureau, 2018). Tropical endemic diseases such as malaria, schistosomiasis and filariasis occur with other emerging and re-emerging infectious diseases (Department of Health, 2012).

Table 1 Top 10 leading causes of death, Philippines: 2016 (Philippine Statistics Authority, 2018b)

Leading causes	*Number*	*%*
All causes of death	582,183	100.0
Ischemic heart diseases	74,134	12.7
Neoplasms	60,470	10.4
Pneumonia	57,809	9.9
Cerebrovascular diseases	56,938	9.8
Hypertensive diseases	33,452	5.7
Diabetes mellitus	33,295	5.7
Other heart diseases	28,641	4.9
Respiratory tuberculosis	24,462	4.2
Chronic lower respiratory infections	24,365	4.2
Remainder of diseases of the genitourinary system	19,759	3.4
Other causes of death	168,858	29.0

Philippine Healthcare System: At a Glance

Health Financial Schemes and Expenditures

The Philippines has four main sources of health financing: insurance (government and private), national and local government, donors and household fees or out-of-pocket payment as shown in Fig. 1 (Department of Health, 2012; Crisostomo, 2018).

In 2018, almost 93% of financing was covered by the Philippine Health Insurance Corporation (PHIC or PhilHealth), (Department of Health, 2010), which initiated single-payer premium-based health financing in the country (Department of Health, 2012). PhilHealth has limited hospital insurance coverage including medicines, (Department of Health, 2010) resulting in a high level of out-of-pocket payments (Department of Health, 2010; Lavado et al., 2011) in private (48%) and public facilities (51%) (Department of Health, 2012). Other health insurance types such as the Government Service Insurance System, Social

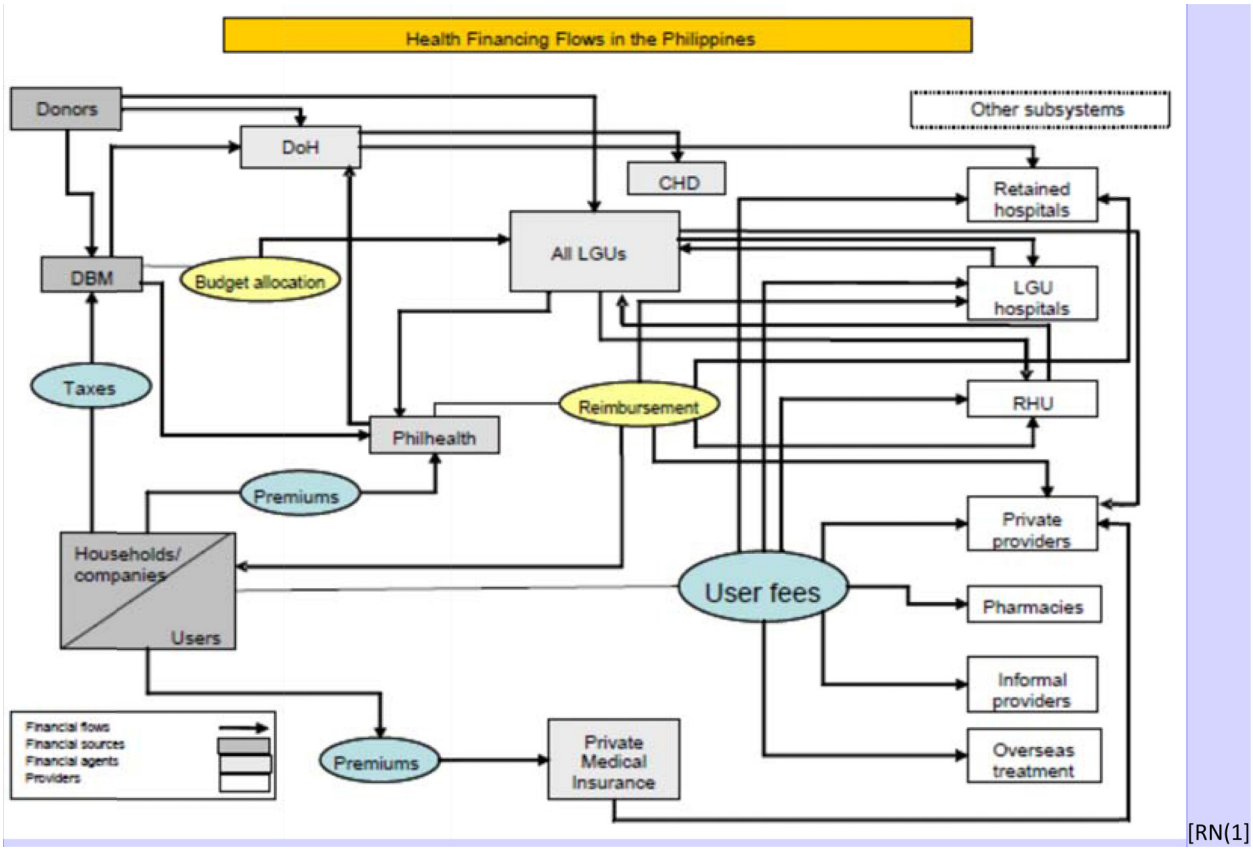

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Figure 1 Health financing flow in the Philippines (Crisostomo, 2018).

Security System or private insurance provided coverage for 24% of the population (Philippine Statistics Authority and ICF, 2018b). Donations from philanthropist, non-government organizations and charity organizations are also some of the major sources of health financing (Philippine Statistics Authority, 2018c).

Healthcare Delivery System

The health scheme in the Philippines has a dual system composed of the public and private sector. The public sector is financed by the government through a tax-based budgeting system, which was decentralized from national to local government units in 1991. The DOH supervises national, regional and specialty hospitals, whilst the Department of National Defense manages military hospitals. The private sector covers half of the health system that is largely market-orientated and paid through user fees at the point of service (Department of Health, 2005b). There are 476 government hospitals, 960 private hospitals, 322 government infirmaries, 312 private infirmaries, 2,598 rural health units and 20,241 village (*barangay*) health stations that are in place for delivery of health services in the country (Medina, 2017). In 2018, the government hospital bed to population ratio was 1:1,121 (88,394 beds) with a target to reach 1:800 (142,500 beds) by 2020 (Antiporda, 2018).

Access to medicines: Filipinos access their medicines mostly in urban or rural private retail pharmacies. Some may purchase medicines in hospital pharmacies, especially for inpatients but prices are usually higher. When medicines are not available or out-of-stock in public hospitals, patients buy medicines at nearby drugstores (Dayrit et al., 2018). Drug retailers are classified into drugstores (chain and independent pharmacy), Botika ng Barangay (BnB), Botika ng Bayan (BNB), Chinese retailers, and retailers of non-prescription drugs. The most common type of retailer was the drugstores (73%), which are mostly found in urban areas, followed by BnB (24%) (Reyes et al., 2011). In 2018, the DOH relaunched BNB to reduce out-of-pocket expenditures for the underprivileged and to increase accessibility of essential medicines in rural areas of the country (Philippine Information Agency, 2018).

Pharmaceutical care: Pharmacy in the country has evolved over the years from a product-focused to a patient-orientated profession (Marin-Calero et al., 2004). Dispensing is the most commonly performed activity in the hospital (Agaceta et al., 2013) and community, alongside management, optimizing patient care and managing public health. Studies conducted by Salenga et al. in 2009 revealed that 36.4% of pharmacists were perceived to be competent in delivering public health services due to their positioning in practice, expertise and education, even though there was a low uptake of pharmacists in public health (Salenga, 2009; Capper and Sands, 2006). Ocampo et al. mentioned that barriers to the implementation of pharmaceutical care in the Philippines include lack of support of physicians and other healthcare professionals, time consuming completion of documentation, lack of economic incentives and inadequate space for pharmacist-patient encounters (Agaceta et al., 2014).

In recent years, community pharmacists have been providing patient care services in the form of medication counseling, blood pressure and glucose monitoring, medication adherence monitoring, provision of daily dose packs (Ball and Salenga, 2017), smoking cessation (Ware, n.d.) and lifestyle modification counseling. The pharmacist also has an expanded role in the Antimicrobial Stewardship Program to provide rational interventions on antimicrobial prescriptions, dose adjustments and education (Department of Health, 2016). Furthermore, public health pharmacists ensure access and availability of essential drugs through village pharmacies (Casis et al., 2011) and contribute in health education, disease prevention and health promotion to achieve optimal public health outcomes (American Public Health Association, 2006).

Human Resources

A recent FIP report on pharmacy workforce revealed that the Philippines have a pharmacist density of 5.8 per 10,000 population compared to Thailand (5.45), Indonesia (2.10) and Malaysia (4.99) (FIP, 2018). The majority of pharmacists work in community pharmacy (77%), hospital pharmacy (15%) and in industrial pharmacy (7%) (Lorenzo and Cruz, 2001). As per 2011 census, there were 101,181 pharmacy technicians or assistants (1 pharmacy assistant in 1000 population), suggesting twice as many pharmacy assistants/technicians (in all sectors) as there were pharmacists (World Health Organization, 2011). However, there is an increasing trend of pharmacists and pharmacy assistants migrating to other countries, (Philippine Overseas Employment Administration, 2016) especially to the USA (Loquias and Robles, 2012) and the Middle East (Casco, 2013).

Pharmacy Education

The University of Santo Tomas (UST) Faculty of Pharmacy was the first to offer the bachelor's degree in pharmacy in the Philippines in 1871 by virtue of the Modification of the Moret Decree. During the Spanish regime, the course duration was 6 years, which was then reduced to 4 years during the American colonization (University of Santo Tomas, 2016). The University of the Philippines College of Pharmacy started as a 3-year Graduate in Pharmacy (PhG) course in 1911 and commenced a 4-year Bachelor of Science in Pharmacy (BSP) course in 1913 (University of the Philippine College of Pharmacy, 2017). A minimum 5-year curriculum was implemented in 1954 (Carson, 1961) and was again reduced to 4-years in 1984 with the integration of some subjects. From then on, pharmacy schools have flourished from north to south in the Philippines. Pharmacy graduates were regulated by the Professional Regulation Commission Board of Pharmacy (PRC BOP) and must fulfill the 4-year BS Pharmacy

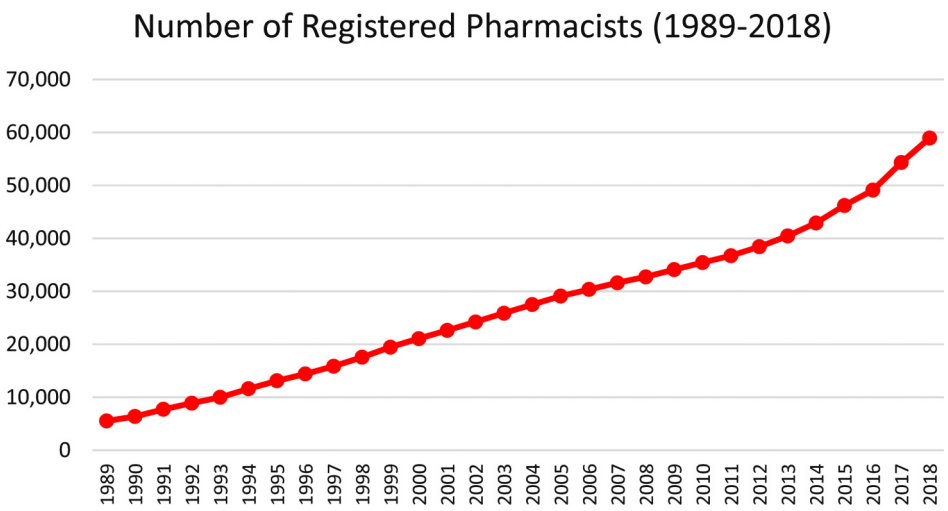

Figure 2 Number of registered pharmacists from 1989–2018. *Source: Professional Regulation Commission and Philippine Statistics Agency; data compiled by authors.*

degree and 960 h supervised internship (community, hospital and manufacturing) to be able to take the Pharmacy Licensure Examination (Professional Regulation Commission, n.d.; CMO, 2006). There are more than 60,000 registered licensed pharmacists in the country (Fig. 2).

Private higher education institutions offering courses in pharmacy must have the Commission on Higher Education (CHED) license to operate, and at least 192 total units of core courses (30 units), professional courses (90) and mandatory general education courses (21) (CMO, 2006). The cost of pharmacy education ranges from Php 20,000 (USD400) to Php 65,000 (USD1250) per semester in private institutions and is 40% to 75% lower in government institutions (Professional Regulation Commission, n.d.). Different universities and colleges offer additional undergraduate programs such as BS in Industrial Pharmacy (recently known as BS Pharmaceutical Science) (UP College of Pharmacy, 2017), a 5-year BS Pharmacy major in Clinical Pharmacy (University of the Immaculate Conception, 2014; Centro Escolar University, 2015; University of Santo Tomas, 2016a; University of Santo Tomas, 2016b) and a 6-year Doctor of Pharmacy (PharmD). Several universities offer a 2-year post-baccalaureate program for PharmD (Centro Escolar University, 2015; University of Santo Tomas, 2016b) and a 2-year mixed mode postgraduate program (coursework and research) Master of Science in Pharmacy and a 3-year mixed mode PhD in Pharmacy with research specializations.

There have been some drastic changes in pharmacy education in the country with an increasing trend of universities offering BS Pharmacy. In 2018, overall 101 universities and colleges registered in CHED for BS Pharmacy, 95% being private institutions and 5% SCU's (Commission on Higher Education, 2018). The Philippine Association of Colleges of Pharmacy, founded in 1975 with 40 pharmacy schools, is preparing for the new Charter Management Organizations (CMOs) on pharmacy education and curriculum, which is in line with the Outcome-Based Education (OBE) integrating the Philippine Practice Standards for Pharmacists (PhilPSP) (Philippine Association of Colleges of Pharmacy, 2017). Pharmacy universities are also preparing for the national reform in basic education known as K plus 12. An upcoming student is required to undergo kindergarten, 6 years of elementary, 4 years of junior high school and 2 years of Senior High school (Marcelo, 2014). This target to prepare students for tertiary education, skills, entrepreneurship and global employment (Arcangel, 2014). By 2021–22, higher education institutions (HEIs) will be affected through a reduction of courses being offered and faculty workload especially for general education lecturers as some subjects are transferred to senior high school curriculum (Acosta and Acosts, 2016).

Continuing professional development: RA 10912, also known as the continuing professional development (CPD) Act of 2016 mandated measures to continuously improve the competence of professionals in the Philippines. Pharmacists are required to obtain 45-credit units within a 3-year compliance period for the renewal of their license. These credits can be obtained through professional, academic, or self-directed learning units (Dayrit et al., 2018; Continuing Professional Development, 2016). There were 59 CPD providers in the country from 2008 to 2018 as approved by PRC BOP (Professional Regulation Commission, in press).

Regulations, Policies, and Standards

A recent reform in the country's pharmacy law was the approval of RA10198 or the Philippine Pharmacy Act of 2016; the act regulates and modernizes the practice of pharmacy in the Philippines, repealing the RA5921 or Pharmacy Law of 1987. RA10918 highlights the following major changes: (1) the expanded role of pharmacists in immunization (2) professionalization of the pharmacy workforce by upgrading pharmacy assistants to NC III, and (3) stringent rules for evaluation of pharmacy personnel and pharmacy licensing (Sambalud, 2017; Asia Pacific Institute for Medication Management, 2017). Furthermore, provisions of mutual

Table 2 Classification and characteristics of hospitals in the Philippines (World Health Organization, 2012a)

General hospitals	Most hospitals at all levels provide services for all kinds of illnesses, diseases, injuries or deformities. They have emergency and outpatient services, primary care services, family medicine, pediatrics, internal medicine, obstetrics-gynecology, surgery including diagnostic and laboratory services, imaging facility and pharmacy.
Level 1 general hospitals	Level 1 hospitals include isolation facilities, maternity, dental clinics, first level X-ray, secondary clinical laboratories with consulting pathologists, blood stations and pharmacy.
Level 2 general hospitals	Level 2 hospitals include level 1 services and departmentalized clinical services, respiratory units, intensive care units (ICU), neonatal intensive care units (NICU), high risk pregnancy units (HRPU), tertiary clinical laboratories, and second level X-ray
Level 3 general hospitals	Level 3 hospitals include level 2 services and teaching/training, physical medicine and rehabilitation, ambulatory surgery, dialysis, tertiary laboratories, blood banks and third level X-ray
Specialty hospitals	A tertiary hospital specializes in the treatment of patients suffering from a particular condition requiring a range of treatment (e.g. Philippine Orthopedic Center, National Center for Mental Health); patients suffering from disease of a particular organ or groups of organ (e.g., Lung Center of the Philippines, Philippine Heart Center); or patients belonging to a particular group such as children, women, or the elderly (National Children's Hospital, Dr. Jose Fabella Memorial Medical Center). Tertiary care facilities located all over the country serve as referral hospitals in the different regions of the country and provide an anticipated range of tertiary services.

recognitions, empowerment of pharmacist's responsibilities, eradication of "ghost pharmacists," board specializations and regulation of antibiotics (Philippine Pharmacist Association, 2016) shall be the future direction of pharmacy in the Philippines.

Accredited organizations: The Philippine Pharmacists Association (PPhA), founded on August 29, 1920, is the accredited professional organization of the PRC for licensed Filipino pharmacists. PPhA has 83 regional and local chapters, 10 affiliate organizations and the membership of about 15,000 pharmacists (Philippine Pharmacist Association, 2017a; Philippine Pharmacist Association, 2017b).

Core Pharmacy Practices

Hospital and Clinical Pharmacy

Hospitals are licensed by DOH (Food and Drug Administration, 1995) and accredited by PhilHealth. There are 1257 PhilHealth accredited hospitals in the country (Philippine Health Insurance Corporation, 2018). Hospitals are classified into three levels as shown in **Table 2** (World Health Organization, 2012a). Level 1 hospitals constitute almost 65% of the accredited hospitals, Level 2 hospitals comprise 26%, and Level 3 hospitals consist of 9%. Currently, five hospitals are accredited by the Joint Commission International (JCI) (Joint Commission International, 2015); 3 by Accreditation Canada (Accreditation Canada, 2019).

Hospital Pharmacy Services

Dispensing: Most hospitals dispense to both inpatients and outpatients. Some hospitals have an outsourced outpatient pharmacy (MedExpress Drugstore, 2018) so that the pharmacists can focus their services to inpatients. Most hospital pharmacists are assigned to the dispensing area to fill and prepare the prescribed medicines of the patient (Sarriff et al., 2011). Pharmacists in JCI-accredited hospitals, such as Asian Hospital and Medical Center (Joint Commission International, 2015), are required to review drug orders for appropriateness before dispensing as stated in the hospital pharmacy practice standards (PPhA Committee, 2015; Philippine Society of Hospital, 2016). Hospital pharmacists in Makati Medical Center (Makati Medical Center, 2017) and Manila Doctors Hospital (Manila Doctors Hospital, 2018) are also involved in dispensing investigational drugs.

Drug distribution system: Hospitals in the Philippines have centralized pharmacies that cater to the hospital wards and units. There are also floor stocks and emergency carts available in different wards to provide immediate access to certain medicines in case of emergency and for use during specific medical procedures. Some hospitals in the Philippines, such as Manila Doctors Hospital (Manila Doctors Hospital, 2018), also provide unit dose dispensing to their patients to aid the nursing staff in drug administration by preventing potential medication errors and minimizing returns and spoilage of prescribed medications (Gutlay et al., 2017).

Compounding: Extemporaneous compounding is common in hospitals. Pharmacists in The Medical City (Philippine Society of Hospital Pharmacists, 2016) receive requests for paper tabs for pediatric patients and other extemporaneous compounding that are not commercially available such as dermatological and topical preparations. Sterile preparations such as total parenteral nutrition, intravenous admixtures and chemotherapeutic agents can be compounded in some hospitals like Makati Medical Center (Makati Medical Center, 2017) and Manila Doctors Hospital (Manila Doctors Hospital, 2018).

Clinical Pharmacy Services

Clinical pharmacy in the Philippines is still developing as more healthcare institutions are realizing the need for the pharmacist to be involved in the healthcare team. Dr. Siopin L. Co is recognized as the dean of hospital pharmacy in the Philippines because of her various contributions in hospital pharmacy practice in the Philippines, especially in the field of clinical pharmacy. During her term as president of the Philippine Society of Hospital Pharmacists (PSHP) in the 1980s, she was known as an advocate of clinical

pharmacy and incorporated training in necessary skills in drug therapy management and pharmaceutical care in continuing professional development (CPD) programs for hospital pharmacists (Philippine Society of Hospital Pharmacists, 2016).

Clinical pharmacy services are usually provided in hospitals rather than in the community setting in the Philippines. Physicians and nurses expect pharmacists to be drug therapy experts and recognize that collaboration with pharmacists improve patient outcomes (Ramones et al., 2015). The hospital pharmacist can readily interact with other healthcare professionals such as doctors and nurses and with the patient in a hospital setting. They can easily access patient medical charts to retrieve necessary patient information. The hospital pharmacist is also in a better position to educate other healthcare professionals and patients on medicines and as a result, can also be involved in policymaking committees within the hospital (World Health Organization, 1994). Pharmacists from private hospitals have a higher level of perceived importance in performing patient care activities than those of government hospitals (Agaceta et al., 2013).

Medication reconciliation: Medication reconciliation is performed in the hospitals with international accreditation (Joint Commission International, 2015; Accreditation Canada, 2019), such as The Medical City (The Medical City, 2018) as this is the requirement in medication management. The outpatient pharmacy of St. Luke's Medical Center provides medication reconciliation as a value-added service to its clients (Samaniego, 2013).

Review of drug orders: Pharmacists should review drug orders before dispensing as stated in the Minimum Standards for Hospital Pharmacy Practice and PhilPSP (PPhA Committee, 2015; Philippine Society of Hospital Pharmacy, 2016). Similar to medication reconciliation, a review of drug orders is performed among hospitals with international accreditation (Joint Commission International, 2015; Accreditation Canada, 2019). In Makati Medical Center (Makati Medical Center, 2017) and The Medical City (The Medical City, 2018), the clinical pharmacist identifies drug therapy-related problems such as inappropriate drug dosing, potential adverse drug reactions and drug interactions, therapeutic duplication and contraindications, and discusses the recommendation or intervention with the doctor, nurse or patient.

Patient counseling: In The Medical City, the clinical pharmacist counsels the patient upon discharge (The Medical City, 2018). In the Philippine General Hospital, pharmacy interns were rotated to perform patient medication counseling services in OPD pharmacy and main pharmacy (Ching et al., 2016).

ADR monitoring: The FDA encourages healthcare professionals such as pharmacists as well as patients to report suspected ADRs (Food and Drug Administration Advisory on Reporting of Suspected Adverse Drug Reactions, 2016) using the Suspected Adverse Reaction Form (Food and Drug Administration, 2012). In 2008, there were only 1167 ADR reports, which is very low in relation to the Philippine population (MeTA Philippines, 2010). Even though hospital pharmacists have a low encounter with potential ADRs compared to doctors and nurses, pharmacists are still encouraged to report potential ADRs (Carandang et al., 2015).

Antimicrobial stewardship program: The DOH drafted the Manual of Procedures for Implementing Antimicrobial Stewardship Programs (AMS) in Hospitals in 2016. The clinical pharmacist plays an active role in the implementation of the AMS program in the hospital, therefore encouraging the adaption of clinical pharmacy services in the Philippines (Department of Health, 2016).

Barriers to clinical pharmacy services: A major barrier cited by pharmacists in implementing these services is the lack of support from physicians and other healthcare professionals. These healthcare professionals perceived pharmacists to be dispensers of medicines, based on their traditional role and not as active participants in the healthcare team. Pharmacists also identified having a lower salary and a lack of proper remuneration and financial incentives as a hindrance to implementing clinical pharmacy services. The workload of the pharmacist can also result in insufficient time to perform reviews of drug orders and provide patient counseling. Another barrier, especially in community pharmacy, is that patients often do not demand clinical services from the pharmacist because they are often pressed for time when they purchase their medicines from the drugstore (Agaceta et al., 2014).

Community Pharmacy

Community pharmacy is more popularly known as a drugstore or "botika" in the Philippines. These drugstores are classified as pharmaceutical outlets, which are licensed by the FDA (Food and Drug Administration, 2014). Based on the FIP Pharmacy Workforce Intelligence–Global Trends Report in 2016–there were 60,029 pharmacists in the Philippines, of these 77% were practicing in a drugstore (FIP, 2018; Lorenzo and Cruz, 2001). In the study on emerging roles of pharmacists in the Asia Pacific Region, it was found that almost 54% of pharmacists worked in a community pharmacy (Faller et al., 2017). Even though most pharmacists worked in the community setting, there was still a shortage of pharmacists in community pharmacy practice due to the increased number of drugstores as well as the fast turnover of pharmacists. Most independent drugstores do not have problems in hiring pharmacists because the business owner is usually a pharmacist. However, drugstores are losing pharmacists due to immigration for work overseas or due to local transfer to a higher paying job such as in business process outsourcing and regulatory affairs, or to government hospitals or clinical research (Loquias and Robles, 2012).

Community Pharmacy Services

Dispensing: Most of the duties of a community pharmacist involve dispensing of medicines to patients or clients (Ramos et al., 2017). The FDA requires that a registered pharmacist is present during the business operations of a drugstore (Food and Drug Administration, 2014). Based on the Philippine Pharmacy Act of 2016, only a registered and licensed pharmacist shall dispense prescription drugs and pharmacist-only over-the-counter medicines in a drugstore. Any prescription drug filled and prepared by the pharmacy assistant or pharmacy technician should be supervised by a pharmacist (Philippine Pharmacy Act, 2016; Implementing Rules and Regulations of Pharmacy Act, 2016). A community pharmacist should also implement good dispensing practices (World

Health Organization, 2012b), which include medication review, maintenance of patient medication record and labeling of dispensed medicines. A community pharmacist often has many different roles, such as being the owner, storekeeper, cashier, purchase officer, and manager of the drugstore. This multitasking can lead to a lack of or limited involvement of the pharmacist in the patient care functions such as medication review, patient profiling and patient counseling (Ramos et al., 2017).

Patient counseling: A community pharmacist faces hindrance in conducting patient counseling. Pharmacy students observed a lack of pharmaceutical care regimen during their community pharmacy internship (Carrido et al., 2016). As a pharmacist has multiple roles in a drugstore, it limits his time for patient counseling (Ramos et al., 2017). Other factors to consider include the lack of involvement and competence of the pharmacist in-patient counseling (Erku et al., 2017). Orientation of the pharmacist and support personnel in pharmaceutical care can help in improving patient counseling services (Faller and Velasco, 2015). Patients and caregivers may also reject patient counseling because they think that it will take up too much of their time. Value-added services such as screening of the vital signs of the patient can be provided to improve patient/client flow in the drugstore (Faller and Velasco, 2015; Faller et al., 2019).

Immunization services: The Philippine Pharmacy Act of 2016 stated the need for the involvement of the community pharmacist in providing immunization services for routine adult vaccination (Philippine Pharmacy Act, 2016; Implementing Rules and Regulations of Pharmacy Act, 2016). Community pharmacists are currently involved as advocates for vaccination but not as providers of immunization services (Echano et al., 2016). Training programs for pharmacists in immunization and vaccination will also be helpful in implementing immunization services (Echano et al., 2016).

Conclusion

Pharmacists have a critical role in UHC as they provide appropriate medication management. Evolution from a product-oriented service to patient-focused care in pharmacy practice is being recognized in the Philippines. Most pharmacists in hospital and community practice are assigned to traditional dispensing and inventory management functions. The clinical role of the pharmacist is being observed but is not being carried out consistently in the community and hospital settings. Factors that contribute to the barriers in implementing the clinical role of the pharmacist include lack of support from other healthcare professionals and upper management, lack of infrastructure, lack of clinical competency and training and fast turnover of pharmacists in the Philippines. The practice standards for pharmacists have emphasized the clinical functions of the pharmacist. Changes in the pharmacy curriculum will provide the necessary knowledge and skills to the pharmacist to provide pharmaceutical care services in the future.

List of Abbreviations

ADR	Adverse Drug Reaction
ASP/AMS	Antimicrobial Stewardship Program
BnB	Botika ng Barangay
BNB	Botika ng Bayan
BS	Bachelor of Science
CHED	Commission on Higher Education
CPD	Continuing professional development
DOH	Department of Health
FDA	Food and Drug Administration
FIP	Federation Internationale Pharmaceutique/International Pharmaceutical Federation
GDP	Gross Domestic Product
HARP	HIV/AIDS and ART Registry of the Philippines
HIV	Human Immunodeficiency Virus
ICU	Intensive care unit
LGU	Local Government Unit
NC	National Competency
NCD	Non-communicable disease
NICU	Neonatal intensive care unit
OBE	Outcome-Based Education
PhD	Doctor of Philosophy
PhilHealth/PHIC	Philippine Health Insurance Corporation
PhilPSP	Philippine Practice Standards for Pharmacists
PPhA	The Philippine Pharmacists Association, Inc.
POEA	Philippine Overseas Employment Agency
PSHP	Philippine Society of Hospital Pharmacist
RA	Republic Act

REU	Rural Health Unit
SCU	State Colleges and Universities
UP	University of the Philippines
UST	University of Santo Tomas
WHO	World Health Organization

Glossary

Accredited professional organization (APO) the duly integrated and accredited professional organization of registered and licensed pharmacists.
Botika ng Barangay (Village Pharmacies) (BnB) refers to a drug outlet managed by a legitimate community organization (CO)/Non-Government organizations (NGO) and/or the Local Government Unit (LGU), with a trained operator and a supervising pharmacist.
Botika ng Bayan (BNB) refers to a variant of Botika ng Barangay government-supported private drug franchise (PITC Pharma Inc) selling generic products with a trained operator and supervising pharmacist.
Clinical pharmacy an area of pharmacy concerned with the science and practice of rational medication use.
Continuing professional development (CPD) the development of advanced knowledge, skills, and ethical values in a post-licensure specialized or in an inter- or multidisciplinary field of study for assimilation into professional practice, self-directed research, and/or lifelong learning.
Dispensing the sum of processes performed by a pharmacist in reading, validating, and interpreting prescriptions; preparing; packaging; labeling; record keeping; dose calculations; and counseling or giving information, in relation to the sale or transfer of pharmaceutical products, with or without a prescription or medication order.
Medication reconciliation the process of creating the most accurate list possible of all medications a patient is taking—including drug name, dosage, frequency, and route— and comparing that list against the physician's admission, transfer, and/or discharge orders with the goal of providing correct medications to the patient at all transition points within the hospital.
Medicines drugs in their appropriate dosage forms, with assured quality, safety and efficacy for humans or animals, or both.
Pharmaceutical outlets entities licensed by appropriate government agencies, which are involved in compounding and/or dispensing and selling of pharmaceutical products directly to patients or end-users.
Pharmacovigilance The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
Philippine Practice Standards for Pharmacists Refer to the established national framework for quality standards and guidelines for the practice of pharmacy that respond to the needs of the people who require the pharmacists' services to provide optimal, evidence-based care as formulated by the integrated APO and approved by the Professional Regulatory Board of Pharmacy.
Retailer any establishment that sells or offers to sell any health product directly to the general public.

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Pharmacy Practice in Primary and Secondary Care Settings Within the UK: An In-Depth Analysis

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General Overview of Pharmacy Practice Within the UK Healthcare System

This chapter will discuss and provide an in-depth analysis of the current practices of pharmacy services within primary and secondary care settings within the United Kingdom. It will describe the major services offered by pharmacy professionals in each sector; in addition, it will further illustrate the different roles and responsibilities the pharmacists have within the United Kingdom.

In addition, this chapter will hypothesize on potential future roles of the pharmacy services within the coming decade, especially in relation to the changing healthcare landscape in the United Kingdom. There will be a short analysis of current and emerging healthcare models within the United Kingdom, with a focus on pharmacy provision coupled with a review of challenges and hurdles that may be evident. The chapter will also provide some short case studies that further depict the broad range of service provision of pharmacy professional across all UK healthcare platforms.

History of Pharmacy and Clinical Practice Across the UK Heathcare System

Pharmacy within the United Kingdom has existed in one form or another for hundreds of years. Within the last half a century, pharmacists and their teams have become the cornerstone of healthcare services irrespective of the setting they are seen. The term

pharmaceutical care has largely been used to describe the historical and habitual practice of pharmacy professionals and has been most aptly coined by Hepler and Strand (1990):

> 'Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are: curing a disease, elimination or reduction of a patients' symptomatology, arresting or slowing down a disease process, or preventing a disease or symptomatology'

This has clearly focused the importance of pharmacists to ensure that medications given, prescribed, or administered to patients are safe, effective, and evidence drive. Medication is the most frequent intervention within healthcare systems worldwide. Achieving the best possible evidence of medication for the quality of life of patients should be the primary aim of all health professionals involved in the medication process.

Primary Care Description Focusing on General Practice and Community Pharmacy

Community Pharmacists are the traditional role seen by many people across the globe and within the UK. A community pharmacist is typically a professional who dispenses prescriptions written by a doctor, although this has changed dramatically within the UK. In recent years, community pharmacists have been developing clinical services in addition to the traditional dispensing role to allow better integration and team working with the rest of the National Health Services (NHS) within the United Kingdom. From medicine reviews, through to blood pressure and glucose testing, community pharmacy in the United Kingdom offers a number of enhanced services pertinent to the needs of the population (Community Pharmacy Scotland, 2019).

Community pharmacies are situated in high street locations, in neighborhood centers, in supermarkets, and in the heart of the most communities (Pharmaceutical Services Negotiating Committee, 2018). Many are open long hours when other healthcare professionals are unavailable. There are several different types and sizes of community pharmacies, ranging from the large chains with shops on every high street or in edge of town supermarkets, to small individually owned pharmacies in small communities, in the suburbs, and often in deprived areas or rural settings.

Within general practice, pharmacists work as part of the general practice team to improve value and outcomes from medicines and consult with and treat patients directly (NHS England). This includes providing extra help to manage long-term conditions, advice for those on multiple medicines, and better access to health checks. The role is pivotal to improving the quality of care and ensuring patient safety remains at the fore front of clinical care. They will also assist with communication across a patient's care pathway, manage medicines shortages by suggesting suitable alternatives where appropriate, and mentor newer pharmacists (Jankovic, 2016).

Having pharmacists in GP practices means that GPs can focus their skills where they are most needed, for example on diagnosing and treating patients with more complex conditions. This helps GPs to manage the demands on their time. This is a typical example of how pharmacy professionals are evolving from their traditional roles of medicine supply and public advice, to now being key professionals with extended roles for the delivery of exceptional patient care.

Secondary Care Description Focusing on Hospital Practice

Pharmacists working within secondary care, mostly within hospital settings, are often termed as hospital or clinical pharmacists, these nomenclatures are often used interchangeably. Although this reference to "clinical" is now less so been associated solely with secondary care, it is still largely reserved for pharmacists who work more in depth or on a 1-2-1 basis with patients. The term clinical pharmacist was first coined in the 1970s (Miller, 1981) and has developed in the hospital setting as a cornerstone of how pharmacy is practiced in secondary care (Walker and Whittlesea, 2011).

A hospital (or clinical) pharmacist is a source of knowledge, information, and relevant application of healthcare to patients, nurses, medical staff, and anyone in contact with hospital services. He or she can inform patients on all aspects of their medicines, including recommending types, as well as administration routes and dosages, which are all very dependent on the individual's needs. Hospital pharmacists can suggest whether tablet, injections, creams, or inhaler may be the best form of medication and frequently liaise with medical staff concerning their patients. Pharmacists in this setting tend to work very closely with healthcare professionals to ensure patients receive medication at the most optimal level. They assess the effectiveness of all medicines using biomarkers such as blood counts, drug assay, renal, and hepatic function and hematological markers.

Within hospital pharmacy, there are a number of differing roles and practices within the wider pharmacy teams, both for pharmacists and equally for pharmacy technicians, certainly in comparison to primary care roles within community and GP pharmacy. Main pharmacy practice subtypes in hospital include:

- Manufacturing
- Aseptic (sterile) production
- Medicine information
- Regulatory
- Clinical effectiveness
- Specialist clinical expert/hospital clinical pharmacist

- Radiopharmacy
- Education and training/teacher practitioner
- Leadership/management or executive

Primary Care

Current Primary Care Platforms and Service Offerings

Community Pharmacy

Community pharmacists work at the front line of healthcare in cities, towns, and villages across the United Kingdom since the 1800s. They work from their own pharmacies or out of local healthcare centers and doctor's surgeries (Royal Pharmaceutical Society, 2018).

Community pharmacists are easily accessible with over 11,600 community pharmacies in England located where people live, shop, and work. The make up of these pharmacies vary from sole/independent contractors through to small-, middle-, and large-sized multiples. As indicated by PSNC (2019):

- 89% of the population in England has access to a community pharmacy within a 20-min walk;
- Over 99% of those in areas of highest deprivation are within a 20-min walk of a community pharmacy; and
- As the accessibility of community pharmacies is greatest in areas of higher deprivation, they may have an important role to play in reducing inequalities

Community pharmacy and the pharmacists working in this setting help to deliver healthcare service providing a convenient and less formal environment for those who cannot easily access or do not choose to access other kinds of health service. The services offered by community pharmacy are categorized into essential, enhanced (or advanced), and locally commissioned, all dependent on the contractual framework in place within the United Kingdom (NHS Community Pharmacy services—a summary, 2015) (**Table 1**).

Pharmacy owners (contractors) must provide all essential services, but they can choose whether they wish to provide enhanced (advanced) service. Furthermore, they can decide with local commissioners regarding the additional service offerings all dependent on population needs.

The General Pharmaceutical Council (2018, p6) has clearly stipulated the core principles and standards that all community pharmacies registered within the United Kingdom should comply with. The five key principles that are overarching across the standards are:

- Principle 1: The governance arrangements safeguard the health, safety, and wellbeing of patients and the public.
- Principle 2: Staffs are empowered and competent to safeguard the health, safety, and well-being of patients and the public.
- Principle 3: The environment and condition of the premises from which pharmacy services are provided, and any associated premises, safeguard the health, safety, and well-being of patients and the public.
- Principle 4: The way in which pharmacy services, including the management of medicines and medical devices, are delivered safeguards the health, safety, and well-being of patients and the public.
- Principle 5: The equipment and facilities used in the provision of pharmacy services safeguard the health, safety, and well-being of patients and the public.

Pharmacy owners are responsible for ensuring the safe and effective provision of pharmacy services at or from a registered pharmacy. They are accountable for making sure that the overarching principles and standards for registered pharmacies are met and that staff are aware of them. Community pharmacy has developed multifold over the last two decades form a supply and manufacturer of medicines through to a clinical provider of care in their own right. All pharmacies now have a private

Table 1 Examples of service offering within community pharmacy

Essential	*Enhanced (or advanced)*	*Locally commissioned*
Dispensing	Medicines Use Review (MUR) & Prescription Intervention Service	Minor ailments management
Repeat dispensing	Flu Vaccination Service	Palliative Care
Disposal of unwanted medicines	New Medicines Service (NMS)	Care Home services
Promotion of Healthy Lifestyles (Public health)	NHS Urgent Medicine Supply Advanced Service (NUMAS)	Gluten Free food supply
Signposting patients to other healthcare providers	Stoma Appliance	Out of Hours services
Support for self-care	Appliance review service	Supplementary or Independent Prescribing
Clinical governance/Signposting		

consultation area specifically for confidential or sensitive discussions (NHS Community Pharmacy Services—a summary, 2015) and community pharmacists are beginning to have access to records that are most often only seen in general practice. This is allowing pharmacists to care for the patients and public in a holistic manner by understanding a complete medical picture of the individual in front of them. Allowing the future of community pharmacy to evolve rapidly to current service provisions such as the management and monitoring of long-term conditions, for example asthma and diabetes, as well as delivering flu vaccinations, and conducting medicines reviews.

Pharmacists and General Practice

The evolution of pharmacists working in general practice has occurred in last 10 years within the United Kingdom, granted in various forms and guises. As indicated by the General Practice Forward View (2016), there has been over £100 million to support an extra 1500 clinical pharmacists to work in general practice in England by 2020, resulting in a large expansion of the general practice pharmacy workforce. There are a number of reasons behind this central investment, namely due to the potential benefit, a pharmacist can add into the management of patients within a practice (Stone and Williams, 2015). Focusing on all aspects of medicines, from application and administration through to prescribing and interactions, pharmacists working in general practice have a number of key roles and responsibilities. Some of these include:

- Providing expertise in clinical medicines review and address public health and social needs of patients in GP practices
- Reducing inappropriate poly-pharmacy and wasteful prescribing through clinical medication review
- Increasing quality and safety of prescribing through mechanisms such as audit and PDSA cycles
- Managing practice formularies to improve the quality, safety, and cost-effectiveness of prescribing
- Acting as a source of medicines information for all of the practice team and patients
- Working within the practice-based team to undertake medication reviews particularly in high risk groups such as frail elderly, renal impairment, hepatic impairment– substance misuse, patients on high risk medicines, and revolving door hospital admissions
- Improving prescribing practice through educational support for all prescribers within the practice
- Leading on where changes in evidence require changes in prescribing across patient population, e.g., where a drug is withdrawn or indications change
- Liaising with colleagues in community pharmacy to align support for medicines adherence
- Implementing drug withdrawals and alerts, e.g., MHRA aimed at improving medicines safety
- Supporting improvements in clinical care through practice-based audit and implementing change
- Prescribing advice to prescribers in practice, e.g., temporary nonavailability of drugs
- Ensuring patient safety when they are transferred between care providers through reconciliation of prescribed medicines

There is a clear assertion that having pharmacists in GP practices means that GPs can focus their skills where they are most needed, for example on diagnosing and treating patients with more complex conditions. This helps GPs to manage the demands on their time.

Scotland, England, Wales, Northern Ireland Variance

Health and the provision of services across the major parts of the United Kingdom vary, as they are devolved to the individual government bodies within each county making up the United Kingdom. Thus, the NHS services and pharmacy-specific provision offered in Scotland does vary from that offered in England, Wales, and Northern Ireland (NI). One of the key differences is around how healthcare and in particular pharmacy services are funded and the types of services being offered. For example, community pharmacy services in Scotland and Wales provide a number of additional services such as a universal wide Minor Ailments service, providing acute and minor aliment care to the patients that need it more, in addition to a number of key patient directed initiatives such as Pharmacy First, which allows patients free advice and treatment of certain conditions (NHSGGC, 2019). Compared to England where this is not currently a common practice, equally variations in General Practice pharmacy provision are evident as in Scotland, there have been pharmacists working in General Practice for over 10 years now, compared to England and Wales, whereas this is still a relatively new phenomenon. In Northern Ireland, the Marking it Better Through Pharmacy in the Community—A 5-year strategy (2014, 2017) seeks to provide a clear direction for the delivery of pharmacy services in the community, which place the individual at the center and aim to optimize their health and well-being at all times. It sees the increased utilization of pharmacists' clinical skills in the delivery of services in the community and greater collaboration of pharmacists with other health and social care professionals to demonstrably contribute to the improvement of the health of the population, thus also bringing Northern Ireland in line with the strategies for the other main counties within the United Kingdom.

As with any part of the United Kingdom, each representative healthcare commissioner or government body has the core guiding principle of making sure that the NHS provides safe, high-quality patient care, and services within primary care and to ensure that the NHS lives within its means.

Challenges Facing Primary Care Pharmacy Within the UK

The challenges facing Primary Care within the UK are real and tangible, coupled with pressures facing not only pharmaceutical services but also the wider practitioners within the primary care sector. Analysis of 30 million patient contacts from 177 general practice found that patient consultations grew by more than 15% between 2010/11 and 2014/15 (Understanding pressures in General Practice, 2016). Specifically, for pharmacy, there is a growing consensus that this health care resource is accessed regularly, approximately 84% of adults visit a pharmacy at least once a year- 78% for health-related reasons. Three-quarters of people have visited a pharmacy in the last 6 months (Department of Health, 2019). This puts pressure on demand, capacity, funding, and appropriate utilization of resource. Some of the key challenges (Department of Health, 2014) can be summarized as:

- Sustainability and Transformation—There is a requirement to ensure Pharmacy within the primary care sector works at transforming itself at a similar pace as other areas. To ensure, it remains efficient operationally and can integrated seamlessly with other healthcare professions.
- Integration and Technology—Integrating community pharmacy into the wider NHS to make better use of their clinical skills by providing NHS mail, Summary Care Record, Skype for Business and the Electronic Prescription Service (EPS) prescription tracker. Local pharmacists and their teams will be able to access relevant clinical information quickly and communicate more easily with patients and other health professionals. Primary care offerings are so varied that systems and processes that exist are so acutely different, that practitioners are unable to share information about patient care between themselves safely and efficiently.
- Financial—Ensure capital and government funding remains in place, and continues to support pharmacy services
- Training and Competence—Working a developing core competency framework and definitions of appropriate training that allow all pharmacy professionals to work to a defined standard across primary care service provisions
- Population changes—An ageing population that lives longer can put a lot of demand on primary care services but also significantly challenges clinicians as patients will ultimately have more complex health needs, ranging from comorbidities through to polypharmacy-related issue
- Quality—There is no clear consensus on what quality and good care looks like within Primary Care; there is a real need to define and standardize the quality of care provided by all sectors of pharmacy and health within primary care

Networks, Classification, and Interaction of Pharmacists

There is a consensus that pharmacist working across primary care, either in Community Pharmacy or General Practice, must be able to communicate effectively and efficiently with each other. Currently, there is a lack of clear and structured communication between pharmacy professionals. There remains great support individually for pharmacists working in either General Practice or Community pharmacy through trade bodies, unions, professional bodies, and commercial entities in the United Kingdom, but a distinct lack of uniformed voice across the wider Primary Care sector. There is an underutilization of communication and technology advances within pharmacy in this sector to ensure a more collaborative approach to pharmacy delivery. Digitizing all aspects of medicines and pharmacy has an enormous potential to improve patient care, increase safety, and make the system in the NHS more efficient. As the world changes at a rate not seen since the industrial revolution, pharmacy has been slow to adjust. There remains a reliance on inefficient, paper-based processes, which slow operational delivery of pharmacy services down, increase the potential for errors, and cost money.

Case Studies

Case Study 1 Mr Pharmacist in General Practice

Mr Pharmacist had worked for 20 years in community pharmacy, but recently moved into GP Medical Centre. He was to use his experience to develop a range of new services within his practice, including:

- Introduced a new repeat medication policy, ensuring more patients have a medicines review, and reducing prescription queries.
- Provides daily telephone consultations for patients with medicines-related questions.
- Runs medication review clinics for people on multiple medicines, which include Quality and Outcomes Framework reviews for patients with long-term conditions.
- Provides a care home's prescription management service for 300 residents.
- Helps the practice fully achieve its annual medicines optimization incentive payments, including improving prescribing of antibiotics and blood thinning agents

Mr Pharmacist is part of a team at Westbourne Medical Centre and works alongside GPs, a community pharmacist, a pharmacy technician, a nurse practitioner, a practice business manager, clinical governance and quality manager, and a receptionist. They are all part of a high performing, integrated, multidisciplinary team dealing with complexity in primary care, centered on clinical pharmacy helping to contribute to team capability within the GP surgery allowing "the unit to deliver care."

Impact

They record all pharmacist activities that directly relate to patients (telephone consultations, face-to-face consultations for patients with polypharmacy, prescription queries, clinical tasks from clinicians, and medicines reconciliations post-hospital discharge) using a template on the practice software.

The team uses metrics to assess all changes in general practice giving them relevant, objective, and easy to collect data. The practice collectively agreed an average time needed to perform regular activities, which otherwise would have been done by a GP, and have estimated that one post saves GPs 80 h a month, excluding indirect patient activities, the equivalent to two working weeks a month across the practice.

Lessons Learnt

The biggest success to date has been seen via two neighboring practicers who have also employed a pharmacist. The benefit to patients is clear—accessibility to health, information, and education on appropriate medicine use and concise medicine advice. In addition to understanding the enhanced roles, pharmacist and their teams can play in General Practice.

Case Study 2 Pharmacy First Scheme in Community Pharmacy

Pharmacy teams in rural part of the United Kingdom have helped more than 8000 patients during the first 5 months of a "Pharmacy First" scheme, which brought together three services to make accessing prescription medicines more convenient for patients and help reduce pressure on out-of-hours services. Patients were not only happy with the service they received, but said that they would also recommend it to others. This Pharmacy First scheme, delivered in a community pharmacy, included a minor ailments service delivered via a PGD, a winter ailments service, and an emergency supply scheme. The services, funded by a central government fund, and the key findings are outlined showed:

The Emergency Supply service saw participating pharmacy teams supply 769 different medicines to patients who had run out of their regular medicine, with the most requested item being salbutamol/Ventolin inhalers. When asked what they would have done if the service had not been available at their local pharmacy, 53% of patients stated that they would have accessed out-of-hours GP services instead. Devon LPC also reported local pharmacies received twice the national average of referrals from NHS 111.

The Pharmacy First scheme also gave patients a more accessible route to medicines for typical winter illnesses as 45% of patients reported that they would have used urgent care centers or visited their GP without the Winter Ailments service. This service was the most well used, accounting for 40% of the total interventions made, with pain relief/antipyretic oral solutions being the medicine type most often supplied.

The Minor Ailments via Patient Group Direction (PGD) service was similarly successful at providing patients with an alternative method of medicine supply. The most popular condition presented to pharmacies was bacterial conjunctivitis, accounting for 56% of all PGD interventions (Devon Local Pharmaceutical Committee, 2015)

Impact

The Pharmacy First services have saved over 4800 appointments with doctors: 3790 appointments in General Practice, 1818 of out of hours GP appointments, and 210 Accident and Emergency appointments.

Lessons Learnt

Community Pharmacy has a vital role to play in Primary Care currently and in the future. There is a clear underutilization of pharmacy services within the community and it can be further developed with the appropriate infrastructure to help it achieve such benefits as seen in this case study.

Secondary Care pharmacy services in the United Kingdom

Current Secondary Care Platforms and Service Offerings

Pharmacy provision is Secondary Care occurs in most parts within a hospital environment. Pharmacy services are delivered in hospitals through teams working in the dispensary, procurement and distribution, clinical trials, clinical pharmacy, ward-based pharmacy, medicines information, aseptic services, education and training services, nonsterile manufacturing, and quality control. Pharmacists work on a rotational or permanent basis in one or more of these departments. The size and activity of each department depend on the type of hospital and the geographical area. Hospital pharmacists are recognized for their expertise in many specialties. Some of these include anti-infectives, cardiology, HIV, mental health, care of the elderly, oncology, pediatrics, palliative care, and renal pharmacy. They have a direct involvement in patient care and influence treatment choices by being involved in decision-making at the point of prescribing (Rodden, 2000) (**Table 2**).

Newly recruited basic grade pharmacists rotate through the various sections of the typical hospital pharmacy department, gaining experience of the different specialties. There is no longer a single career structure for hospital pharmacy. Instead, there is a myriad of possibilities. Importantly, specialization in one area does not bar pharmacists from posts in other areas. Pharmacists are graded in a banding structure, which is based on experience, expertise, and professional education. As a pharmacist progresses through the band, experience and seniority structure, this is complemented with relevant salary increases, as well as changes to the responsibilities and professional practices. Notably, within the hospital sector, there are opportunities to study for a clinical diploma or Masters qualification in relevant fields and a strong commitment to continuing professional development.

Clinical pharmacy forms a large part of hospital pharmacy work. Clinical pharmacists are part of the healthcare team on the ward, working with medical and nursing staff and the various therapy professions. Within the team, they are seen as the experts on drugs and their advice is sought by the other members. Clinical pharmacists work closely with both prescribers and patients. They often attend consultant ward rounds where they can influence prescribing, as well as prescribing themselves if an independent prescribing qualification is attained. A typical working day of a hospital pharmacist can vary significantly in role and day-to-day responsibilities, with a focus on the provision of clinical care most commonly at the heart of their daily duties (**Fig. 1**).

Table 2 Structure and examples of a pharmacist workforce within a typical hospital pharmacy department

Banding	*Title(s)*	*Years qualified*	*Expectation of learning*	*Examples of some typical duties*
Band 5	Pre-registration Pharmacist	0	Completion of undergrad and pharmacy degree	Shadowing pharmacists within clinical settings, dispensing, and learning technical skills
Band 6	Basic Grade Pharmacist, Hospital Clinical Pharmacist	1–2	Passing the General Pharmaceutical Council exam	Working on a ward, in a dispensary, checking, rotations through specialist areas such as aseptic, medicines information and clinical areas
Band 7	Hospital Clinical Pharmacist, Senior Clinical Pharmacist	2–4	Starting and completion of postgraduate diploma in clinical pharmacy	Autonomous clinical work on wards and departments, mentoring band 6, further exposure to clinical settings, conduct audits
Band 8a	Specialist Clinical Pharmacist	4–8	Completion of Masters within Clinical Pharmacy, starting and completion of Independent Prescribing qualification	Working on a specialized ward, attendance on ward round, conducting an outpatient clinic, teaching students, Quality improvement projects
Band 8b/c	Lead Clinical Pharmacist, Principal Pharmacist, Consultant Pharmacist, Head of Department or service	8-12	Further postgraduate degree in related discipline or clinical specialty, project management qualification, recognized leadership program	Managing a group of senior pharmacists, delivering on strategy and performance, attendance at meetings, shaping policy
Band 8d/Band 9	Head of Pharmacy, Director of Pharmacy, Chief Pharmacist	12+	Master of Business Administration, or additional leadership/management qualification	Leading the pharmacy service offering within hospital, Executive representation of pharmacy at platforms/meetings, strategizing and vision setting

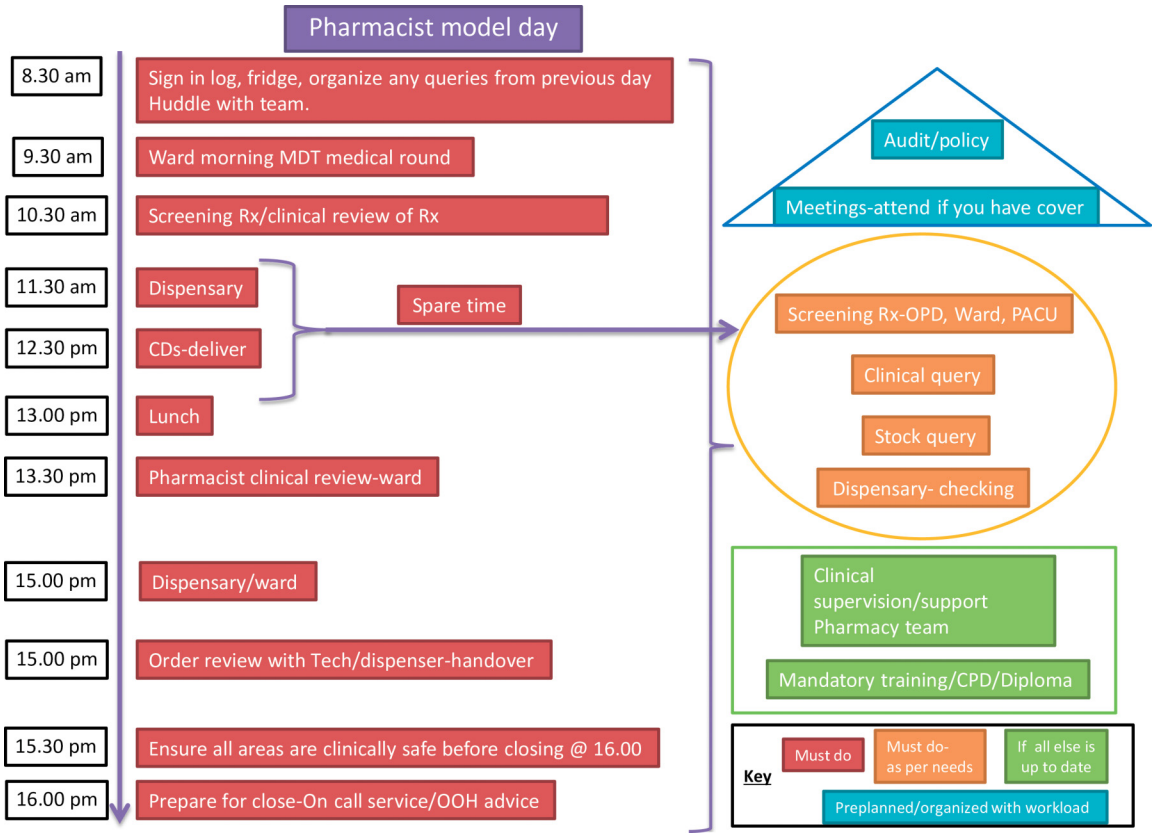

Figure 1 Typical day of a band 6/7 pharmacist.

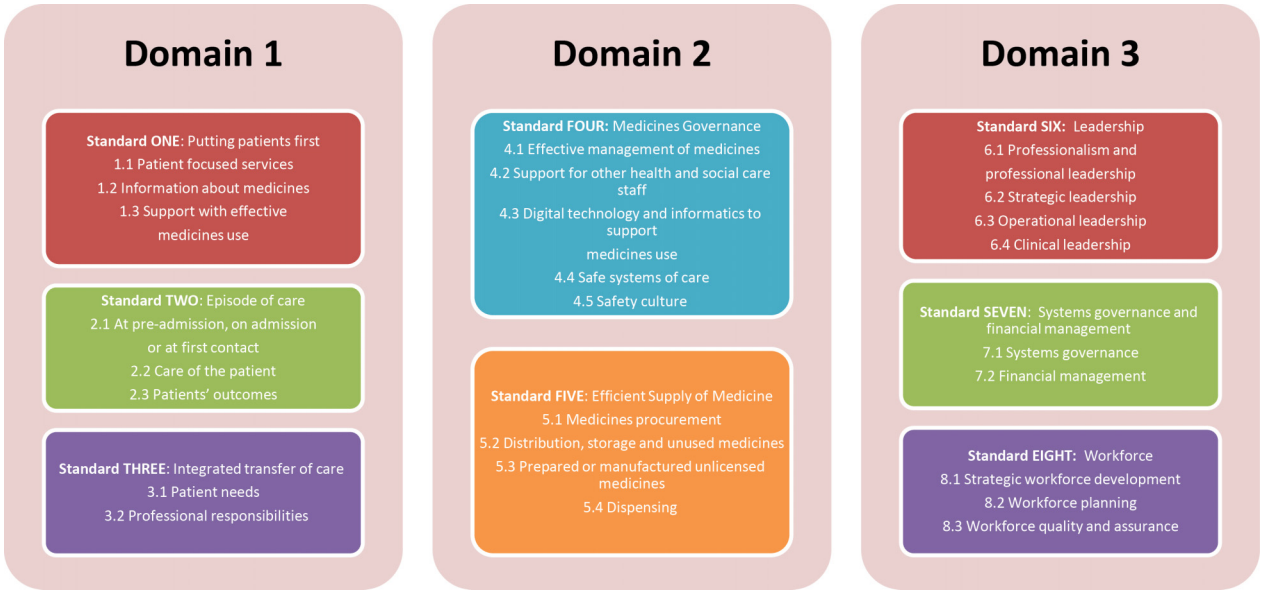

Figure 2 Eight overarching standards grouped into three domains (Royal Pharmaceutical Society, 2017).

Within the past 5 years, there has been great effort made at standardizing and recognizing the core elements of hospital pharmacy. The Royal Pharmaceutical Society (2017) created a revised version of Hospital standards, which heralds the first publication of key standards in relation to practice within this sector. The professional standards describe quality pharmacy services and key examples of excellence in this field. The standards provide a broad framework that will support pharmacists and their teams to continually improve services, shape future services and roles, and deliver high-quality patient care across all settings and sectors (Royal Pharmaceutical Society, 2017).

The professional standards support professional practice and encourage a culture of openness, transparency, and candor that puts patients first by encouraging professionalism. These standards help patients experience a consistent quality of service within and across healthcare providers that will protect them from incidents of avoidable harm and help them to get the best outcomes from their medicines (Fig. 2).

Scotland, England, Wales, Northern Ireland Variance

Within Secondary Care, the variance in practice of pharmacist and pharmacy teams is very minimal across the counties of Scotland, England, Wales and Northern Ireland. The differences that may exist would be reconciled to: variations in job roles and titles, slight salary fluctuations, and a contrast of clinical duties, but frequently their day-to-day practices would largely be very similar. The hospital sector traditionally within the United Kingdom has developed in a uniformed manner, allowing a clear understanding of pharmacists working in Secondary Care.

Origins of Clinical Practice Within Secondary Care

The role of pharmacists working in the Secondary Care sector in the NHS has evolved rapidly since the evolution of healthcare in the 1940s. Growing from what was originally a supply service to becoming a clinical orientated practice in hospitals, and with a range of new roles in clinical specialties, pharmacists are now recognized as a valuable part of the multidisciplinary clinical team (Jankovic, 2019).

Pharmacists were quite often only seen as the departments they worked in and rarely on a ward or taking to patients, compared to the current climate where pharmacists are routinely based in clinical environments such as wards and outpatient departments. Pharmacists were quite often only seen within the pharmacy departments they worked in and rarely visible on a ward or talking to patients. This is distinctly different to the current climate where pharmacists are routinely based in clinical settings, including wards, accidents and emergency departments, and outpatient areas. It can be acknowledged, this has come about due to the transformative difference in how the NHS is being delivered with a focus on ensuring that patients see the right health care professional in a timely manner for their care needs.

Current Pharmacists Roles Within Clinical Practice and Professional Development

Providing the best care to patients requires hospital pharmacists to build on the knowledge acquired during the 5 years of pharmacist training and to develop this knowledge further throughout their careers. The hospital sector provides excellent

development opportunities and some NHS departments provide financial support for postgraduate qualifications. Newly registered hospital pharmacists are encouraged to advance their practice by studying for postgraduate certificates or diplomas in clinical pharmacy or pharmacy practice. Exposure to different practices at this point in their career develops their knowledge, skills, and experience in order to decide on a specific area of practice in which to specialize. Clinically specific, secondary care pharmacists' role includes:

- Oncology clinical pharmacist
- Renal pharmacist
- Palliative care pharmacist
- Clinical effectiveness pharmacist
- Wound care pharmacist
- Cardiology pharmacist
- Pharmacoeconomics pharmacist
- Principal pharmacist
- Lead clinical pharmacist
- Pain management pharmacist

At all stages of a hospital pharmacist's development, training opportunities are provided, including in-house training from within the pharmacy department or hospital, regionally or nationally organized study days, courses, or conferences covering specific topics and specialty and management training. This ensures that pharmacists working in this sector are aptly trained and experienced to provide the level of specialized care needed.

Case Studies

Case Study 1 Ms Clinical Pharmacist in a hospital setting specializing in Renal Transplant and Urology

My daily routine involves: applying my expert knowledge to advise on dose adjustments for medicines in renal (kidney) impairment, pharmacokinetic interactions, drug administration and management of adverse drug reactions (side effects). In renal and transplantation the drug regimens are highly complex and a failure to manage them correctly could have catastrophic consequences, so the pharmacist is an important and respected member of the multidisciplinary team. I am also an independent prescriber and run a medication review clinic for transplant patients. Being able to suggest changes to make it easier for patients to manage their condition is very rewarding. Other roles that I have include writing guidelines, financial management of drug budgets and teaching and training undergraduates and junior pharmacists.

Impact

I am able to directly influence and shape the care patients get from the medicine patients receive. I am able to understand and evaluate the effects medicines are having on patients and appropriate correct and prescribing.

Lesson Learnt

An appropriate trained and experienced hospital pharmacist has a number of roles within the care of patients, and is able to effectively communicate and demonstrate the impact to the quality of care being delivered.

Case Study 2 Utilization of Technology and Informatics in Hospital Pharmacy (NHS England, 2016a,b)

The clinical informatics team at a NHS Hospital was created when the trust introduced an electronic patient record (EPR). The electronic prescribing (ePx) component of the system was implemented by the pharmacy department with the assistance of a multidisciplinary project team. Over the last decade, the system has been continually developed and is now digitally mature. Key to their ongoing informatics development is the department investment in a permanent pharmacy informatics team. The pharmacist-managed team of pharmacy technicians led the initial implementation being involved in process mapping, process design, system build, and user engagement. They also designed the testing, training, and governance processes to ensure safe successful implementation and compliance with information standards for clinical systems.

Experience, through continuity of the team, has been an important factor in ongoing improvement. This has been developed through the trust supporting the pharmacy informatics team to undertake informatics qualification, for example, informatics degrees, system architecture courses. With a wider understanding of the technical and operational aspects of developing and maintaining an EPR, the team has improved in troubleshooting, rule creation, report writing, interface development an example utilizing all of these being the development of an EPR-generated and automated community pharmacy referral process (Clinical Handover).

Another key to success is ensuring the pharmacy informatics teams are represented on key hospital groups and committees. Representation at these has been essential to ensure that informatics is developed according to hospital priorities and to ensure that informatics and its opportunities are embedded into new hospital developments with the engagement of key stakeholders.

Impact

The team have subsequently developed the system in close collaboration with the hospitals IT services. They have provided leadership on several system upgrades, for example, JAC upgrades and creation of a network version of the Trust's chemotherapy ePx system. They have also led on the uptake of new EPR functions. An example of this being the development of clinical pharmacy prioritization tools, which provide a supplement to traditional decision support models. The skills gained during this have benefited medicines optimization and wider applications of the EPR such as laboratory services.

Lessons Learnt

This department is one of several hospitals nationally that have focused on developing and implementing a best practice model to prioritize patients. This has enabled them to target and provide patients with a structured 7-days a week clinical pharmacy service. Electronic prescribing systems have the added value of providing intelligence of prescribing activity that occurs during the patient pathway in hospitals.

Case Study 3 Medicine Reconciliation

The hospital department have developed a Medicines Reconciliation checklist that is used for all nonelective adult hospital admissions. It is designed to be used by a pharmacist, technician, or preregistration student who has an underpinning knowledge of the medicines reconciliation process (any new member of the team is competency assessed on completing the activity by senior pharmacist or technician).

Each statement in the checklist is designed to act as a prompt so that the right information is elicited in a logical manner such that the best possible drug history is established. The final prompt is to ensure the patient's prescription chart reflects reality and any anomalies are resolved, so the drug history can be considered as clinically checked.

Impact

The checklist is designed to provide the hospital and pharmacy department with the assurance that an effective process has been followed in order to achieve medicines reconciliation. They carry out occasional audits of it; sometimes, we have incidents reported where the process has not been followed. If the checklist is used and the SOP is followed, invariably the drug history is correct.

Lessons Learnt

Medicines reconciliation is a process that helps to minimize significant medicine-related harm. More importantly, this case highlights the role that each health care professional can have at completing an accurate medicine reconciliation process.

Integration Model and Healthcare Redesign—What Does This Mean for Pharmacists?

Current and Future Landscape of Healthcare Delivery Within the United Kingdom

Healthcare in the United Kingdom is complex and variant. As mentioned, there are key sectors where healthcare and pharmacy services are delivered. New treatments for a growing and aging population mean that pressures on the service are greater than they have ever been. But treatment outcomes are far better—and public satisfaction higher compared to 10 or 20 years ago. Medicines are the single biggest intervention for the prevention and treatment of ill health, the overall medicines cost in the NHS in 2017/18 was £18.2 billion, an increase of 4.6 per cent from £17.4 billion in 2016/17, and an increase of 28.4% from £13.0 billion in 2010/11 (NHS Digital, 2019).

Medicine and pharmacy services are situated in every major clinical service within the United Kingdom. The future of healthcare delivery in the United Kingdom will need to transform to ensure sustainability; quality and capacity can be maintained. Patients, diseases states, medicine regimens, and patient pathways continue to evolve and develop as medicine research improves. Consensus of challenge of the future of healthcare delivery includes:

- legacy technology and commercial arrangements
- complex organizational and delivery structures
- a risk-averse culture
- limited resources to invest
- a critical need to build and maintain public trust

Current Government Policy and Strategy on Pharmacy Services Within the United Kingdom

There are multiple key pharmacy strategies across the United Kingdom, which detail the benefits of pharmacists with vision setting of what pharmacists can achieve in the delivery of health care across all platforms.

In Scotland, Achieving Excellence in Pharmaceutical Care (2017, p3) lists two key priorities for pharmacy:

1. Improving NHS pharmaceutical care
    a. Improvements to NHS pharmaceutical care services across Scotland
    b. Delivering safer use of medicines for the people of Scotland
2. Enabling NHS pharmaceutical care transformation
    a. Ensuring capability and capacity by further developing the pharmacy workforce
    b. Developing a digitally enabled infrastructure
    c. Planning and delivery requirements for sustainable NHS pharmaceutical care services

In England, the Pharmacy Integration Fund Strategy (2016) and Integrating NHS Pharmacy and Medicines Optimisation into Sustainability & Transformation Partnerships and Integrated Care Systems (NHS England, 2019a,b,c) describe a clear drive for the greater use of pharmacists and pharmacy technicians in new, integrated local care models. The initiatives provide opportunities for pharmacy teams to spend more time delivering safe and effective clinical services and health improvement for their patients; work in a variety of NHS settings as part of an integrated local primary care team; and to be supported by improved technology.

The priorities and visions for the future of NHS pharmaceutical care that are set out in these strategies, indicate how pharmacists and pharmacy teams can be integrated within a modern digitally enabled health and social care system and have the potential to open up new and rewarding career pathways for pharmacists and pharmacy technicians in increasingly clinical roles.

Current and Future Patient Demographics Within the UK National Health Service

It is widely accepted that the population in the United Kingdom is living longer; therefore, the challenges, demands, and changes required to provide adequate on-going health care are vast. Patients living longer can result in more complex care, through the development of comorbidities and the relevant polypharmacy that originates from this. Pharmacists and pharmacy services need to transform appropriately to cope with the change of patients and populations.

Pharmacist Utilization Analysis and Discussion Within the Health Systems Across the United Kingdom

Making the best use of a pharmacist can be difficult; there remains a distinct lack of utilizing pharmacists and their teams optimally within health systems across the United Kingdom. The NHS is using the clinical skills of pharmacists and pharmacy technicians to review people's medicines in GP surgeries, hospitals, care homes, and urgent care, working as part of the wider healthcare team, but currently there is limited research in how pharmacists are utilized appropriately.

Examples and Realization of Integrated Primary and Secondary Care Services

The integration strategy of health systems in the United Kingdom has resulted in the formation of a number of innovative pharmacist roles. Some of these include:

- Pharmacist in Telehealth—working at providing pharmaceutical care through telephony health
- Secondary Care Pharmacists working in Primary Care—pharmacists providing specialist care within the community via clinics
- Evolution of GP Pharmacists—identifying patient groups for pharmacists to care for autonomously, development of prescribing clinics and managing repeat prescriptions
- Pharmacist within the Care home setting—polypharmacy reviews of elderly patients
- Community Pharmacists developing long-term condition management clinics—where pharmacists within the community run disease-specific medicine management.

Emerging and Innovative Roles Currently and Within the Next 10–20 Years

Description of a Potential Healthcare Landscape Within the Next 10 Years

The healthcare landscape of the next 10 years is complex and constantly changing as indicated. The core principles that will help to describe and shape what the next 10 years will look like (NHS England, 2019a,b,c) are:

- Further joined-up and coordinated care
- Breaking down traditional barriers between care institutions, teams, and funding streams so as to support the increasing number of people with long-term health conditions, rather than viewing each encounter with the health service as a single, unconnected "episode" of care;
- Proactive in the services provision—with a focus on preventative care than cure
- Technological advances—how does innovation in technology can help to seamlessly integrate and transform care
- Workforce changes—ensuring appropriately trained staff are available and apt to be utilized

The recently published plan focuses on building an NHS fit for the future by enabling every patient to get the best start in life, continually helping communities to live well and helping people to age well.

Potential Examples of Pharmacist Roles

Many of the current strategies and government policies mentioned, recognize the potential for pharmacy, highlighting that there should be far greater use of pharmacists in the prevention of ill-health, support of self-care for minor ailments and long-term conditions, and as part of more integrated local care models. Subsequently, there are multiple roles that are emerging for the future. In Primary Care, the further evolution of General Practice Pharmacists continues, and the future will bring more patient ownership and self-governance of practice. Within Community Pharmacy, there is a real potential that this group of pharmacy

professionals are being shaped to become the cornerstone of health care within the community, a stronger focus of developing clinical skills of community pharmacists, in addition for this sector to be at the forefront of preventative health care and wider public health agenda. Within Secondary Care, there is a consensus that pharmacists working in this setting must start to care for patients out with the typical hospitals setting. Thus, the future will see a more portfolio approach to pharmaceutical care, where pharmacist's potentially will work routinely across care boundaries. Technological advances in automation, telehealth, informatics, and pharmacogenomics will herald new clinical settings and opportunities for pharmacists and pharmacy teams, and the traditional descriptors of primary and secondary care will potentially no longer be sufficient to illustrate where pharmacists will typically practice.

Obstacles and Hurdles and How is This Reached and What is Needed to Make This a Reality

There are some obstacles and hurdles facing pharmacy reach its true potential. Some include:

- Finance—the lack of assurance of funding within some sectors such as community pharmacy will destabilize the progress made, compared to other settings such as general practice, where much government funding has been given recently
- Sustainability—how best to ensure the on-going continuation of any potential new service model is not clear, in addition to fully implementing processes to cover the work done in the past by pharmacists in new and emerging roles
- Workforce—both undergraduate and postgraduate training of pharmacists will need to be developed to appropriately educate pharmacists to a competence that will allow them to deliver pharmaceutical care in other settings and in more specialized arenas.
- Reaching the potential and making it a reality—Traditionally, pharmacy services have been poorly represented in executive levels of health systems; the ability to influence key stakeholders will inevitably pose the biggest hurdle in making the future practice of pharmacy a reality

Role of Regulation, Professional, Academia, and Unionized Bodies

Regulatory, professional, and unionized bodies, coupled with academia, all have distinct roles in ensuring the continuation of pharmacy services within the traditional settings of care, but more importantly at ensuring the future landscape of care, have appropriately pharmacists and pharmacy services embedded in. Regulatory and professional bodies must ensure the regulation and representation of pharmacy is adequately explained and voiced at the most senior platforms within the United Kingdom. Unionized bodies must be able to change their stance in protecting the changing workforce, as the parameter of care will inevitably be different. Equally as important, the academia structures are vital to train, educate, and develop the future of the profession. The pharmacist and pharmacy team of the future are far removed from the typical primary and sector care descriptors; thus, they require a different skillset and knowledge base to be ready to practice.

Conclusion

Pharmacists and pharmacy services, teams, and departments in the United Kingdom have varied and challenging roles. Within primary and secondary care, we have pharmacists that have a number of patient facing roles, which have direct impact on the quality and provision of care offered within the wider health systems. Pharmacists in these sectors dispense, manufacture, prescribe, and advise on the most optimal use of medicines. The pharmacy professionals within each sector are quite unique in their practice and knowledge base, but as the future of heath care in the United Kingdom is being formed, we see more of a need for a collegiate pharmacist that has a unified competence base to care for patients adequately. The typical sectors of pharmacy in the future will be widely different in the future, and thus pharmacy in the United Kingdom in the next 10 years will look markedly different to that of now.

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Pharmacy Practice in Portugal

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Introduction

As in most countries worldwide, the focus of pharmacy in Portugal has shifted from a drug-oriented to a person-oriented practice. Historically, patients would go to a pharmacy and see the pharmacist spending most of his time in the laboratory, preparing ointments, syrups, and even suppositories. The existing space for the pharmacist to talk to medication users was practically nonexistent. In fact such a space was not even needed because no great interaction occurred, apart from informing how to use the magisterial or official preparation. By the 1980s and 1990s, there was refurbishing of many premises, increasing the public and consultation areas. At this time, aspirins and other over the counter medication appeared on the shelves behind the counter, although much of the space was still left for antique vases because many pharmacists still appreciated the relationship between pharmacy and art. More recently, a specific separate space within the public area was created so that people living with a disease could have their biomarkers measured, and this space was also used to counsel people on more sensitive matters that would require

discretion. Today, pharmacists have witnessed and supported the most recent investments, focusing on a second separate and larger space where vaccines could be administered, and also the acquisition of cars with the required legal conditions of strict humidity and temperature control for domiciliary delivery of medication.

What is Pharmacy Practice?

There are various definitions of the term Pharmacy practice. The World Health Organization (WHO), early in 2006, mentioned pharmacy practice as a natural evolution of the profession, moving away from medicines supply into patient care, profoundly influenced by the emergence of pharmaceutical care (World Health Organization, 2006). This practice change may be considered a landmark because the practitioner starts to be held responsible for patient outcomes (Hepler and Strand, 1990).

The International Pharmaceutical Federation (FIP) described Good Pharmacy Practice (GPP) and it proposed to be defined as "*the practice of pharmacy that responds to the needs of the people who use the pharmacists" services to provide optimal, evidence-based care*' (International Pharmaceutical Federation, 2011). The adoption of GPP both in the community and in the hospital setting contributed enormously to the practice model we have today in most developed countries.

More recently, a conceptual model for pharmacy practice has been proposed, where apart from the concepts of professional activities comprised into the above definition, broader roles of the pharmacist are considered, including the involvement in health policy (Scahill et al., 2017).

This chapter will adopt this broader model, aiming to provide a more comprehensive overview of how the pharmacist profession has evolved in Portugal, for which aspects of clinical pharmacy and pharmaceutical care have had an enormous contribution, but also wider disciplines including public health, without forgetting the contribution of pharmacy advocacy organizations to promote greater outreach of pharmacists' most traditional activities.

The Face of Pharmacy in Portugal

The pharmaceutical profession emerged in Portugal in the 13th century, with the establishment of the first apothecaries. Currently, there are approximately 14,500 practicing pharmacists, with 79% of them being female and 68% less than 45 years old (Ordem dos Farmacêuticos, 2018). This demographic profile reflects the substantial increase in the number of pharmacists in the country in the last two decades, as a result of the number of faculties of pharmacy having tripled, from three in the late 1980s to nine in 2018. Since 2011, more than 700 new pharmacists start practicing each year, which places the pharmacist density in Portugal at 1.4 pharmacists per 1,000 inhabitants.

As a result of their scientifically based education, pharmacists carry out their activity in several areas, with community pharmacy (59%), hospital pharmacy (9%), and clinical biology (5%) as the most predominant. However, pharmacists have been taking up new roles in other areas such as the pharmaceutical industry (5%), wholesale distribution (4%), research (1%), medical devices, and health technology assessment (Ordem dos Farmacêuticos, 2018).

Pharmacists in Portugal currently work in the more than 2900 existing community pharmacies—which operate with an average of 3 pharmacists/pharmacy, one of the highest ratios in the European Union (PGEU, 2016)—more than 200 hospitals, 400 clinical biology laboratories, 120 pharmaceutical industry companies, and 25 wholesale distribution warehouses.

Pharmacists are a highly trusted professional, with community pharmacies being the first place Portuguese citizens' visit when they have a minor health problem (CESOP, 2018). A recent survey further showed that 96% of the population is satisfied or very satisfied with the service received, highlighting aspects such as professional competence (95%), quality of services (95%), counseling appropriateness (92%), operating hours (90%), and location (89%). The overwhelming majority of respondents were also favorable to the development of new services by pharmacists (CESOP, 2018).

A study commissioned by the Portuguese Pharmaceutical Society in 2015 aimed at evaluating the social and economic value of public health interventions conducted by pharmacists in Portuguese pharmacies documented more than 120 million pharmaceutical interventions per year, covering 4.2 million users, which contributes to the improvement in citizens' quality of life of 8.3% and to an economic value of 879.6 million euros (Félix et al., 2016). Each individual pharmaceutical intervention represented an economic value of €7.30.

Moreover, the authors noted that potential savings of more than 144.8 million euros, if pharmacists could be given the opportunity to fully exercise according to their scope of expertise, in services covering adherence enabling strategies, renewal of chronic prescriptions, and provision of travellers' advice.

Overview of the Portuguese Health-Care System

Origins and Values of the Portuguese National Health Service

All Portuguese citizens have access to a National Health Service (PNHS), publicly funded by taxes, and free of charge at the point of delivery. The PNHS was created in 1979 and embedded into the constitution, to ensure all citizens have the right to preserve their heath, regardless of their socioeconomic status.

The creation of this service had an enormous impact and resulted in the improvement of various health indicators, namely, infant and maternal mortality. Portugal is now ranked as one of the best performing health systems in the world (Félix et al., 2016).

The PNHS is based on two pillars; it is universal, meaning it is accessible to all the population; it is of high quality, as it provides highly effective care. However, it is not comprehensive because not all treatment options are available within the PNHS. The choices made on what gets included are based on the state's budget, which in the Portuguese case, as in most countries, is somehow limited. The funnel of Dunning criteria are used to prioritize, and health technology assessment is used to select the most cost-effective options. Because of limited funds, in some cases, restrictions may be imposed to beneficiaries of a given treatment (e.g., only those having a BMI ≥35 are entitled to a paid bariatric surgery) or to the level of co-payment applied. Co-payments exist in the form of access fees, which are intended to promote a judicious use of healthcare (i.e., unplanned care has a higher fee than planned care) but are also applicable to medicines financing. To establish the different levels of co-payment for medicines, various criteria exist, including the prevalence of the disease, its severity, and the pharmacotherapeutic class demonstration of efficacy. These range from 15% to those considered borderline in terms of efficacy, a level normally applied when there is some uncertainty, to 100%, where the remainder is paid by the patient out-of-pocket. In all co-payment forms, however, the principles of solidarity apply, that is, those socially disadvantaged are awarded exemption of access fees or higher co-payment levels by the PNHS.

The Portuguese Health-Care System

Although the Beveridge principles prevail, in the recent decades, alternative models of care provision have emerged. Currently, care may be received in private, public services and also in mixed models of service provision. As a citizen, the citizen by birth or residency is entitled to benefit from the public facilities, which fit into the PNHS, and may then also choose to contract an insurance (which may be voluntarily made by the individual or the employer). This organization implies the person may choose to use one or the other, or even both depending on perceived needs, severity of the situation, or simply commodity. However, it may also be seen as a way of creating inequality because most of the uninsured will not be able to pay for care provided in private facilities.

PNHS Sectors

All these services are organized in three levels of care provision summarized below.

- Primary care is aimed primarily at disease prevention (including vaccination and screening) and management of chronic conditions. These are located at the heart of communities and organized in different formats. Primary care in Portugal is delivered by a mix of public and private providers, including primary care units integrated within the NHS, private sector clinics (both profit and non-profit), and groups of professionals in private offices (OECD, 2018). In the public sector, there are five regional health administrations, subsequently divided into Primary Health Care Clusters (ACES). These are public health services distributed throughout the country (n = 55 in 2018), with administrative autonomy, intended to provide proximity and tailored care to the population covered (which may range between 50 and 200 thousand inhabitants). The family units, hierarchically under the former, are the most recently developed structure, characterized by the use of technology, multidisciplinary work, where professionals are paid according to their performance, as dictated by contracted indicators periodically established and assessed. There are currently 532 family units in Portugal (ACSS, 2018). Under this model, each family is assigned a healthcare team, comprising a minimum of one GP, one nurse, and one administrative assistant. Other healthcare professionals may also be available in some of these structures, namely, psychologists, dentists, nutritionists, and even some additional medical specialties, but more seldom. PNHS GPs act as gatekeepers and refer patients for specialist care. There are other structures within primary care, not detailed here because they are more specific and less common.
- Secondary care is basically organized as hospital units or hospital centers and traditionally, their main goal has been to treat acute conditions or exacerbations of chronic conditions requiring surgical interventions or hospital admission. However, this has substantially changed in the past decade, with an increase in outpatient consultations and day surgeries which have, in conjunction with the bolstering of the long-term care network, led to a decrease in the total number of inpatient hospital beds and a shift of costs where currently the highest proportion of hospital costs (roughly 70%) is attributable to outpatient appointments (OECD, 2017).
  In 2018, there are 225 hospitals, of which 107 are public and 118 are private (ACSS, 2018). These include units from public administrative sector, public entrepreneurial entities, and institutions under a private–public partnership. A recent measure adopted in Portugal was the system of free access and circulation of NHS users, through which since 2016 any citizen may choose in agreement with his/her family physician the hospital to be monitored for the required medical specialty. Hospital care is currently also paid by performance according to contracted indicators, which may include clinical outcomes, such as mortality, or process indicators enabling evaluation of the quality of care, such as readmission rate, waiting time, or referrals to tertiary care (ACSS, 2018).
- Tertiary care is aimed at providing specialized care to people requiring temporary or permanent recovery services. Within tertiary care, the National Network for Continuous Integrated Care was created as part of public services enabling access to any citizen. This network covers care provided to adults, children, mental health patients, and those staying at home but requiring assistance (domiciliary care). In each of these levels, there are units for long term, intermediate and short-term stay. In March 2018, the total number of vacancies available within this network was 14,700, a number much lower than the necessary for an aging population.

PNHS Budget for Medicines

Health expenditure in Portugal was 7.5% in 1995, and since 2004 surpassed 9%, remaining quite steady since then (Simões et al., 2017) and in line with the EU average. The most recent published data points to the same value of 9.0% (OECD, 2018). There have been periods of lower investment in health, namely, during the 2008/2011 economic recession, when many cost-containment measures were imposed. In general terms, one can say that even though the value spent on health as a percentage of the GDP is apparently in line with the EU context, if we look at the public sources of spending as a percentage of the total health expenditure, Portugal has one of the lowest values in the EU (64.8% in 2014). In fact, although the Portuguese health-care system functions quite well, the proportion of out-of-pocket (OPP) payments made by our citizens is probably one of the lowest in the world. In 2014, the OOP payments as a percentage of the total health expenditure reached 26.8%. Health expenditure per capita was reported to be 2066€ in 2017, a value below the 2773€ for the EU28. In addition, Portugal was the country with the second greatest reduction in costs between 2011 and 2017, only surpassed by Greece (OECD, 2018).

Regarding pharmaceutical expenditure, following the Memorandum of Understanding signed after the economic recession, a target of 1.25% of the GDP was set for 2012 and 1% for 2013. In 2014, 1.23% of GPD was achieved (Simões et al., 2017). During this period, Portugal was portrayed as the country with the second highest reduction on pharmaceutical expenditure, mostly achieved through price reduction (OECD, 2016). However, it has later been shown that the reduction in costs for pharmaceuticals was only for the period 2008–12 (−0.7%), immediately followed by an increase in 2012–16 (0.8%) (OECD, 2018). Breaking down to setting, we can observe that the reduction of costs was mainly achieved through measures applicable to the ambulatory setting. In fact, for the period 2009–16, the reduction for retail was 5.4%, contrasting with an increase in hospital pharmaceuticals of 0.7% (OECD, 2018).

Portuguese authorities set several policies to control pharmaceutical expenditure. These start at the moment of market introduction, where the price is set based on a clinical evaluation complemented by economic considerations, i.e., the price of existing medicines and international prices considering at least three reference countries (Spain, France, Italy, and Slovenia established for 2019; Portaria n.° 326-A/2018, December 14th which modifies Portaria n.° 314-A/2018, December 7th). Internal reference pricing applies, through which INN prescription is mandatory and pharmacies will have to dispense one of the five cheapest products within the same active ingredient, form and dosage (reference pricing), except if the patient chooses otherwise, in which case he would have to pay the price difference. Promotion of generic substitution is also a popular measure to contain costs and the current target set is for 60% of the PNHS market (European Commission, 2016).

From 2014 onward, pharmaceutical expenditure has been monitored so that the introduction of innovative medicines is possible. The ambulatory market has been increasing 0.5% per year and hospital consumption increased 8% in 2016. In 2016, the value spent on ambulatory and hospital care on medicines was about even (1190 and 1107 million €, respectively). Again, as in care provision in general, the proportion of OOP payment applied to medicines may be considered quite high, although decreasing from 2011 to 2016, and perhaps an aspect worth improving in the country's functioning (World Health Organization, 2018). Medicines supplied in hospitals under the PNHS are fully reimbursed, but in ambulatory care, reimbursement varies from 15% to 100% depending on the pharmacotherapeutic subgroup and on eventual population exemptions. The average spent per capita on pharmaceuticals in Portugal was reported to be 297 €, a much lower value than the 402 € reported as the EU average (OECD, 2016).

There are specific areas where a budget is allocated per patient treated (within the NHS). For example, for Hepatitis C, the agreed price per patient treated in 2019 is 6922€. For HIV, the agreed price for treatment in ambulatory care (as long as registered under the national database) is 5997€ per year per equivalent patient. There are other areas for which a price is set, which will not be detailed, namely, pulmonary hypertension, multiple sclerosis, oncology (six types of cancer), paramyloidosis, and lysosomal diseases (ACSS, 2018).

Pharmacy Regulation in Portugal

Pharmacy Education

Education in Portugal is regulated by the Ministry of Education, and this applies to basic, high school, and university education, regardless of the professional area pursued at a later stage. As such, the education of pharmacists occurs at university and requires a 5-year degree, according to the Bologna declaration, which results in a Master's degree. This degree may be obtained in any of the existing nine faculties of pharmacy in Portugal, four of which public and five of which private. The quality of education in these establishments is supervised by the Ministry of Education, and there is limited input from the Profession. However, following recent developments of quality assurance systems, namely, those in the European area, the Portuguese Government decided to create an Agency for Assessment and Accreditation of Higher Education ("Agência de Avaliação e Acreditação do Ensino Superior"-A3ES), by Decree-Law no. 369/2007 (November 5th), with the purpose of promoting and ensuring the quality of higher education. The Agency is a foundation under private law, established for an indeterminate period of time, with legal status and deemed of public utility. The Agency takes independent decisions but in accordance to guidelines set by the Governmental structures. The assessment and accreditation regime to be developed by the Agency is defined in Law no. 38/2007 (August 16th). A3ES conducted a national evaluation on the pharmaceutical sciences degrees in all the schools of pharmacy across the country during 2016/2017. This evaluation comprised the quality of teaching, considering the syllabus and the curricular units, the laboratory facilities, the physical structure of the institutions and the qualification of the teaching staff, just to name a few. The standards are established according to the European Union. The jury created to evaluate all schools of

pharmacy included one president who selected a panel of 3–5 members of internationally reputed and distinguished professors and one student representative (Portuguese). A report was then issued in 2018 for each individual faculty stating whether the degrees were approved, given conditional approval for a time frame while pending further information or action, or totally failed in the evaluation. Following this evaluation, some of the existing degrees had a curricular change imposed.

Portuguese Pharmaceutical Society (PPS)

Once the Master in Pharmaceutical Sciences is awarded, the master may register with the Portuguese Pharmaceutical Society, which issues the professional license and is then responsible for establishing the standards for pharmacy practice.

The Portuguese Pharmaceutical Society is the professional public association that represents the Portuguese pharmacists and regulates the pharmaceutical profession in Portugal.

As a collective body governed by public law, the Society maintains the traditional designation of Lusitanian Pharmaceutical Society, of which it is a legitimate continuator, presenting the following statutory duties:

1. Collaborate in the definition and execution of health policy in cooperation with the State;
2. To defend the dignity of the pharmaceutical profession;
3. To promote and defend the interests of the pharmaceutical profession.

In order to carry out these functions, the Society exercises its mission in the social, scientific, cultural, deontological, professional, and economic fields of pharmaceutical activity.

This institution is also responsible for the accreditation of continuous professional development (CPD) courses provided by various independent entities, through its Council for Quality Accreditation (CQA). Since 2004, pharmacists in Portugal have compulsory CPD cycles of five years, following which a minimum number of CPD credits must be obtained to keep their license to practice (Aranda da Silva et al., 2004). The activities included in the portfolio awarding pharmacists credits are proof of practice, attending educational courses, participating in research activities, and contributing to training or education of pharmacists (supervision of internships is included).

The PPS is also the body responsible for awarding specialization degrees in the different areas of the profession, including in Clinical Analysis and Human Genetics, Hospital Pharmacy, Community Pharmacy, Pharmaceutical Industry, and Regulatory Affairs.

The CQA has also been actively involved in the development of accreditation norms for the emerging new services in pharmacy practice. The regulation for administration of vaccines was the first to be developed and was extremely important to standardize education and practice and to ensure high-quality service provision.

Another body within the PPS is the National Council for Quality (NCQ), which focuses on the development of good pharmacy practice norms for various areas of the profession. Two recently developed norms worth mentioning are the "Multicompartment Aids Service Provision Norms" and the "Medication Review Service Norms."

Medicines and Health-Care Products Regulatory Agency (INFARMED)

Medicines and Health-Care Products Regulatory Agency (INFARMED) is responsible for evaluating, authorizing, and regulating medicines, medical devices, and health products in Portugal. The main goal of INFARMED is therefore to protect public health by ensuring all medicines available are effective, safe, and meet high-quality standards. INFARMED also has a role in the evaluation of medicines, even if centrally approved, in terms of pharmacotherapy and pharmacoeconomic studies, and ultimately decides on the level of reimbursement, which will obviously impact on accessibility. Also as a contribution to the responsible use of medicines, INFARMED is responsible for providing up-to-date and reliable information to consumers and to health-care professionals, which is achieved by various publications, among which the Therapeutic Handbook and the National Formulary of Medicines are of particular importance. Still in the context of medicines use, INFARMED is particularly concerned about the constant monitoring of adverse drug reactions, through its National Pharmacovigilance System. This agency is also responsible for licensing and auditing pharmaceutical activity and pharmacy premises.

Sectorial Associations

Associations Representing Community Pharmacy Owners

There are two professional associations representing the interests of community pharmacy owners in Portugal, the *Associação Nacional das Farmácias* (National Association of Pharmacies, ANF) and the *Associação de Farmácias de Portugal* (Association of Pharmacies of Portugal, AFP), to which membership is voluntary.

The National Association of Pharmacies (ANF) was founded in October 1975, following the extinction of *Grémio das Farmácias*. It represents the majority of pharmacies in Portugal, totaling around 2800 associates, approximately 95% of the total number of community pharmacies in the country. Its mission is "to make pharmacies the most valued primary health-care network by the Portuguese citizens." To achieve this goal, throughout the years, it has developed companies, structures and projects which cover areas of impact on pharmacies, namely political, professional (education and pharmaceutical services), business, and financial. In order to ensure a close relationship between the executive structure and its associates, it has a decentralized structure, consisting of

groups of 50 pharmacies (circles). These are represented locally and in General Assemblies by circle, zone, and regional delegates, directly elected by the members.

The Association of Pharmacies of Portugal (AFP) was established by a group of six pharmacies in 1991 and has grown to represent more than 150 pharmacies in 2018. Its mission is to ensure that community pharmacists are recognized as medicine experts and valued as important members of the public health provider's network. For this purpose, it provides logistic support to the handling of prescriptions, provides continuing education opportunities, supports pharmacies in legal matters, and establishes protocols with several entities for the benefit of pharmacy owners and pharmacy teams.

For both organizations, one of the main activities is the relationship with the government and health-related public administration structures, in order to ensure that pharmaceutical legislation and regulation, as well as its operationalization, take into account both the specificities and the actual and potential added-value community pharmacies can bring to the health of the population.

Associations Representing Hospital Pharmacists

The *Associação Portuguesa de Farmacêuticos Hospitalares* (APFH) is an association of hospital pharmacist associates that perform their activity in Pharmaceutical Services of public and private Health-Care Units. According to their statutes, the APFH aims to:

- Promote the technical-scientific and deontological enhancement of its associates;
- Stimulate the improvement of practice conditions, as well as the social promotion of the Hospital Pharmacists' role;
- Represent Hospital Pharmacists near all other entities, such as regulatory bodies, both at the statutory and administrative levels;
- Encourage the realization of studies of technical and scientific nature and promote their dissemination within associates;
- Organize or sponsor the organization of courses, congresses, seminars, or similar activities, related to the subject of hospital pharmacy.

Community Pharmacy

The Development of Pharmacy Services

The development of pharmacy services in Portugal can be traced back to almost 20 years ago. Starting in 1999, the National Association of Pharmacies (ANF) developed a strategy, methods, and tools for the implementation of pharmacy-based disease management programs. When they were developed, these were set for asthma and COPD, diabetes, and hypertension, the latter subsequently broadened to include hyperlipidemia. In 1997, as a natural result of the St Vincent Declaration, a National Protocol for Diabetes was implemented (Primeiro Protocolo da Diabetes, 1998). The second protocol marked an important change, as it foresaw two levels of care, the second being the provision of pharmaceutical care (Segundo Protocolo da Diabetes, 2003). At this stage, remuneration of the diabetes program was successfully negotiated with the government (Costa et al., 2006), which was maintained when the Third agreement was signed (Terceiro Protocolo da Diabetes, 2008). The value set was 15 €/month/patient, where the Government would cover 75%. By April 2005, there were over 2500 patients integrated in these programs, followed-up in 328 pharmacies distributed nationwide. An evaluation of this program undertaken in 2007 using a retrospective intervention cohort suggested the program was effective in 21% of the patients to reach glycemic control (Martins et al., 2008).

The health gains shown by this service would hopefully inform the decision to also remunerate other pharmacist-led interventions. However, that has not happened and at the end of the mandate, the agreement was not renewed, that is, the program lost remuneration in 2010 (Protocolo de Colaboração entre Ministério da Saúde Ordem dos Farmacêuticos Associação Nacional de Farmácias Associação de Farmácias de Portugal. 2008).

Concurrently, the Dadér programme promoting patients' planned pharmacotherapeutic follow-up started its implementation in some pharmacies in 2001 (Santos et al., 2005). Although they had different approaches, both programs aimed to promote pharmaceutical care as part of the pharmacist's role.

In the year 2007, several legislative changes impacted the practice of pharmacy in Portugal. Pharmacy ownership was opened to nonpharmacists, nonprescription medicines were allowed to be sold outside pharmacies, and the sale over the Internet of pharmaceutical products was permitted, among other measures. In addition, pharmaceutical care provision was finally legislated (Portaria 1429/2007). This legislative piece established a total of eight services that could be provided by pharmacies, including four new services: home support, administration of first aid assistance, administration of vaccines not included in the National Vaccination Plan, and administration of medicines (e.g., intramuscular or subcutaneous routes). Four already existing services were also legally established in this decree or augmented in their scope: the utilization of auxiliary means of therapeutic and diagnostic (i.e., any service that may be used as a screening activity, e.g., cardiovascular risk, eye check, but also the possibility to utilize the expertise of other health-care professions to this end); provision of pharmaceutical care; engagement in health information campaigns, and collaboration in health education programs.

Some of these new services implied pharmacists' accreditation, or foresaw the possibility of subcontracting other health-care professionals, namely, nurses to provide them. The services for which pharmacist accreditation is compulsory include the administration of vaccines and the administration of injectable medicines.

This decree was updated in 2018, further expanding the scope of practice of community pharmacists to include medication adherence interventions, provision of multicompartment aids dispensing service, educational interventions targeted at using

medical devices, and medication reconciliation; health literacy promoting interventions, including health prevention campaigns and healthy lifestyle promotion; point of care testing for HIV, HBV, and HCV including referral to appropriate hospital care for reactive cases. In addition to these, other services to be provided by allied health-care professionals and made available at the pharmacy premises were also included, namely, nutrition service; simple nursing services, including wound treatment and care provision for ostomized patients; and the prevention and treatment for diabetic foot.

In 2016, a new dispatch has been published focusing on health reforms in general, while stating that community pharmacies need to be valued as providers of care, and therefore announcing the intention to test the delegation of the dispensing of specific medicines, which until this date were restricted to hospital use, namely, oral oncology and infectious diseases medicines (HIV and Hepatitis C) (Despacho n° 199/2016). A pilot for the dispensing of HIV medicines in community pharmacies has started in 2016 and is still ongoing, with preliminary results showing high patients' satisfaction rates.

The Role of Pharmacy in Health Promotion

The role of pharmacists in health promotion has a long history worldwide. Portugal is no exception and arguably is a good example of how pharmacists can go beyond their most traditional roles and visibly contribute to public health.

Needle Exchange Program

This program was initiated in 1993 as a response to the sudden period of drug use expansion lived in Portugal. The program resulted from a partnership established between the National Commission Against Aids and the National Association of Pharmacies, with the main aim of minimizing risks associated with the use of injectable drugs. The idea of this program was very innovative and controversial for which the role of Prof. Odette Ferreira was essential, recognizing the inability to stop the use of drugs, while recognizing that something could be done to prevent disease dissemination. The motto of the program was "do not use a second-hand needle." To achieve this, drug users would deliver their used needle in a pharmacy or in a street van and receive a new one in return. This initiative resulted in needles no longer being on the pavement and also that there was no need to share needles.

Later developments of the program based on needs assessments extended the scope of the program to also include condoms, citric acid, distilled water, and a metal recipient. This year, the 25-year anniversary of this successful program was promoted, where some of the key achievements were recognized publicly by the Health Directorate:

- A total of 56 million needles were exchanged;
- Over 30 million condoms distributed;
- In 2018, the lowest value of notifications was reached, with 18 new cases among 1064 total cases infected by this means.

This program is internationally recognized for its contribution to minimize HIV, HCV, and HBV infections. Portuguese pharmacies have been recognized for their 25 years contribution against HIV and other blood–borne diseases through their engagement in the needle exchange program. In 2016, the government recognized that the contribution of pharmacists resulted in a net benefit of 3.01€ per needle exchanged, originating overall system savings of over 2 million euros in a 5-year period, hence originating a reimbursement system which values at 2.40€ each package of 2 needles exchanged (Borges et al., 2016).

Opioid Substitution

This program also had an important role in fighting drug endemics. However, its scope is quite different as it aims to "cure addiction to opiates." The program exists in two main formats, where the first corresponds to the low-level provision and is available at the health-care center. In this phase, the intention is to provide methadone free of charge at specific moments so that opioid consumption using other substances and administration routes is progressively diminished. The second level, named high-demand level, is available in pharmacies and requires the individual to be free of drugs to be entitled to receive one daily dose of liquid methadone. To ensure this, there is no parallel drug consumption, and frequent analyses are made. The program is currently inactive in Portugal since 2014, mostly due to lack of funding, with no date anticipated for its revival.

Collection of Unused Medicines

Since 1999, a program for collecting unused medicines was created, which aims to promote adequate disposal of contaminated material, preserving the environment, while also contributing to improve responsible medication use. This is achieved by having a container available on the public area of the pharmacy, where people are encouraged to deliver the expired medication, but also those medicines they will not be using anymore, preventing, e.g., subsequent reutilization of unfinished courses of antibiotics. This program in 2015 was expanded to also collect veterinary medication.

Early Detection of Various Chronic Conditions

The community pharmacist has a privileged position in the center of communities, and being available through wide pharmacy operating hours, places him in an ideal situation to actively contribute to early detection programs. The fact that he is often the first health-care professional citizens seek when encountering a minor health problem, which may eventually hide a more important problem, also contributes to this role in disease prevention. Point of care testing is a regular service provided by all pharmacies throughout the country.

Table 1 Summary of most relevant or recent early detection initiatives in Portuguese community pharmacies

Disease	*Detection method used*	*Number of involved individuals*	*Number of referrals*	*Confirmed diagnosis*	*References*
Diabetes	Findrisk	7007	24.0%	Not available	Jacinto et al. (2016)
		1539	3.7%	Not available	Mendes et al. (2018)
	Glycemia measurements	7719	23.9%	Not available	Horta et al. (2010)
Cardiovascular risk	Blood pressure and total cholesterol measurements	12,930	21.0%	50.0%	Santos et al. (2011)
	SCORE	945	378	Not available	Brito et al. (2018)
Atrial Fibrillation	Pulse palpation and Kardia Alive Cor	2573 (internationally) 998 (Portugal)	23.7%	1.4%	Lobban et al. (2018) Cunha et al. (2017)
COPD	Spirometries	1266	31.1%	6.6%	Mendes et al. (2018)
Asthma and allergic rhinitis (uncontrolled)	Control of Allergic Rhinitis and Asthma Test (CARAT)	224	87% potentially to be referred	Not available	Lourenço et al. (2014)
Allergic rhinitis	Allergy Diary (MASK-rhinitis)	23,000 (internationally)			Bosnic-Anticevich et al. (2018)
Colorectal cancer	Presence of hidden blood in faeces	1143	5.7%	60.4% have been subject to a colonoscopy	Rosa et al. (2018)
HIV	Saliva swab	589	0.7%	Not available	Madeira et al. (2014)

The scope of services available varies, where glycemia, weigh, and blood pressure are almost universal (>95%); cholesterol measurement is also very common (>90%), and then other services are still progressively being implemented, namely, full lipid profile, HbA1c, INR, etc., some of which are estimated to exist in 5%–10% of the pharmacies.

Point of care testing may be provided as an isolated or continuous service, as a way to monitor medication effectiveness and safety and also as a means to detect some specific diseases early on, mostly when preventable, asymptomatic and those with improved prognosis when detected early. But early detection programs may also make use of symptom evaluation, isolated or in combination with biomarkers measurement.

In Portugal, the first "early detection" initiatives focused on people at risk for diabetes and a few years later on cardiovascular risk. In both these initiatives, pharmacists made use of symptom assessment and biomarker measurement. More recently, pharmacies started using standardized questionnaires to asses risk, such as the Findrisk instrument (Jacinto et al., 2016).

More recently, some of the innovative areas where community pharmacists have been engaged and even recognized internationally include the detection of COPD based on spirometries, or atrial fibrillation based on the use of portable mobile devices.

For all these services, the procedure is very similar. The pharmacist invites the person to participate, as part of a campaign that offers this assessment free of charge, or as part of a sustained service available at the pharmacy, in which case the patient usually pays out-of-pocket. Whenever results suggest a possible undiagnosed disease, there is a referral to the physician. In the process, pharmacists also strive to obtain medical confirmation in an effort to estimate their contribution to better patient care. This last flow of information is still suboptimal and for which technology-based direct communication is being tested, as described in Section Use of Technology in Community Pharmacy.

Table 1 presents a noncomprehensive summary of early detection initiatives developed in Portugal and presented at the Portuguese Pharmaceutical Society Congress in 2017, the National Association of Pharmacies Congress in 2018, the International Pharmaceutical Congress from 2016 to 2018, and/or published in Pubmed indexed journals the last 5 years.

Colorectal Cancer Screening

In Portugal, colorectal cancer is the most prevalent malignant tumor (14.5%), with about 7000 new cases diagnosed every year (GLOBOCAN, 2012). Many of the deaths caused by cancer could be prevented through measures such as reducing exposure to risk factors and promoting early diagnosis through systematic screenings. Early detection is key to survival, as colon cancer patients diagnosed early (stage I) have a 5-year survival rate of 92%, whereas if diagnosis is delayed and colon cancer is not detected until stage IV, the 5-year survival rate drops to 11% (American Cancer Society, 2014). Current national legislation establishes that all patients aged 50–74 be screened every 2 years for colorectal cancer (Despacho n.° 8254/2017). However, the enactment of this legislation has been unequal in the national territory. Therefore, the national association representing patients, Europacolon Portugal, has been working with a group of community pharmacies for the past 5 years in order to make screenings available free of charge to patients within the recommended age group. Screening is made by asking patients to collect stool samples and bringing them to the pharmacy. Pharmacies then send the samples to a clinical biology laboratory to test for the presence of blood. The results are subsequently sent to the pharmacy and delivered to the patient along with counseling based on the result. If the test is positive, the patient is referred to the physician for follow-up, namely, to perform a colonoscopy and eventually confirm a diagnosis and initiate treatment.

In 2018, 131 pharmacies participated in the awareness campaign and screened a total of 1143 individuals. Of these, 12.6% (n = 143) had a positive result in the screening and were referred to the physician.

HIV and Hepatitis Screening

New legislation that allows pharmacies to deliver point-of-care tests for HIV, Hepatitis C, and Hepatitis B without the need for a prescription has been published in March 2018 (Despacho n.° 2522/2018). With this measure, the Government aims to improve accessibility within the context of the early detection of HIV and viral hepatitis infections as a complementary means to the diagnosis already made in primary health care, hospital care, counseling and detection centers, pneumological diagnostic centers, and community-based organizations.

Several stakeholders were involved in the subsequent regulation and implementation of this service, including the Portuguese Pharmaceutical Society (to ensure pharmacists' competence to deliver the service) and the associations representing community pharmacy owners (to ensure pharmacies' readiness for execution).

In October 2018, the first 22 pharmacies launched the service in the municipality of Cascais. This municipality was chosen to introduce the service due to its involvement in the "Fast-Track Cities" initiative. The Fast-Track Cities is a global partnership, which was launched on World AIDS Day 2014 in Paris, where mayors from 27 cities in over 50 countries convened to sign a Declaration committing to accelerate and scale-up their local AIDS responses. Within this initiative in Cascais, the screening tests are made available free-of-charge to patients. Tests are also provided in an anonymous and confidential manner. However, if the test is reactive, the pharmacist is prepared to refer the patient to the appropriate level of care for follow-up.

This service is now projected to be rolled-out to other regions of the country.

The Role of the Pharmacist in Medicines Management

Many of the pharmacy-based initiatives have traditionally arisen from the National Association of Pharmacies, as mentioned in Section, "The Development of Pharmacy Services." However, in elderly care, the contribution of Universities has been profuse, through the development of various interventions focusing on medication use in this specific setting (Advinha et al., 2014; Costa et al., 2016a,b; Silva et al., 2015). Also, in the hospital setting, various studies, mostly focusing on potentially inappropriate medication and potential prescribing omissions, have been led by academia (Borges et al., 2012; Correia et al., 2014; Costa-Dias et al., 2014).

Medication review practices are normally encompassed by advanced services provision but may be developed in different moments in time. According to the Pharmaceutical Group of the European Union (PGEU), all pharmacies provide simple medication reviews (level 1), i.e., review of pharmacotherapeutic records (PGEU, 2017). This may be executed in the back office by periodically evaluating population subgroups (e.g., elderly; polypharmacy). Intermediate medication review (level 2a) includes contact with the patient to obtain additional information and may occur at each dispensing moment, as long as a standardized procedure is used. In a recent study, MR level 2a was reported as the most common MR in Portugal, although estimated to have a low implementation rate (Soares et al., 2019).

Current Scope of Practice in Community Pharmacy

The scope of practice of Portuguese community pharmacists is quite broad in European terms. Previously published work suggests Portugal to be the European country with more services available (Martins et al., 2015). This works refers to Portugal as only not being able to prescribe, a competency currently only existing in the United Kingdom in the European context.

When you contact a community pharmacist, you may expect to receive standardized counseling and information to ensure the responsible use of medicines, generic substitution, home delivery of medicines, various programs contributing to public health (e.g., needle exchange and others mentioned in Section The Role of Pharmacy in Health Promotion) in all the pharmacies throughout the country. Of course, you may also expect to be able to acquire medication (prescription, nonprescription, and pharmacy-only lists), medical devices, cosmetics, and veterinary products. In most of the pharmacies, you may also have access to intermediate level services, including assessment of inhalation technique, adherence and support monitoring (including the use of multicompartment aids, new medicines service, and other enabling strategies), smoking cessation, health screening, point of care testing, and immunization services. To a lower extent, advanced services such as pharmaceutical care, medication review, and administration of injectable medicines may also be found. The services currently not within the scope of practice of Portuguese community pharmacists include prescription renewal, prescribing, dose adaption, and personalized medicine. As mentioned earlier, opioid substitution is currently unavailable (although within the scope of practice). This implies that although the range of services available is wide, the implementation of such services is not homogeneous. In fact, some of the longer existing services, namely, pharmaceutical care, perhaps because they have a higher degree of differentiation, have been reported to have suboptimal implementation, although slowly increasing in the last decade (Costa et al., 2017; Hughes et al., 2010).

However, it is interesting to point out that some new services have had quite a good uptake by pharmacies, one of them being the immunization service. Since the publication of the legislation in 2007, more than 3000 pharmacists have been accredited by the Portuguese Pharmaceutical Society to deliver the service, and more than 2300 pharmacies have the service available, which represents almost 80% of the total number of pharmacies (International Pharmaceutical Federation, 2016).

Use of Technology in Community Pharmacy

Pharmacies in Portugal have long been early-adopters of technology. The process for implementing a pharmacy-specific software was conceptualized at the 1st Congress of the National Association of Pharmacies in 1981, and the first pharmacy started operating with a computer in 1987, after which there was a national roll-out (Machado and Martins, 2015). It is widely acknowledged that many Portuguese citizens saw their first computer in a pharmacy, and the same can be said about robots, since dispensing robots have been installed since 2002, with a total of over 200 robots operating in pharmacies throughout the country.

Several projects have been initiated that make use of technology. One of these projects is a mobile application, named "Farmácias Portuguesas." This app offers pharmacy-related services and personal management of some health data, including (1) a plan for medicines intake for the user or his family member, with a pill reminder; (2) information about health that allows the user to access useful and adequate information on medicines and effective use of these medicines; and (3) a personal area with a record of the user's point-of-care measurements, in which the results of the tests made at the pharmacy can be transmitted automatically by the pharmacy software to the user's mobile phone (Pinto et al., 2016).

Moreover, as previously mentioned, since 2007, pharmacies have the possibility to deliver medication requested over the Internet at the citizens' homes, provided the pharmacy is previously registered with the regulatory agency to provide the service (Portaria n° 1428/2007). For this purpose, interested pharmacies have launched Internet websites, which are either individually developed or make use of the platform made available by ANF.

Since November 2015, a paperless prescription process has been rolled-out, with over 95% of all PNHS prescriptions now dispensed within this system. The paperless prescription process involves the issuing of a dispensing code that the user can see either in an email, via an SMS text message or on the Health Data Platform. Once issued, the patient then uses the code number to obtain the medicines by showing his or her citizen card or other means of identification at the pharmacy. Besides decreasing the bureaucratic burden, due to the fact that there is instant confirmation of the reimbursement status, further benefits for the health system would include facilitated transfer of information between the dispensing pharmacist and the prescriber. However, until now, this has not materialized, given that the pharmacist still does not have access to the patient health record.

Whilst this access is being assessed by the National Data Protection Agency, the Health Ministry, and ANF initiated a pilot project in July 2017, intended to facilitate this communication exchange and collaboration between community pharmacists and physicians. The communication between pharmacies and primary care centers, or pharmacies and hospital care, is done via their respective computer systems. The list of predefined therapeutic notes is included in the software systems, and pharmacists can select and send the intended message to the prescribing physician. The physician may then provide feedback (useful/not useful) about the therapeutic note sent. The objective of this pilot is to better understand the needs of communication between the two stakeholders, and its results will allow drawing the next stages of development of this tool.

Currently, Portuguese pharmacies are preparing themselves for the implementation of the Falsified Medicines Directive (Directive 2011/62/EU), bearing in mind that all stakeholders must be ready to meet their obligations on February 9, 2019, in terms of the safety features within the medicines' packages, and the authenticity verification against a central database.

Transformation of Community Pharmacies Into Care Centers

For the past three decades, community pharmacies in Portugal have invested in competent human resources and adequate infrastructures to provide optimal care to citizens. Many of the advances have been initiated by pharmacists and their representative structures, very often within a gray legislative framework. To this end, pharmacies have offered an increasingly comprehensive portfolio of services and initiatives in order to respond to consumers' different needs, as depicted in the previous subchapters.

The publication of the pharmaceutical services legislation in 2007, subsequently updated in 2018, allowed pharmacies to further increase their intervention scope and, within this context, work in multidisciplinary teams in order to provide integrated health solutions that allow for better preventive care and management of the burden of disease.

In fact, many of the most prevalent diseases require a team approach, as is the case, for instance, of diabetes. Apart from adequate pharmacological interventions, a good nutrition plan, feet monitoring, and self-management techniques are essential for disease control and prevention of complications. This is why an increasing number of pharmacies have been integrating other health-care professionals such as nutritionists, nurses, and podiatrists in their teams.

Pharmacies are thus not focusing only on access to medicines and to services that enhance their correct use but also on access to other services that increase medicines effectiveness and safety. This requires a shift in approach every time a pharmacist receives a prescription. Instead of interpreting that prescription as a request for a specific medication, the pharmacist must interpret that prescription as an intention to control a disease or a symptom—which in that case, means that the patient will probably need much more than just the medicine to achieve the envisioned goal.

This new approach is especially relevant considering that throughout the country, there are many regions where pharmacies are the last health-care resource available. And, in other regions, are the ones with the most convenient opening hours. This, coupled with the competency of its human resources, makes pharmacies a much-needed health resource in the community.

In addition, pharmacies have been recognized globally as a gateway to care (International Pharmaceutical Federation, 2017), and this is also the case in Portugal. Pharmacies and pharmacists are well used access points for citizens seeking medicines, but also advice for common minor ailments, in addition to services involved in and related to prescriptions and medicines use. Considering the constrains in accessing other health-care resources in Portugal, pharmacists are being recognized as a trustworthy source of

information and advice, as well as in the process of personal empowerment for people who increasingly want to enact shared decision making in what relates to their health-care needs (CESOP, 2018).

Hospital Pharmacy

Hospital Pharmacy Standards

There are two main overarching international societies used by Portuguese hospital pharmacists to set their standards. These are the European Association of Hospital Pharmacists (EAHP) and the International Pharmaceutical Federation (FIP). To a lower extent, the European Society of Clinical Pharmacy (ESCP) and the American College of Hospital Pharmacy (ACHP) are also looked up to establish good practice standards.

The two first mentioned are particularly important in the context of establishing hospital pharmacy standards and these have been used to benchmark good practices and motivate pharmacists to constantly improve their practices. The Revised FIP Basel Statements on the future of hospital pharmacy, approved in 2014 as a revision of the initial 2008 version, constitute an important part of the process of alignment of Portuguese hospital pharmacy with international good practice standards (International Pharmaceutical Federation, 2009; International Pharmaceutical Federation, 2015)

The European Statements of Hospital Pharmacy, issued by the EAHP in 2014, are a set of statements to be ranked using a four-point agreement Likert scale, clustered into six main domains that characterize the areas of activity for hospital pharmacy (Preece, 2014). When initially launched, a baseline assessment of most European countries was made but then the use of such statements for national continuous improvement was left to member states. In 2017, the PPS carried out a survey using these standards, sent to all hospitals, in an effort to characterize hospital pharmacy in Portugal. Responses were obtained from 37 hospital pharmacies, providing a quite good picture of the national reality. For each of the six sections, we highlight the statement where higher agreement (green) and lower agreement (red) were reached, together with three statements we believe characterize quite well the domain (**Table 2**).

Table 2 State of implementation of selected EAHP statements in Portugal

	Totally agree (%)	*Partially agree (%)*	*Partially disagree (%)*	*Totally disagree*
Section 1: Introductory statements and governance				
At least one of the pharmacists in our team is a member of the Commission for Pharmacy and Therapeutics	94.6	2.7	0.0	2.7
At least one of the pharmacists has an active role in the antimicrobial resistance commission of the hospital	69.4	16.7	8.3	5.6
The pharmacists in our hospital are involved in the supervision of all steps of the process of medication use	40.5	56.8	2.7	0
The pharmacists in our hospital routinely work as part of the multidisciplinary team	40.5	51.4	0	8.1
Our hospital is able to prioritize the hospital Pharmacy activities according to agreed criteria (i.e., approved activity plan).	13.9	69.4	16.7	0
Section 2: Selection, Acquisition, and Distribution				
Our hospital has transparent processes implemented on drug purchasing	81.1	18.9	0.0	0
The pharmacists in our hospital take responsibility for all the logistic associated with medicines and health products, including experimental medicines	70.3	29.7	0	0
The pharmacists in our hospital coordinate the development, maintenance, and utilization of a drug formulary system	64.9	32.4	2.7	0
The acquisition of medicines not included in the Drug Formulary is made through a solid process	61.1	25.0	11.1	2.8
The pharmacists in our hospital have been involved in the development of a policy to handle medication brought in by patients	51.4	18.9	13.5	16.2
Section 3: Production and Preparation				
Before producing or preparing a medicine in the Pharmacy, the hospital Pharmacist determines if the medicine is available in the market	91.9	8.1	0	0
When medication require production or preparation, they are produced by hospital Pharmacy or externalized under the responsibility of the Pharmacist	94.6	2.7	2.7	0
Pharmacists in our hospital evaluate risks to determine safe practices demands before initiating a pharmaceutical preparation	86.5	8.1	0	2.7

(*Continued*)

Table 2 State of implementation of selected EAHP statements in Portugal (*cont.*)

	Totally agree (%)	*Partially agree (%)*	*Partially disagree (%)*	*Totally disagree*
Pharmacists in our hospital ensure the implementation of a quality management system for pharmaceutical preparations	66.7	30.6	0	2.8
The pharmacists in our hospital were involved in the development of written procedures that ensure that staff involved in the medicines preparation and reconstitution have received adequate training	45.7	34.3	8.6	11.4
Section 4: Clinical Pharmacy Services				
All the prescriptions in our hospital are reviewed and validated as soon as possible by a pharmacist	70.3	24.3	2.7	2.7
Pharmacists in our hospital are an integral part of multidisciplinary shared decision and collaboration, namely, through counseling, implementation, and monitoring of therapy	37.8	45.9	0	16.2
Pharmacists in our hospital have access to patients' medical record	62.2	18.9	2.7	16.2
Pharmacists in our hospital provide other health-care professionals all the necessary and relevant information to ensure the responsible use of medicines and health products	54.1	40.5	5.4	0
Pharmacists in our hospital optimize all medicines during admission	2.7	29.7	24.3	43.2
Section 5: Patient Safety and Quality Assurance				
The pharmacists in our hospital ensure that medicines are adequately packaged and labeled so that they are administered safely	91.4	8.6	0	0
The pharmacists in our hospital report drug adverse reactions to the National Pharmacovigilance System	61.1	33.3	2.8	2.8
The pharmacists in our hospital were involved in the development of quality assurance strategies for drug utilization processes that enable the identification of errors and priorities for quality improvement	47.2	47.2	2.8	2.8
Our hospital has procedures in place to adequately identify high-risk medicines and minimize the errors associated with the processes of acquisition, prescription, preparation, dispensing, administration, and monitoring	40.5	54.1	2.7	2.7
The pharmacists in our hospital ensure the adequate registry of all allergies and other relevant drug-related information in the patient's medical record	3.1	28.1	18.8	50.0
Section 6: Research and Education				
Pharmacists in our hospital may demonstrate their competencies through the activities they develop	61.1	36.1	2.8	0
Pharmacists in our hospital actively participate in all phases of clinical trials for experimental drug research	63.9	22.2	0	13.9
Pharmacists in our hospital participate in relevant education opportunities throughout their career	45.9	37.8	10.8	5.4
Pharmacists in our hospital regularly publish scientific papers on hospital pharmacy practice	5.6	36.1	25.0	33.3

Data made available by the Portuguese Pharmaceutical Society, 2018 (full report per request)

The Role of the Hospital Pharmacist

Hospital pharmacy has changed dramatically in the last 50 years. Parallel to the scientific and technological development, the growth and diversity of functions and responsibilities took place and new opportunities were included. Hospital pharmacists went from a product-oriented (medicine) practice to a practice focused on patient care.

In this sense, the current concept of hospital pharmacy focuses on the existence of two major areas: logistics and clinical area. The first involves all the activities of a more mechanical nature that function as support to activities of clinical nature. It integrates management and organization, acquisition and stock management, storage and conservation, repackaging, compounding, and distribution. The clinical area is constituted by all the activities related to hospital pharmacist's intervention in the patient medicines process, including clinical pharmacy/ pharmaceutical care (e.g., medicines selection and medicines information, pharmacovigilance, clinical pharmacokinetics, nutritional therapy, therapeutic review and management, medication reconciliation, pharmaceutical consulting, clinical trials). Thus, hospital pharmacy is not only product or patient-oriented pharmacy but also a combination of both.

In this activity "core" redefinition, where contemporary basilar practices are incorporated along with the promotion of advanced pharmacy practices, including a greater emphasis on multidisciplinary care and direct interaction with the patient, maintaining efficient support services remains a prerequisite for the development of sustained clinical activities that provide greater patient value

and optimal value through practice sustained by excellence. To this end, the commitment to continuous training, experience and awareness is a minimum requirement.

The national dispatch Number 14215/2013, November 11th and the Recognition of Qualifications, as well as the consequent harmonization among member states (9/10/2013), represented the long-desired opportunity for the revision of the hospital pharmacist's professional framework in the Portuguese national health system (NHS), in its various aspects. The recent publication of the Pharmaceutical Career diploma (Decree Law n° 108 and 109/2017, August 30th) embodies an important step for hospital pharmacist's professional identification since it corresponds to the spectrum of pharmaceutical interventions and reflects the high degree of training (pre- and postgraduate) and specialization required. We hope it will be soon complemented by the regulation of the precareer training period (a four-year pharmaceutical internship), which is a postgraduate training, leading to the specialty in hospital pharmacy (titled both by the Pharmaceutical Society and Ministry of Health).

In Portugal, hospital pharmacists have conferred responsibilities such as medicines/other technologies selection, acquisition, storage, and distribution, the implementation and monitoring of the drug policy defined by the Pharmacy and Therapeutics Commission and the management of the experimental medicines circuit. Other already mentioned functions/activities and functional areas are also recognized and have progressively increased, in accordance to today's patient needs and demands. All has been increasingly "hooded" by quality management systems and ethics, focusing on patient-centered care ("the exercise of the pharmaceutical activity has as essential objective the person of the patient/citizen"; art 72°, Pharmaceutical Society Statutes).

The implementation of quality management systems (QMS) in Portugal had a significant increase after the publication of the dispatch n. ° 25811/2006, November 24th, by the office of the Minister of Health. It was then established the Hospital Medicine Program (HMP) and created a Working Group to draw up an intervention program within the scope of hospital medicine, sustained in projects with quantified measurable targets and monitoring mechanisms. The hospital pharmacy landscape assessment at that time advised to the implementation of a specific support program through funding measures included in HMP. This intention of valuing hospital pharmacy was strengthened by the results obtained within the 1st National Survey conducted, which identified areas that needed priority intervention. By order of the Health Secretary of State, in 2008 a vertical funding program for the measures included in the HMP was created. The HMP was based on three main projects of action: (1) Good Practices in the field of medicines, (2) Therapeutic Plan Integrated Circuit and (3) Pharmacy and Therapeutics Committees.

A key objective of the HMP was the implementation of quality policies based on good practices particularly in the existence of quality assurance programs and definition of standards and procedures of the developed activities. At the time, some strategic points were identified considering which the working group presented proposals regarding the implementation of a quality policy through a certification process (Management/Procurement and Logistics, Distribution, Pharmacokinetics, and Clinical Pharmacy) and the certification development promotion of the activities related to hospital medicine. Several pharmacy services, by their own funding or through HMP funding, achieved certification of its activities in various functional areas (organization and management, drug procurement, reception and storage, compounding, distribution, information, nutritional therapy, pharmacovigilance, pharmacokinetics, pharmacotherapeutic monitoring, and other activities of clinical pharmacy, clinical trials, research, and teaching), or part of them. The concern for quality and safety focus has had an important growth since then and implementation of methodologies for evaluation and certification by competent bodies are a purpose for continuous improvement.

Hospital pharmacists have made efforts to improve the Quality programs through their participation in risk management, patient safety protocols, therapeutic reconciliation (improved care transitions), counseling on discharge and follow up, pharmaceutical consulting among others, all of which are quality improvement initiatives to promote patient safety, improved medicines use and risk management procedures (patients, professionals, and organization).

Today, on the one hand, we are experiencing a period of constant technological advances, social and political changes, and economic constraints but, on the other hand, we are aware of the global economic impact of health care, which has been conditioned by the aging population and increasing demand for health care, the incorporation of new, more complex and costly technologies, and the allocation of resources by a growing number of providers and consumers. In this context of declining birth rates, increased life expectancy, technological growth, and a consequent increase in care costs, the challenge lies in allocate and use resources efficiently and equitably, on the basis of an accessible, universal, egalitarian, and regulated health service. Hospital pharmacists have continuously contributed to the responsible use of economic and financial resources related to the quality of care delivered to the population. The path taken by hospital pharmacists and hospital pharmacies, at different rates, with greater or lesser difficulties, has been traced in the sense of safe practices, therapeutic monitoring and pharmacovigilance, optimization of drug use, pharmaceutical care, teaching, and research. Some have already achieved it in large, others have been pursuing the common goal. In addition, the articulation with other pharmacist specialties (clinical analyzes and human genetics) and other health-care professionals has itself an enormous potential for optimization of care with an impact on the rationalization of the use of available resources.

Currently, hospital pharmacy services are required to be governed by defined objectives, committed to their mission, vision, and values; they demand planning and organization and are based on minimum standards of performance and quality. Certainly, the pharmacists activity is framed by both plates of a scale: one of the plates there is the professional and deontological context, legally conferred by the statute of the Pharmaceutical Society, also mirrored into the Pharmaceutical Career and the other plate, regards to the Good Practices, which are based on scientific evidence and rendered by the Hospital Pharmacy College and Societies such as the EAHP and FIP.

Hospital pharmacists within the health-care team play an important role in patient care due to their interventions in improving the better use of medicines, medical devices, and other health technologies. The commitment to efficient and safe use of

pharmacotherapy is demonstrated by their intervention in medicines management, technical commissions, medicines information and monitoring, in the prevention, detection, and resolution of drug-related problems (interactions, adverse drug reactions, medication errors), pharmacotherapeutic follow-up, therapeutic reconciliation, active pharmacovigilance and spontaneous notification, therapeutic counseling and health education, evaluation of drug use, and other activities.

Hospital pharmacists may influence the correct use of medicines at three different stages:

- Before prescription (drug information, drug-related policies formularies clinical trials),
- During prescription (counseling activity; influence on prescription; monitor, detect, and prevent medication-related problems—*untreated indications, improper drug selection, subtherapeutic dosage,* medication *failure to receive, medication overdosage, adverse drug reactions, drug interactions, medication use without indication*; therapeutic drug monitoring, etc) and
- After the prescription (counseling, preparation of personalized formulation, drug use evaluation, outcome research, pharmacoeconomic studies, etc).

Hospital pharmacists' present responsibility/challenge is to promote the responsible use of medicines, in its broadest sense, providing integrated pharmaceutical assistance in a multidisciplinary complex environment, and measuring performance using principles continuous quality improvement (limit/minimize nonconformity and error, reporting adverse events, identifying opportunities for improvement, and promoting the care process optimization).

The Portuguese health-care system continues to evolve; hospital pharmacists participate more actively than ever in direct patient care. The direct interaction with the patient, in the context of hospitalization and outpatients, has resulted the development of a set of initiatives, including the Pharmaceutical Consultation and the Home Hospitalization project.

Medication errors are a major cause of morbidity and mortality (Aspden et al., 2006) and are common in care transitions as a result of gaps in communication and information transfer between health-care providers and between them and their patients. They occur when patients are discharged, admitted, or transferred to health services. According to Rozich and Resar (2001), 60% of all medication errors occur in such care interfaces, thus constituting a problem of quality and patient safety. The literature shows that between 10% and 70% of drug histories contain at least one error; up to 1/3 of these errors have the potential to cause harm to the patient; more than 50% of medication errors occur in the transition between care; patients with one or more drugs missing from the discharge are 2.3 times more likely to be readmitted to the hospital than those who have the correct drug information; and 85% of discrepancies are due to failures in the collection process of patient medication information (DGS STANDARD N°018/2016).

Medication reconciliation (MR) then emerges as a process designed to limit medication errors and discrepancies in care transitions (Gleason et al., 2004), and "evidence shows that the process has the potential to identify many drug discrepancies and reduce possible damage" (Lehnbom et al., 2014). It is a multidisciplinary, patient-centered process; it differs from the usual process of reviewing medication by incorporating other information, such as nonprescription medicines, natural products and dietary supplements, as well as by using other sources of information (e.g., list of medication delivered by the patient and/or caregivers; the medicines delivered by the patient; information available in computerized systems).

The Hospital Garcia de Orta, EPE in Almada developed a pilot project with the integration of the pharmacist into a new entity providing care, the Home Hospitalization Unit. Home hospitalization promotes dehospitalization and prevention of rehospitalization and is distinguished from the health and social support responses at home already implemented in the NHS, insofar as it affects the acute phase of the disease and/or exacerbation chronic disease. After an experimental phase and the home stay of more than 100 patients, the first national Home Hospitalization Unit reveals itself as an alternative care model to conventional hospital admission. The pharmacist's intervention in this unit reflects the relevance of its integration since the project's genesis and meets the requirements outlined in the National Plan for Patient Safety 2015–20 that dictates the implementation of therapeutic reconciliation in the transition of care. Patient's safety was the focus of the pharmaceutical intervention, through which all medication omissions and incorrect doses were detected and rectified. Pharmaceutical intervention also emphasized storage of medication, identification and collection of expired drugs, and further enhanced adherence to prescribed treatment (Brito et al., 2017). This is a recent practice in Portugal, but international experience has shown several advantages, such as reducing the risk of complications, such as falls, pressure ulcers, disorientation or confusion, reduction of hospital readmissions, and reduction of infection rate hospital. It also has the potential to contribute to improving access to hospital health care and to improved bed management available for the treatment of acute patients in the NHS.

The complexity of the pathologies and pharmacological and nonpharmacological therapies of patients is inter- and intravariable, so patients with acute and/or complex needs may benefit from more targeted pharmaceutical care integrated within the multidisciplinary team (chronic and complex therapies; technological development/alternatives; polypharmacy, presence of comorbidities, aging, risk of interactions and adverse drug reactions, etc.). Therefore, in addition to the process of medication reconciliation of hospital in-patients, this process can also benefit patients with chronic pathology in outpatient follow-up, reason why targeted pharmaceutical consultations (PC) have been developed in areas such as oncology, geriatrics, renal transplantation, and HIV. There, medication reconciliation is performed, as well as the evaluation of drug interactions, therapeutic simplification, allergies, among others. These PCs have been developed in some centers; we emphasize the PC that present as a process a predefined schedule, referral by physician, prior definition of referral criteria, report issuance, and its documentation in the clinical process (e.g., Centro Hospitalar de Lisboa Ocidental, EPE). PC allows the prevention/correction of drug-related problems, detection and resolution of interactions, simplification of the therapeutic regimen, optimization of responsible use, increased safety, promotion of adherence, health education, and multidisciplinary integration. Nevertheless, in addition to the PC value recognized by patients and the multidisciplinary team, the measurement of clinical outputs is essential for the effective evaluation of its impact.

Trends in the development and use of medicines are one of the key factors that are and will shape the profession in the coming years; others are related with the national and global economy status and health-care reform. These factors will demand that hospital pharmacists continue to move toward team leadership of drug therapy management, aiming patient care improvement and institutional sustainability.

Use of Technology in Hospital Pharmacy

The increasing changes to hospital pharmacy practice have resulted from expanded roles, changes in patients' expectations, introduction of new/renewed pharmacy practice models, and development of new technologies in the drug-use process.

Information and communication technology (ICT) can enable the storage of organized patient records, enable the electronic prescribing, dispensing and administration of medicines, automate the handling of medicines in the supply chain, and provide tools for monitoring the efficacy and safety of medicines in use. Therefore, it can improve patient safety, allow professionals to provide higher quality care, and help patients make proper use of their medicines. Here are some examples.

Electronic prescribing (CPC healthcare-Glintt; ST+I; etc): This has been shown to reduce medication errors, and it has a major impact on patient safety. However, the effect on error reduction is dependent on system design, that's why hospital pharmacists must be involved in the design, specification of parameters, and evaluation of ICT within the medicines processes (European statement 1.7).

Barcode medicine identification: This has been used with electronic prescription systems in some hospitals (e.g., Cascais Hospital) and has been shown to reduce medicine administration errors, as well as improve the extensiveness of the medication history. It seems to have a major impact on pharmacy workflow.

Automated dispensing: Pharmacy robots have been shown to reduce the incidence of dispensing errors, improve the speed and efficiency of the dispensing process, and optimize use of space in the pharmacy (e.g., Kardex—automated storage and retrieval solution for unit dose preparation; Consis—drug dispensing system that improves space and facilitates picking)/wards (e.g., Pyxis—automated medication dispensing system that supports decentralized medication management).

Mobile technology: Sophisticated apps have been developed for disease monitoring (e.g., medication adherence support and health education). These apps will have a larger impact on pharmacy practice in future.

Adherence monitoring: Various technologies for adherence monitoring are now available, such as "smart" packaging, where a microchip-containing tablet blister pack is able to monitor when doses are popped out (not necessarily taken) and prompt the patient to record side-effect monitoring information for the medicine in question. These data can then be transmitted to a mobile telephone or tablet device. Due to cots these are not fully implemented.

Telecare: It involves the use of digital communications technology (audio and visual) to provide health-care consultations and services to patients remotely at home. Their use for pharmacist consultations of long-distance outpatients is not yet fully implemented.

Pharmacists must be involved in ICT development since they are important players in the patient medication circuit, intervening on it early, when perceiving the patient need for a specific medicine, during, by monitoring medicine use and in the end, when evaluating medicines utilization. Additionally, pharmacists must ensure that they harness technologies in a way that will support and help their professional aspirations.

Future of Pharmacy

Rethinking the Segregation Between Public and Private

Since the very inception of the Portuguese National Health System, there has been an interaction between the public and private sectors. Although a recent doctoral thesis by the former Portuguese Minister of Health identified that in the last 30 years, the private sector in the health system has contributed to improve efficiency through health-care competition and cooperation, a more rational use of resources, sharing of responsibilities and increased productivity (Fernandes, 2015), the growth of the private sector has been subject to much discussion and sometimes criticism by some of the parties with a seat in the Parliament.

However, data have shown that overall, the private participation in the Portuguese health system, in the period of study (1983–2013), had an important role in the increase of equity in access, through increased supply and geographical coverage, reduction of access barriers, reducing of waiting lists, and also by better coordination between public and private sectors converted on a global improvement of health outcomes (Fernandes, 2015).

The debate about the public and private mix has been highlighted in the discussions leading up to an update of the "*Lei de Bases da Saúde*," which is the law that establishes the general framework of the national health system, namely, the National Health Service. In the new text, which is significantly different from the one that had been included in previous iterations of the document, it is stated that "the Government (. . .) intends to reduce the recourse to the private sector to what is strictly necessary."

This further amplifies the segregation between both sectors, which has been detrimental to community pharmacies in particular, given their private status.

However, pharmacists should remain optimistic considering the most recent Government Program for Portugal, in which the role of pharmacists and the integration of community pharmacies in the health-care system as part of the primary health-care

network are emphasized. Legislation that has been published subsequently, as highlighted in previous chapters, has reaffirmed this position.

This follows international trends, including from the World Health Organization, which in its Global Conference on Primary Health Care 2018, invited pharmacists to participate and present their contributions. Indeed, forty years after the milestone Alma-Ata Declaration, country representatives have again gathered in Kazakhstan, this time in Astana, and endorsed the Declaration of Astana, which renews political focus on strengthening primary health care from governments, nongovernmental organizations, professional organizations, academia, and others. The declaration states that the success of primary health care will be driven by knowledge and capacity building, human resources for health, technology, and financing. For this purpose, all health-care professionals have a role to play, irrespective of where they work.

Pharmacists' Integration into the PNHS

It is often stated that pharmacies are an untapped resource to improve health systems' efficiency (International Pharmaceutical Federation, 2012). The same can be said for pharmacists as providers of care. Facing the enormous challenges related to the demographic changes and subsequent burden of disease, countries cannot afford to waste pharmacist knowledge and expertise.

As the OECD/EC report pointed out, access to care will remain a challenge in future years, and a workforce strategy should be in place to ensure that citizens receive the services they need when they need them (OECD, 2017).

However, the integration of pharmacies in health-care systems is limited and most of the time only valued within the context of the medicines dispensing process.

Internationally, this has started to change, with more and more pharmacists and pharmacies being remunerated for services they provide (International Pharmaceutical Federation Pharmacy at a Glance, 2017).

Portuguese pharmacists are available and ready to take on further roles and have greater intervention in care areas, in conjunction with other health professionals acting at different levels of care.

With a forward-thinking vision, pharmacists have been preparing themselves for the various challenges of the present and the future in health care, with the aim of fully addressing the needs of citizens, health professionals with whom they work, the National Health Service, and the country in general.

To this end, processes already initiated such as ensuring access to the health data platform, extending the services to be provided in community pharmacies, hospitals and clinical biology labs, and the regulation of the pharmaceutical career in the National Health Service are fundamental.

Based on the value generated, a new remuneration model should be established that recognizes and aligns agreed-upon incentives and health gains.

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CONTENTS OF ALL VOLUMES

VOLUME 2

VOLUME 3A

VOLUME 3B

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His research interest includes pharmacy practice especially pharmacists' expanded scope of practice, outcome-based research, pharmacoepidemiology and medication safety, and health promotion. Dr. Ahmed Awaisu has conducted training sessions and workshops on research methodology and biostatistics, drugs in sports, developing cognitive pharmacy services, and responding to symptoms in pharmacy practice. He presents regularly at continuing professional development programs for healthcare professionals in Qatar and other countries.

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Professor Timothy Chen is a registered pharmacist and Professor of Medication Management, School of Pharmacy, The University of Sydney, Australia. Tim is nationally and internationally renowned for his research in medication management review and strategies to reduce medication related harm. Tim's research directly informed the Australian Government funded Home Medicines Review programme (MBS Item 903). Tim is an experienced educator and health services researcher, with experience in both community pharmacy and hospital pharmacy practice. Tim leads a productive research team (>160 peer-reviewed papers) and has completed main supervision of 15 PhDs, amongst other postgraduates. Tim has delivered >70 invited presentations at conferences and meetings across the globe. Tim has received university and national awards (Australian Government) for teaching, is an International Pharmaceutical Federation (FIP) Fellow (2016), and is President of the Social and Administrative Pharmacy Section, FIP.

Louise Curley

Louise Curley is a pharmacist and Senior Lecturer in Pharmacy practice at the School of Pharmacy. Louise's area of research focuses on the effects of recreational drug use in humans. She began her research as an undergraduate by investigating the subjective and electrophysiological effects of the Party Pill drugs using electroencephalography (EEG) and graduated with a PhD in pharmacy in 2012. Her thesis investigated the effects of the main constituents of "Party Pills" benzylpiperazine (BZP) and trifluromethylphenylpiperazine (TFMPP) on executive functioning and reward using functional magnetic resonance imaging (fMRI). Currently, her focus is developing new fMRI paradigms to investigate different aspects of risk, specifically by comparing populations of dependent versus non-dependent participants. Louise also has an interest in pharmacy practice research including innovative methods of teaching undergraduate students using different technologies and evaluating the effects of these innovations. She has recently been awarded the Butland Teaching Award: Innovation in Teaching.

Danijela Gnjidic

Dr. Danijela Gnjidic (BSc PhD MPH) is an NHMRC Dementia Leadership Fellow and Senior Lecturer at the School of Pharmacy, Faculty of Medicine and Health, University of Sydney. Her research expertise is in clinical and geriatric pharmacology, clinical studies on polypharmacy, high risk prescribing, and deprescribing in older people, pharmacoepidemiology, and the quality use of medicines. Danijela's academic track record includes 115 publications, 3-book chapters, with over 2500 citations on Scopus and $4M in research funding. Danijela was awarded the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Denis Wade Johnson & Johnson New Investigator Award in 2012. Internationally, Danijela's contribution to the filed was recognized with the 2018 American Society of Clinical Pharmacology and Therapeutics William B. Abrams award in Geriatric Clinical Pharmacology. Danijela is an Associate Editor of the *Journal of Alzheimer's Disease* and Academic Editor of the *PloS One Journal*.

Arijana Meštrović

Dr. sc Arijana Meštrović, MPharm, FFIP has been working as a community pharmacist and she was responsible for education, services, and competency development in the biggest pharmacy chain in Croatia. She is now independent consultant and educator in Pharma Expert international agency, providing lectures and workshops in CPD programs for pharmacists, pharmacy technicians, medical representatives, implementing new services in pharmacy chains, and teaching Social Pharmacy and Pharmaceutical Care at universities in Croatia and Cyprus as Assistant Professor. Her Doctor's degree is in biomedical sciences—competency development in pharmacy. Arijana serves as member of the International Services Program Advisory Group the Accreditation Council for Pharmacy Education (ACPE, USA), member of PCNE (Pharmaceutical Care Network of Europe), ExCo member of FIP (Pharmaceutical International Federation) Academic section, and WHO international expert consultant in Pharmaceutical care field. She used to serve as Co-Chair of the FIP World Congress Programme Committee, Expert Member of the Board of Pharmacy Practice at FIP. In Croatia, she is a leader in Croatian Pharmaceutical Society and Croatian Chamber of Pharmacist as a Lecturer and Co-author of New services model in community pharmacy practice. Arijana is dedicated to promoting competency-based education in CPD cycle, so her teaching usually addresses all components of competencies—knowledge, experience, and motivation. In collaboration with ACPE International Services, she has founded and implemented SMART Pharmacy CPD model for pharmacists in more than 12 countries all over the world. She was invited speaker and consultant in more than 40 countries.

Kath Ryan

Kath is Professor of Social Pharmacy at the University of Reading, and Visiting Professor at Bournemouth University, United Kingdom. She has 45 years of experience as a pharmacist in the pharmaceutical industry, community practice, and academia. She has held posts at the University of Otago, New Zealand; Bournemouth University, United Kingdom; La Trobe University, Melbourne, Australia; and the University of Reading, United Kingdom. She also has experience in academic nursing and midwifery. Her research interests include extended roles for pharmacists, especially in general practice; application of the behavioral sciences to pharmacy practice; personal experiences of health and illness; and public and patient involvement, engagement and participation in research, and the education of health professionals. She has expertise in quantitative, qualitative, and mixed methods research. She also has an interest in infant feeding,

particularly breastfeeding research, promotion and support, from lay, professional, and academic perspectives. She has been a health advisor to La Leche League International and La Leche League New Zealand. Kath has been on Scientific Committees for the International Social Pharmacy Workshops and the Australasian Pharmaceutical Sciences Association. She has consulted for the National Institutes of Health, USA; Canadian Forces; Health Technology Assessment, NHS UK; and the NZ Ministry of Health.

Kath has over 100 publications in peer-reviewed journals and several book chapters and reports. She produced two multimedia, online resources for Health Talk: women's experiences of breastfeeding in the United Kingdom, and people's experiences of ageing in Australia. She was a Founding Co-Director of Health Talk Australia.

FOREWORD

This first edition of the Encyclopedia of Pharmacy Practice and Clinical Pharmacy is one-of-a-kind and the most comprehensive amalgamation of an inclusive range of topics relevant to the pharmacy profession brought together to ensure safe and effective provision of pharmaceutical care across the world. Professor Zaheer Babar is a Professor in Medicines and Healthcare at the University of Huddersfield and also a global expert in pharmacy practice and pharmaceutical policy. He has united over hundreds of researchers and practitioners from across the world in a collaborative endeavor to provide a unique insight into current best practice and strategies for the future for the profession of pharmacy and its practice.

As patient care becomes more complex with advances in medicines and new developments in practice, including pharmacogenomics and pharmacoeconomics, there is an ever-evolving demand for practice and policy to keep pace. This encyclopedia contains 180 chapters, from all fields of pharmacy practice and clinical pharmacy, providing an in-depth coverage of modern approaches to the practice of pharmacy and highlighting the directions that will enable advancement to continue.

This encyclopedia includes definitions, concepts, theories, and applications of clinical pharmacy and pharmacy practice, providing background knowledge of the area that will provide valuable information for students of pharmacy practice. By providing relevant and topical summaries on a broad range of subjects, this book is also an excellent resource for those seeking information beyond their specific areas of expertise. In addition, the information contained in this book and its communication is of importance to a range of stakeholders, such as physicians and other healthcare professionals, health regulatory authorities, and the pharmaceutical and health industry, in addition to patients and their caregivers.

This encyclopedia also provides an excellent insight into pharmacy practice research and methods, as well as pharmacovigilance, pharmacoeconomics, social and administrative pharmacy, public health pharmacy, pharmaceutical systems research, the future of pharmacy, and new interventional models of pharmaceutical care. In addition, new treatments, algorithms, standard treatment guidelines, and pharmacotherapies regarding diseases and disorders are also covered.

The six key strands around which this encyclopedia is arranged pay testament to the complex and broad nature of the topic and are key topics of interest in pharmacy today and drivers of change for the future, for the benefit of public health across the world.

1. Pharmacy practice
2. Pharmacy practice research methods
3. Clinical pharmacy education, professional standards, and workforce
4. Clinical pharmacy and pharmacotherapy
5. Pharmacoepidemiology and pharmacovigilance
6. Socio-behavioral and administrative pharmacy

Topics range from the education and training of pharmacists, technicians and assistants to counterfeit medicines, pharmaceutical pricing policies, and implementation of change. As pharmacy practice evolves to meet the ever-more-complex health and medicines needs of patients, practitioners need an understanding of the social, political, and economic contexts across the world, noting particular highlights and challenges in developing countries to reach high standards. While it is acknowledged that there are differences between countries in terms of legislation, regulations, and guidelines (as detailed in individual chapters), the vision for the profession must be for a world in which everyone can access safe, effective, and affordable medicines and pharmaceutical care. The chapters include many examples of innovation and best practice in delivering health

services for the future, embracing additional roles beyond the supply of medicines in a robust manner underpinned by scientific and evidenced practice. Quantitative, qualitative, and mixed methods of pharmacy practice research are presented alongside expanded and evolving roles for pharmacists and where technology may take us. More quality research and coordinating efforts will bring a range of theoretical concepts and an evidence-based practice to the forefront of our activities, to focus a global workforce to meet the challenges of this exciting new era for pharmacy practice. This timely volume exemplifies the willingness and ability of the profession to work collaboratively on global issues, representing an unprecedented opportunity to shape the future of pharmacy practice.

With ever-increasing demands on healthcare systems, alongside growing financial pressures, it is essential that we work collaboratively with other pharmacists and the wider public health workforce who have the expertise, opportunity, and capacity to support and inform development.

In this context, this encyclopedia is an important resource with far-reaching impact on global healthcare community, and I hope this will be well liked by students, researchers, and academics.

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March 2019

PREFACE

Encyclopedia of Pharmacy Practice and Clinical Pharmacy

This encyclopedia has 180 chapters in total and it covers all domains of pharmacy practice and clinical pharmacy, including pharmacy practice research, socio-administrative and behavioral pharmacy, pharmacy education, pharmacoepidemiology, and the pharmacotherapy. One main question being asked is the need for this work. *What encyclopedia of pharmacy practice and clinical pharmacy adds to the current body of literature and what it means for global pharmacy community?* The answer to that is, though there were a number of books available on pharmacotherapy, however, current landscape lacks material comprehensively covering aspects, such as pharmacy practice, pharmacy practice research, social pharmacy, pharmacoepidemiology, pharmacy education, and the linking of clinical pharmacy with the health system. This encyclopedia aims to provide a collection of chapters on the above-mentioned areas. It also developed, synthesized knowledge, and provided policy guidance in the areas where there were gaps in the literature. For example, filling the gaps and including chapters on health systems, pharmaceutical policy, evidence and impact in pharmacy practice research, and on pharmacy education.

Here is a brief summary of what is being covered in its three volumes: Volume 1, 2, and 3.

Volume 1 includes chapters on pharmacy practice and pharmacy practice research. The pharmacy practice section starts with the historical evolution of pharmacy practice, medicines management, expanded roles of pharmacists, cognitive pharmacy services, community, and ambulatory pharmacy practice, ethics and regulation, and the new models of pharmaceutical care. There are also chapters on prescribing standards, practices, and competencies, interpersonal communication, evidence-based medicine, models on patient counseling, innovative pharmacy services, technology in pharmacy practice, and the pharmacist's role in substance misuse. The case studies chapters include pharmacy practice in high, low, and middle-income countries; United Kingdom, Western Europe, Australia, New Zealand, China, India, Gulf States, Philippines, and Portugal.

It is vital to understand and discuss the quality of evidence in pharmacy practice research, for example, how the evidence is produced and how it could impact on health outcomes. This is a niche section in the encyclopedia covering chapters on quantitative and qualitative methods in pharmacy practice research, quality of qualitative research, philosophical perspective and theories applied in pharmacy practice research, meta-synthesis, mixed methods research, discrete choice experiments, and the use of network meta-analysis in pharmacy practice. There are also chapters on evolution and definition of practice research, evidence, impact, and gaps in pharmacy practice research in low- and middle- and high-income countries.

Volume 2 covers pharmacovigilance, pharmacoepidemiology, and the socio-behavioral and administrative aspects of pharmacy and medicines use. The knowledge regarding pharmacoepidemiology and pharmacovigilance significantly impacts on medicines safety. The chapters included are on definitions, principles, and application of pharmacoepidemiology, descriptive and drug utilization studies, case-control and cohort studies, methodological challenges in epidemiological studies, data sources, and the issues related to medicines safety and comparative effectiveness research.

The socio-administrative and behavioral pharmacy section covers two broad aspects, namely, social pharmacy and pharmacy administration. Social pharmacy section covers concepts, development, and theories related to social pharmacy, public and patient engagement, sociology for pharmacists, implementation of change in pharmacy practice, and the social perspectives in addiction. There are also chapters on medicines adherence, compliance, and concordance, medication narratives, investigating medicines use among elderly

from a sociological perspective, changing nature of pharmacy as a profession, the impact of culture and religion on medicine use, and the issues related to disease mongering.

The understanding of health system is vital when promoting access and the use of medicines, hence in this context understanding administrative aspects of pharmacy are crucial. This section explores the dynamics between public policy, pharmaceutical policy, pharmacy practice, health systems, and patient-health outcomes. It covers a range of pharmaceutical policy and health system issues including access to biosimilars, access to high-cost medicines, counterfeit medicines, factors influencing pharmaceutical policy implementation, funding mechanisms for community pharmacy services, generic drug policies, national medicine policies, essential medicines list, pharmaceutical company sponsored medication assistance programs, and the pharmaceutical pricing policies.

Volume 3 covers clinical pharmacy education and pharmacotherapy. Pharmacy education training and the workforce have a great impact on global health. There are 25 chapters or more on pharmacists' training, and certification exploring the relationship between education, regulation, and practice. This is one of the largest collection of chapters covering pharmacy education and regulation at the global level. This includes chapters on pharmacist workforce, competency standards for clinical pharmacists, quality assurance in the pharmacy education, developing and evaluating clinical skills, continuing professional development, experiential education, inter-professional learning, leadership in pharmacy education, and the needs-based education. There are also case studies chapters on clinical pharmacy professional standards in the United States of America, Canada, the European Union, and in the low- and middle-income countries.

The pharmacotherapy section covers over 70 chapters discussing standard treatment guidelines, pharmacist's role in the central nervous system, infectious diseases, cardiovascular disorders, skin and endocrine disorders, musculoskeletal disorders, neurology, gastrointestinal disorders, and the respiratory disorders. The other key chapters include clinical pharmacy concepts, history, and development, clinical governance principles, pharmacokinetics, therapeutic guidelines, end of life care, palliative care, long-term care, fundamentals of pharmaceutical care planning, health outcomes and quality of life, the role of the pharmacist in the military and prisons, and the pharmacotherapy and deprescribing.

It has been a challenging task to complete this encyclopedia within a short span of 2 years. However, I am very thankful to the support of my section editors, reviewers, and hundreds of authors from all over of the world to come together and to contribute to this exciting project.

I hope you will like this effort and it will serve its purpose.

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Editor-in-Chief
Encyclopedia of Pharmacy Practice and Clinical Pharmacy

March 2019

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What is Social Pharmacy?

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Introduction

The practice of pharmacy, and consequently, the pharmacy curriculum and the focus of research in many countries have changed considerably over the last 20 years in response to a rapidly changing economic, political, and social environment. The cost of providing health care continues to escalate, with a greater range of health technologies available to an ever-increasing aging population. The costs of medicines continue to rise and there is heightened awareness of patient safety issues and the occurrence of errors and adverse events. People are increasingly knowledgeable about the medicines they take and many will have already consulted the Internet to find out more information by the time they seek professional help. Some people will also demand more information about their health and well-being and not blindly trust the advice of health professionals. If pharmacists are technically excellent and also communicate in a patient-centered manner, patients will not only be better informed but will also be more satisfied with their care. In a UK study, only 16% of patients prescribed a new medicine took it as prescribed, experienced no problems and received as much information as they needed. Ten days after starting a medicine, almost one-third of patients were already nonadherent. Pharmacists need to have skills to support people in their medicines taking and to advise prescribers about safe and rational prescribing (Elliott et al.).

In many countries, there has been a blurring of roles between health-care professionals leading to increased competition, for example, in the United Kingdom, Canada, and New Zealand accredited pharmacists are able to prescribe medicines and in the UK pharmacists are being trained as advanced practitioners alongside other health-care professionals like physiotherapists, nurses, and paramedics in areas like urgent and emergency care. The pharmacy profession has had to face up to key technological developments, in particular the development of original pack dispensing, robotics and artificial intelligence but also the evolving role of the pharmacy technician which has meant that community pharmacy has lost one of the components that sustained its professional status, compounding and to an increasing extent dispensing. In the United Kingdom, for example, technicians can now dispense and perform the final check for dispensed medicines. This leaves pharmacists free to provide patient facing clinical and public health services such as medicines use reviews, smoking cessation services, immunization and diagnostic testing, and case finding. These patients facing roles mean that pharmacists need to have excellent communication and consultation skills as well as an understanding of people's health beliefs and their concerns about taking medicines.

As a result of these developments, the pharmacy curricula in many countries have evolved from being dominated by the physical and biological sciences meeting the needs of drug discovery, development and control only, to including clinical, social, psychological, and administrative and practice elements. The basic sciences of pharmaceutical chemistry, pharmaceutics, pharmacognosy, and pharmacology, with their heavy reliance on the teaching of the drug entity, its chemical nature, its derivation from plant and animal sources, its action within the body and formulation, have become more integrated with a greater emphasis on subjects based around the clinical and social needs of patients and a knowledge of medicines and diseases. If a pharmacist understands something about patient behavior regarding health and illness and taking medicines he or she will be better equipped to support people in their decisions to make changes to their behaviors and to adhere to their medicines.

The idea of social pharmacy has developed as a term to embody and express these changes. It can be argued that social pharmacy, like social medicine, is a multidisciplinary hybrid, drawing on the theories and methodologies of the social and behavioral sciences. Social pharmacy like pharmacy itself is a hybrid discipline, drawing on the theories and methodologies of the social and behavioral sciences, including sociology, social psychology, psychology, political sciences, critical studies, educational studies, communications, economics, history, and anthropology.

Defining Social Pharmacy

The development of social pharmacy as a discipline has been internationally diverse and it has been defined in many ways. We asked some international colleagues to define it: the first said, social pharmacy is the application of sociological epistemologies,

frameworks and approaches to pharmacy phenomena. The second, the term is derived from social medicine and means the application of social and behavioral sciences to the medication use process and the patients who use medicines. It also has come to include epidemiology and other public health sciences. The third said, it addresses the fact that only medicines that are taken work, and we need to try to uncover and support the implementation of safe, effective and acceptable drug treatments. The fourth said, social pharmacy is the application of the social and behavioral sciences to pharmacy practice.

Johnson and Wertheimer (1979) proposed a general definition for what they then called "behavioral pharmacy": the field concerned with the development of behavioral science knowledge and techniques relevant to the understanding of drug use, drug effects, drug selection and prescribing, behavioral-therapy adjuncts and alternatives to drug therapies, the professional behavior and well-being of pharmacy practitioners, and the application of this knowledge and these techniques to prevention, diagnosis, treatment, and rehabilitation.

Nettleton et al. (1994) argued that social pharmacy (perhaps like social medicine) is a multidisciplinary hybrid, drawing on the theories and methodologies of the social and behavioral sciences. As such, it can be conceived of as part of a socio-environmental, or bio-psycho-social approach to understanding health and illness as distinct from the biomedical approach. One of the chief contrasts between these two approaches is that the former emphasizes the social and psychological determinants of health, whereas the biomedical approach has been criticized for its overly reductive approach. Harding and Taylor (1993) stated that social pharmacy cannot be equated to the sociology of pharmacy but that it explores the ...

> "... hitherto neglected social domain in which pharmacy is practised from the practitioner's social perspective."

This differs considerably from the definition by Sørensen et al. (2003) who stated that *"social pharmacy is the interdisciplinary discipline that enables the pharmacy profession to act, take part in and take responsibility for drug matters at a societal level"*. These authors appeared to see social pharmacy more broadly from a societal perspective rather than from the perspective of pharmacy as a profession.

More recently low- to middle-income countries have made significant contributions to the discussions surrounding social pharmacy (Babar and Jamshed, 2008; Hassali et al., 2011).

In addition to the lack of unified terminology, the discipline of social pharmacy has lacked consensus and a common understanding of what the research area covers (Almarsdottir et al., 2014). This is quite obvious when studying the definitions that have been put forward and from the lack of literature about what constitutes the field of social pharmacy.

Traulsen and Herborg (2016) beautifully captured the essence of the discipline when they wrote their introduction to a special issue on Social Pharmacy of the open access journal *Pharmacy*:

> "Social Pharmacy is the multidisciplinary field of education and research that focuses on the role, provision, regulation and use of medicines in society. The scope is broad, covering the social, psycho-social, economic, and organizational aspects of medicines. It analyzes policy decisions made on the local, national, international and global levels concerning medicines. It spans a variety of themes, including medicine distribution and use; economics and financing; decision-making; health behaviour; health knowledge, health beliefs, health literacy; health and pharmaceutical policy; pharmacoinformatics; ethics; and pharmacoepidemiology and pharmacovigilance."

Social pharmacy combines pharmacy with theories and methods from the social sciences, psychology, and humanities. Social pharmacy research encompasses the behavior and perspectives of people, patients, governments, local health authorities, third-party payers, health-care professionals, and the pharmaceutical industry. A central theme is people's perspectives on using medicines.

Sørensen et al. (2003) describe the remit of social pharmacy as studying

> " . . . the drug/medicine sector ... from the social scientific and humanistic perspectives. Topics relevant to Social Pharmacy consist of all the social factors that influence medicine use, such as medicine and health-related beliefs, attitudes, rules, relationships, and processes."

Scahill et al. (2017) in an attempt to define pharmacy and its practice argue for a global model of pharmaceutical practice in which social pharmacy is but one of four parts that include social and administrative sciences, community pharmacy, clinical pharmacy, and pharmaceutical sciences.

If we turn to medicine for some help with the definition, Horton (2013) while writing about social medicine quoted Ryle who said *"Whereas public health confined itself to housing, safe water, and sanitation, social medicine included "the whole of the economic, nutritional, occupational, educational, and psychological opportunity or experience of the individual or the community"* and concluded that it unites the clinical with the public. Porter (2006) defined social medicine as including topics such as the social and economic structure of health-care provision, health policy, and clinical holism, through to evolving concepts of the field, such as concerns with doctor/patient relations in culturally diverse societies. She says that the evolution of social medicine as an academic subject has been internationally diverse and a coherent definition of the discipline has remained elusive. So in attempting to define social pharmacy and borrowing Horton's definition of social medicine, that it unites the clinical with the public, it can be said that social pharmacy unites pharmacy policy and clinical pharmacy with the people who take medicines and use pharmacy services.

Concepts and nomenclature other than social pharmacy are used within the literature such as pharmacy practice and pharmaceutical policy. Social pharmacy research is well developed as an academic discipline in the Nordic countries, the United Kingdom, and the United States. In the United Kingdom, there is some overlap with what is often called pharmacy

Table 1 Overview of social pharmacy section of Encyclopedia of pharmacy practice and clinical pharmacy

Section	*Contents*
People's behaviors and perspectives	Culture, literacy adherence, stigma, addiction, aging populations
Organization	WDGs, gender, community pharmacy operations and management, public perceptions of pharmacy services, professional boundaries
Policies	Medicines and pricing policies, counterfeit medicines, access to medicines, funding pharmacy services, corporatization
Marketing	Marketing professional services, pharmaceutical industry marketing
Research and theory	Health inequalities, human factors, medication narratives, pharmaceuticalization, public and patient involvement, sociology

practice and policy and in North America pharmacy practice is also known as a research discipline, primarily carried out by clinical and/or hospital pharmacists. In North America, the term pharmacy administration is also used for social and administrative aspects of pharmacy but in the past two decades this label may also refer to pharmaceutical outcomes, pharmacoepidemiology, and policy analysis.

The International Social Pharmacy Workshop (ISPW) has long been a focus for the development of the research networks within the discipline. The focus of the workshop has at least until recently been on research directed toward pharmaceutical policy, access to medicines, medicine use and pharmacoepidemiology, pharmacoeconomics, organizational behavior, and individual pharmacist practice. *Research in Social and Administrative Pharmacy (RSAP)*, the major social pharmacy journal, includes a number of topics of interest such as outcomes evaluation of drug products, programs, or services; pharmacoepidemiology; medication adherence; disease management; medication use policy; drug marketing; evaluation of educational paradigms that could impact practice and/or patient behavior; and other topics related to public health in the context of pharmacy or medication use.

Social Pharmacy

Table 1 shows an overview of this section of the Encyclopedia of pharmacy practice and clinical pharmacy.

Horizon Scanning

Social pharmacy should maintain its cross-disciplinarity working together with scholars from associated social behavioral science disciplines to develop new understandings and theories. Social pharmacy has too often focused on psychology and behavior change to the detriment of other social science disciplines. It should be wider in its focus not just looking in a prescriptive way at the pharmacy profession and the way services are delivered but also cover broader societal and patient issues. So, if we say social pharmacy unites pharmacy policy and clinical pharmacy with the people who take medicines and use pharmacy services, how then do we develop the field?

We should meet people in their world, rather than bringing them into ours, using patient's own language and engaging with their understanding of medicines in their lives. Are patients really at the center of all we do? Do we have a holistic view of patients? Or does the system mitigate against that? Do we need to develop more user-friendly medicines and medicine regimens that fit into patients' lives rather than the other way around?

Social pharmacists need to align the development of the field with global challenges as exemplified by the Sustainable Development Goals. This includes climate change and health, security, migration, global inequalities in access to medicines, workforce issues, shifting modes of delivery of health care, for example impending focus on primary health care, increasing use of technology, the advent of artificial intelligence and the various agendas for medicines' design and development.

Social pharmacy should maintain an important place in the pharmacy curriculum, with the aim of educating well-rounded individuals who are critical thinkers and do not accept everything at face value. Pharmacy is an art form based on scientific knowledge and its application to the human condition. As such, rigid adherence to standard operating procedures at the cost of professional judgment and tailored patient encounters should be a thing of the past.

Conclusions

No more intellectual endeavor should be wasted trying to come up with a definitive definition of social pharmacy as it is now an established discipline. Social pharmacy needs the flexibility to continue to evolve as a distinct field within the broad and ever changing healthcare environment. We need to strengthen the application of theory as we develop new knowledge about the practice of pharmacy for the benefit of patients.

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Access to Biosimilars

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Historical Background

Historically, biological medicines have been used to effectively treat a number of acute and chronic diseases, such as HIV/AIDS, cancer, inflammatory, and autoimmune diseases and more recently, Ebola and the ZIKA virus. Statistics for cancer alone indicate that it is still one of the leading causes of death worldwide. The number of new cancer cases is expected to rise to 22 million within the next two decades (NIH Factsheets - Cancer, 2017), which warrant the development of new therapeutic strategies and interventions.

The increasing demand for new therapies has led scientists and pharmaceutical companies to explore the field of "biologics"—which are extracted from or semi-synthesized from biological sources. They include blood components, vaccines, allergenics, gene therapies, recombinant therapeutic protein, tissues, and living cells. One textbook definition of biologics is as follows:

> By definition biologics are proteins and/or derivatives thereof that modulate the immune system, downregulate the inflammatory response or support tumor-specific defense. Biologics—also known as 'biologicals' or 'recombinant therapeutics'—do not represent one homogeneous group of drugs. Monoclonal antibodies, fusion proteins (along with other proteins, toxins, and radionucleotides) and recombinant proteins, growth factors, anti- and proangiogenic factors, and expression vectors generating proteins in situ may all be included as members of this class of pharmaceuticals (Boehncke and Radeke, 2007).

The European Medicines Agency (EMA) and World Health Organization (WHO) exclude vaccines, plasma-derived products, and their recombinant analogs from consideration as biosimilars due to their complexity and variable biological and functional characteristics. The EMA guideline states that "due to complexity and the likelihood that they cannot be thoroughly characterized at the molecular level, vaccines must be considered on a case-by-case basis" (EMA, 2017).

Historically, the term "biologics" was first coined in the United States more than a hundred years ago in connection with national health-care legislation and the control of vaccine synthesis (Schwerin et al., 2013). Currently, biologics comprise a growing portion of the pharmaceutical market. Biologics have had and continue to have a profound impact on a number of medical disciplines, including rheumatology and oncology, and have allowed for an increase in therapeutic options for the treatment of several diseases, where existing therapies proved ineffective (Oo and Kalbag, 2016). On the contrary, however, the emergence of biologics has led to several regulatory and pharma-economic concerns, as biological therapies bring with them a high cost in comparison to their conventional counterparts. Moreover, preclinical and clinical research prerequisites to the synthesis of biologics are costly as they require a strictly controlled environment and advanced technological parameters

(Bradford and Gary, 2014; Chow, 2014). For example, the monoclonal antibody, Trastuzumab, which targets HER2-overexpressing breast cancers, although an effective therapy, is not a cost-effective intervention. Compared to the average wholesale price of other cancer therapies, monoclonal therapies are expensive, and clarification is needed about whether such expensive therapies offer value for money (Neyt et al., 2006).

Although several biologics are under scientific research or at clinical trial phase, few have found their way to market as successful treatments for disease. Biologics are important therapeutic medicinal products; however, health-care costs for biologics are unsustainable for the average consumer. Consequently, biologics are either not available or have limited availability in several countries due to their high price and lack of accessibility by most consumers (Bradford and Gary, 2014; Francois and Pascal, 2015). Thus, a number of issues, including the increasing price of new biologicals, continuing pressure on health-care budgets, as well as patent expiration, have opened the door for new alternatives like "biosimilars" to emerge. As the patents for individual originator medicines expire, biosimilar medicines can be introduced to provide additional options for patients and the health-care system.

The EMA approved its first biosimilar for marketing authorization in 2006 and since has approved the highest number of biosimilars worldwide (EMA, 2017). On the other hand, the U.S Food and Drug Administration (FDA) has approved 11 biosimilar products, including five in 2017 (Biosimilars Action Plan, 2018). Biosimilars are now expected to make up an increasing share of the biologicals market, where more than 200 new biotechnology products are in the pipeline (phase II to registered), all of which could be future targets for biosimilars (EMA, 2017).

Biosimilar Clinical Features

Biosimilar medicines must possess certain specific clinical features for them to meet the strict criteria of the approval process as outlined by bodies such as the EMA and Food and Drug Administration (FDA). These are as follows:

1. Biosimilars must possess physical, chemical, and biological properties *highly similar* to the originator molecule, hence the term, "biosimilar." There may be minor differences from the reference medicine, but these must be clinically insignificant in terms of the drugs' safety and efficacy.
2. Biosimilars must possess *no clinically significant differences* from the reference drug as demonstrated through extensive and rigorous clinical studies to support their approval.
3. *Variability of biosimilar kept within strict limits*. Variability for a biosimilar should not affect the drug's efficacy, mechanism of action, or safety where the range of variability should be the same as that allowed between batches of the reference medicine. This is achieved through robust manufacturing processes to ensure that all batches of the medicine are of proven quality.
4. Same *strict standards of quality, safety, and efficacy*. Biosimilars must follow the same strict guidelines for quality, safety, and efficacy as any other medicine approved for use. For the finished medicine, both biosimilar and reference medicine must have the same dosage and route of administration. Some variations with regard to differences in the formulation of the medicine (e.g., excipients), presentation (e.g., powder to be reconstituted versus solution ready for injection), and administration device (e.g., type of delivery pen) are permitted (EMA, 2017).

Approval Process and Impact

To ensure biosimilars do not possess differences in safety, potency, and efficacy in comparison to their respective originator, products require stringent analytical studies to demonstrate their "biosimilarity" as outlined by the respective regulatory bodies (Surya and Karen, 2015). In 2003, the EMA introduced an adapted pathway for biosimilars, termed, "similar biological medicinal products." The basis of this pathway is to ensure a thorough demonstration of "similarity" to the existing approved drug through rigorous preclinical and clinical testing (Bui et al., 2015). In the United States, the Patient Protection and Affordable Care Act of 2010 created a shortened approval pathway for biologicals shown to be similar to, or interchangeable with, an FDA-licensed reference biological (FDA, 2018). These guidelines have evolved to help developers conform to strict regulatory requirements but also to keep pace with their increasing demand.

Development and Approval of Biosimilars in the EU

The EU approved its first biosimilar in 2006 where a robust regulatory framework ensured that all biosimilars conformed to the same stringent regulatory guidelines and requirements. The EMA has paved way for developers to adhere to these strict regulatory guidelines as a route for the introduction of a number of other biosimilars. These guidelines have been developed to keep up with the increasing pace of drug development and advances in biotechnology (EMA, 2017).

All medicines using biotechnology and those for specific clinical indications must go through a "centralized procedure" as outlined by the EMA. Data collected from the prospective drug go through a regulatory pathway that includes the EMA's scientific committee on Human Medicines and Safety, EU experts on biologics (Biologics Working Party), and specialists in biosimilars

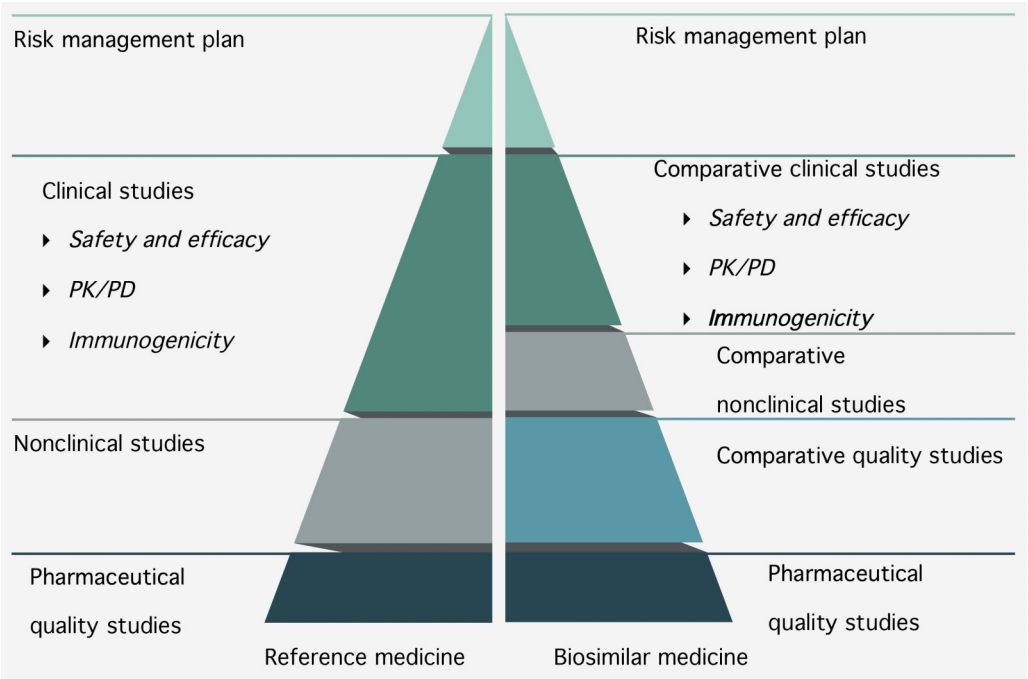

Figure 1 Comparison of data requirements for approval of a biosimilar versus the reference medicine (Biosimilars in the EU, 2017).

(Biosimilar Working Party). Analysists monitor the "positive benefit–risk balance" for the medicine as demonstrated through a series of nonclinical and clinical data for the drug of interest. Additionally, comparability (by means of safety, efficacy, and immunogenicity data) studies must also demonstrate the "biosimilarity" of the biologic to its originator where any possible impact on safety and efficacy is compared. Once reviewed by the EMA, results are sent to the European Commission which ultimately grants an E.U-wide marketing authorization. Fig. 1 illustrates the data requirements for approval of a biosimilar versus the reference medicine (EMA, 2017).

Development and Approval of Biosimilars in the United States

To date, the FDA approved has approved 11 biologics, including five in 2017 (Biosimilars Action Plan, 2018), where the FDA plays a pivotal role in the approval process and transition of biologics to market. In order to meet with the increasing demand for innovative therapeutic drugs that are more accessible to patients, the U.S Congress passed the Biologics Price Competition and Innovation Act (BPCI Act) in 2009. The purpose of the act was to establish an abbreviated pathway for biosimilar approval (Biosimilars Action Plan, 2018), thereby striking a balance between access and innovation of biosimilars and a pathway of entry to biosimilars once the period of exclusivity for originator compounds lapsed. The FDA may not approve an application for a biosimilar until 12 years after the date on which the originator product was first licensed. This bears some similarity to the pathway adopted through amendments made to the Hatch-Waxman Act (the Drug Price Competition and Patent Term Restoration Act—Hatch-Waxman Act—was introduced in 1984 to encourage the manufacture of generic drugs and established the regulatory pathways for these compounds), to strike a balance between innovation and availability of follow-on biologics and small molecule drugs. The new framework under the BPCI Act allowed for a pathway that would encourage the approval of new biosimilar products thus keeping up with market competition and providing access to patients.

A recent Biosimilars Action Plan, as introduced by the FDA (2018), recognized the critical role of the FDA in facilitating increased access to biosimilars. In doing so, they are taking several crucial steps including, developing, and implementing new FDA tools to improve the review process and increase public awareness on the process, creating resources and development tools for sponsors of biosimilars, including more information about approved biological products, establishing a new Office of Therapeutic Biologics and Biosimilars that will facilitate coordination of the processes, developing a FDA's Biosimilar Education and Outreach Campaign, that will provide much needed awareness about biosimilars to health-care professionals and other stakeholders (Biosimilars Action Plan, 2018). Several other strategic steps will also be taken as a part of BAP to promote and increase the efficiency biosimilar development and approval, increase scientific and regulatory clarity for biosimilar development, innovation and competition, and ensuring equitable access to safe and effective biosimilar medicines (Biosimilars Action Plan, 2018).

Impact of Biosimilars in the Global Market

The National Institute of Health and Care Excellence (NICE), WHO, FDA, EMA, and regulatory authorities of other respective countries are now receptive to the advantages of biosimilars and their cost-effectiveness in health care. Their common objective is to ensure equitable access of biosimilars to patients and to develop efficient and safe treatments similar to their originator products but at significantly reduced prices (Blackstone and Fuhr, 2010; Bradford and Gary, 2014; Francois and Pascal, 2015; Haustein, 2012).

In addition to cost-effectiveness of a biosimilar in comparison to its originator, other key factors are also important to their underlying rationale of replacing already approved medicines. These include their role in improving health-care professional and patient experience through value-added services and improved delivery devices; evidence-based research on product safety and efficacy, especially, when used to replace a patients' existing therapy and creating valuable engagement with strategic stakeholders in the market.

Biosimilars have the potential to provide reduced health care economic burden, which may allow ease of access to other biological therapies and may result in the development of innovative drugs in the future. Leading regulatory organizations such as the EMA, FDA, and WHO have issued and revised guidelines for the development and approval of biosimilars ensuring their equitable uptake across the global arena (CHMP, 2014, FDA, 2015b; WHO, 2009). Biosimilar products, as lower-cost alternatives of biological products, have the potential to provide savings for health-care systems, especially in countries where affordability of drugs is an issue (Christian et al., 2017). Due to the increasing impact of biosimilars in the global health-care system, "biosimilarity" is currently an area of discussion among clinical researchers, policy makers, and physicians (Christian et al., 2017; Dörner and Kay, 2015). Moreover, continuing development of biosimilar medicines creates increased choice for patients and clinicians, increased commercial competition, and enhanced value propositions for individual medicines. **Tables 1 and 2** highlight FDA- and EMA-approved biosimilars and follow-on biologicals, respectively, their scope of use and respective approval years.

Global Market Scope and Accessibility of Biosimilars

Detailed information regarding growth drivers, patterns of growth, opportunities, and barriers to growth has helped inform and educate key market players, researchers, and health-care professionals on biosimilar development (Tsiftsoglou et al., 2013).

Global Biosimilars Market: Regional Outlook

The global biosimilars market is expected to reach US$10.90 billion by 2021 up from US$3.39 billion in 2016, at a Compound Annual Growth Rate (CAGR) of 26.3%. The majority of biosimilars have been registered and commercialized in Europe (Francois and Pascal, 2015). Moreover, Europe is expected to lead the global biosimilars market and account for a large share of the global economic market over the next few years. This high growth can be attributed to the presence of several biosimilar drugs including AccofilBemfola, Abasaglar, and Omnitrope and other new products in the pipeline (EMA, 2014). The EMA approved four additional biosimilars in 2016, including three biosimilars in two new product classes: a biosimilar of Amgen's Enbrel (etanercept) and two biosimilars of Sanofi's Clexane (enoxaparin sodium) (Royzman and Seigelr, 2018). Moreover, growing pressure to overcome increasing health-care costs, patent expiry, and increased incidence of chronic diseases, such as cancer, diabetes, and rheumatoid arthritis, has led to Europe being market leaders in biosimilar growth.

European dominance is followed by Asia, North America, and the Rest of the World (RoW) where the Asian market is projected to grow substantially over the next few years due to their developing economies and progressive growth rate in the future markets (Rumore et al., 2016). In contrast, however, strict regulatory policies in North America are predicted to lower growth in this region.

Key players in the biosimilars global market include Pfizer Inc. (US), Sandoz International GmbH (Germany), Teva Pharmaceuticals Industries Ltd. (Israel), Amgen Inc. (US), Biocon Ltd. (India), Dr. Reddy's Laboratories Ltd. (India), F. Hoffmann-La Roche Ltd. (Switzerland), Celltrion, Inc. (South Korea), and Samsung Bioepis (South Korea) ("Market Report for Biosimilars" www.marketsandmarkets.com).

Global Biosimilar Market Drivers to Accessing Biosimilar Medicines

One of the major market drivers for biosimilars is their low cost compared to their reference biologicals. In addition, the increasing incidence of chronic diseases is predicted to substantially push growth in the future. The increasing level of competition owing to the growing participation of key players in Biosimilar innovation and development, is predicted to encourage market growth in the coming years (Tsiftsoglou et al., 2013).

The global market scope of biosimilars is expected to increase substantially over the next few years, and the factors influencing this growth are the accessibility of new innovative technology, market competition, patent expiry, cost-effectiveness, and an increasing demand due to the prevalence of chronic diseases (Tsiftsoglou et al., 2013). Although biosimilar development is growing

Table 1 FDA-approved biosimilars and follow-on biologicals[a]

Product name	*Active substance*	*Therapeutic area*	*Approval year*	*Manufacturer/ company name*
Admelog[#]	Insulin lispro	Diabetes	2017	Sanofi
Amjevita (adalimumab-atto)	Adalimumab	Ankylosing spondylitis Crohn's disease Juvenile arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2016	Amgen
Basaglar[#]	Iinsulin glargine	Diabetes	2015	Eli Lilly/Boehringer Ingelheim
Cyltezo (adalimumab-adbm)	Adalimumab	Ankylosing spondylitis Crohn's disease Juvenile arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2017	Boehringer Ingelheim
Epoetin Hospira	Epoetin alfa	Anemia (chronic kidney disease, Zidovudine, chemotherapy) Reduction of allogeneic red blood cell transfusions	Recommended for approval by FDA's Oncologic Drugs Advisory Committee (ODAC) in 2017	Pfizer (Hospira)
Erelzi (etanercept-szzs)	Etanercept	Axial spondyloarthritis Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis	2016	Sandoz
Inflectra (infliximab-dyyb)	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2016	Pfizer (Hospira)
Ixifi (infliximab-qbtx)	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2017	Pfizer
Mvasi (bevacizumab-awwb)	bevacizumab	NSCLC Colorectal neoplasms Renal cell carcinoma Ovarian neoplasms Breast neoplasms	2017	Amgen/Allergan
Ogivri (trastuzumab-dkst)	Trastuzumab	HER2 breast cancer HER2 metastatic gastric or gastroesophageal junction adenocarcinoma	2017	Biocon/Mylan
Renflexis (infliximab-abda)	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2017	Samsung Bioepis
Zarxio (filgrastim-sndz)	Filgrastim	Autologous peripheral blood progenitor cell collection and therapy Bone marrow transplantation Cancer Myeloid leukemia Neutropenia	2015	Sandoz

NSCLC, Non-Small-Cell Lung Carcinoma.

http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-the-US

[a]Data collected on September 30, 2016, updated January 9, 2018.

Table 2 EMA-approved biosimilars[a]

Product name	*Active substance*	*Therapeutic area*	*Approval year*	*Manufacturer/Company name*
Abasaglar (previously Abasria)	Insulin glargine	Diabetes	2014	Eli Lilly/Boehringer Ingelheim
Abseamed	Epoetin alfa	Anemia Cancer Chronic kidney failure	2007	Medice Arzneimittel Pütter
Accofil	Filgrastim	Neutropenia	2014	Accord Healthcare
Amgevita	Adalimumab	Ankylosing spondylitis Crohn's disease Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	2017	Amgen
Benepali	Etanercept	Axial spondyloarthritis Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis	2016	Samsung Bioepis
Bemfola	Follitropin alfa	Anovulation (IVF)	2014	Finox Biotech
Binocrit	Epoetin alfa	Anemia Chronic kidney failure	2007	Sandoz
Blitzima	Rituximab	Non-Hodgkin lymphoma Chronic B-cell lymphocytic leukemia	2017	Celltrion
Cyltezo	Adalimumab	Crohn's disease Hidradenitis suppurativa Juvenile idiopathic arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Uveitis	2017	Boehringer Ingelheim
Epoetin alfa Hexal	Epoetin alfa	Anemia Cancer Chronic kidney failure		Hexal
Erelzi	Etanercept	Ankylosing spondylitis Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis	2017	Sandoz
Filgrastim Hexal	Filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	2009	Hexal
Flixabi	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2016	Samsung Bioepis
Grastofil	Filgrastim	Neutropenia	2013	Apotex
Imraldi	Adalimumab	Ankylosing spondylitis Arthritis Crohn's disease Hidradenitis suppurativa Psoriatic arthritis, Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	2017	Samsung Bioepis
Inflectra	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2013	Hospira

Table 2 EMA-approved biosimilars[a] (*cont.*)

Product name	*Active substance*	*Therapeutic area*	*Approval year*	*Manufacturer/Company name*
Inhixa	enoxaparin sodium	Venous thromboembolism	2016	Techdow Europe
Insulin lispro Sanofi	Insulin lispro	Diabetes mellitus	2017	Sanofi-Aventis
Lusduna	Insulin glargine	Diabetes	2017	Merck (MSD)
Movymia	Teriparatide	Osteoporosis	2017	Stada Arzneimittel
Mvasi	Bevacizumab	Breast neoplasms Fallopian tube neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Peritoneal neoplasms Renal cell carcinoma	2018	Amgen
Nivestim	Filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	2010	Hospira
Omnitrope	Somatropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome	2006	Sandoz
Ontruzant	Trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	2017	Samsung Bioepis
Ovaleap	Follitropin alfa	Anovulation (IVF)	2013	Teva Pharma
Ratiograstim	Filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	2008	Ratiopharm
Remsima	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	2013	Celltrion
Retacrit	Epoetin zeta	Anemia Autologous blood transfusion Cancer Chronic kidney failure	2007	Hospira
Ritemvia	Rituximab	Wegener granulomatosis Microscopic polyangiitis Non-Hodgkin Lymphoma	2017	Celltrion
Rituzena (previously Tuxella)	Rituximab	Wegener granulomatosis Microscopic polyangiitis Non-Hodgkin Lymphoma Chronic B-cell lymphocytic leukaemia	2017	Celltrion
Rixathon	Rituximab	Chronic B-cell lymphocytic leukemia Microscopic polyangiitis Non-Hodgkin Lymphoma Rheumatoid arthritis Wegener granulomatosis	2017	Sandoz
Riximyo	Rituximab	Chronic B-cell lymphocytic leukemia Microscopic polyangiitis Non-Hodgkin Lymphoma Rheumatoid arthritis Wegener granulomatosis	2017	Sandoz
Silapo	Epoetin zeta	Anemia Autologous blood transfusion Cancer Chronic kidney failure	2007	Stada Arzneimittel
Solymbic	Adalimumab	Ankylosing spondylitis Crohn's disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	2017	Amgen
Terrosa	Teriparatide	Osteoporosis	2017	Gedeon Richter

(*Continued*)

Table 2 EMA-approved biosimilars[a] (*cont.*)

Product name	*Active substance*	*Therapeutic area*	*Approval year*	*Manufacturer/Company name*
Tevagrastim	Filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	2008	Teva Generics
Thorinane	Enoxaparin sodium	Venous thromboembolism	2016	Pharmathen
Truxima	Rituximab	Chronic lymphocytic leukemia Granulomatosis with polyangiitis Microscopic polyangiitis Non-Hodgkin's lymphoma Rheumatoid arthritis	2017	Celltrion
Zarzio	Filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	2009	Sandoz

CHMP, Committee for Medicinal Products for Human Use; *VF*, *in vitro* fertilization.
http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europ
[a]Data collected on May 12, 2011, updated on February 2, 2018.
Source: EMA

globally, defining which countries are "all in" depends upon a number of criteria that define their respective efforts and progression. These include, conducting expensive and extensive preclinical studies, clinical trials accompanied by initial scale up and process optimization, product manufacturing capacity, approval of applications, number of approved products, whether biosimilars in a given country are manufactured there or imported, product revenue, extent of discounts on biosimilars relative to reference biological, and the extent of government and industry involvement and funding (Rader, 2017).

Another key factor driving the increase in biosimilar demand and production is the imminent patent expiry of currently administered biological drugs. This cluster of patent expiry termed as the "patent cliff," awaits top biologics in the global market and warrants development of new biosimilars (Ghia et al., 2015). Biosimilars seem like a lucrative option as with patent expiry, large pharmaceutical companies are seeing the end of holding exclusivity on biologic drug treatments losing billions in revenue. Moreover, global sales of biologics are rising at a rate of 5.5% per year paving way for other drug manufacturers to gain entry into the ever competitive global biosimilar market. The estimated expiration of patents for biologicals is highlighted in **Table 3**.

Another crucial driver for biosimilar research and development is global market competition. An example of the stiff competition in the biosimilar market can be observed with Humira (Adalimumab). Humira (Scheinfeld, 2003), used to treat rheumatoid and psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis supurativa, and juvenile idiopathic arthritis, is owned by AbbVie. From 2012 to its patent expiry in 2016, Humira was listed as one of the top selling pharmaceutical compounds and boasted $16 million in global sales (Philippidis, 2016). In 2014, India manufactured and brought its first Adalimumab biosimilar to market. Subsequently, another Indian drug manufacturer, Torrent Pharmaceuticals, has launched a second biosimilar ("Torrent launches world's second biosimilar of generic auto-immune drug", Business Standard, 11th January 2016 include full date of publication). Moreover, another pharmaceutical company, Amgen, similarly filed an application for their

Table 3 Estimated expiry year of the patents of biological products

Expiry year	*Patent products*	*Drug*	*Indication*
2013	Avonex	Interferon beta-1a	Cytokine used to treat multiple sclerosis
	Byetta	Glucagon-like peptide-1	Hormone used against diabetes mellitus
	Epogen	Epoetin alpha	Artificial protein to produce red blood cells
2014	Remicade	Infliximab	Monoclonal antibody to treat autoimmune diseases
	Novolog	Insulin aspart	Fast acting insulin used against diabetes mellitus
2015	Lantus	Insulin glargine	Artificial hormone used against diabetes mellitus
	Herceptin	Trastuzumab	Monoclonal antibody used against breast cancer
	Neulastra	Pegfilgrastim	Recombinant human granulocyte colony-stimulating factor that simulates white blood cells
	Synagis	Palivizumab	Monoclonal antibody used to prevent respiratory syncytial virus infection
2016	Humira	Adalimumab	Monoclonal antibody used to treat rheumatoid arthritis
	Aranesp	Drabepoetin alfa	Synthetic erythropoietin used to treat anemia
	Enbrel	Etanercept	Protein used to target tumor necrosis factor
	Rituxan	Rituximab	Monoclonal antibody used to treat leukemia and lymphoma
2017	Avastin	Bevacizumab	Monoclonal antibody that is an angiogenesis inhibitor
	Pegasys	Pegylated interferon alfa-2a	Proteins used to treat viral infections including hepatitis C and HIV

own version of the drug and is in the process of fighting two of AbbVie's patents. If successful, Amgen will own a significant portion of the US biosimilar market.

Similarly, in Europe, Etanercept (trade name Enbrel), a biopharmaceutical that treats autoimmune diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis and psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis, by acting as a tumor necrosis factor (TNF) inhibitor, reaches its patent expiry in 2016, opening the market to biosimilar competitors. In January 2015, Samsung and Biogen's joint venture "Samsung Bioepis" successfully submitted Benepali, a biosimilar version of the drug, for review to the European Medicines Agency (EMA). It was approved in 2016, opening the door to further competition.

Another important factor pushing the development and distribution of new biosimilars is their low cost compared to the comparator biologic. In the EU, the average cost savings from opting to use a biosimilar versus a branded drug is roughly 35%, as compared to the Federal Trade Commission's projected 10%–30% discount in the US market. It is relatively easier to bring new biosimilars to market in Europe compared to the United States, as the FDA has a set of processes in place to determine interchangeability on any given biosimilar. The EMA recently updated their guidelines so substitution policies are done on a country-by-country basis. Once such approval processes have been revised and implemented, the increased competition could result in further discounts.

A report by Bloomberg Intelligence highlighted that biosimilars pose a threat to over US$190 billion in global pharmaceutical sales over the next decade, where companies such as Amgen, Merck, Samsung Bioepis, and Novartis could have their own follow-on biologics for drugs such as Humira, Enbrel, and Remicade. The success of biosimilars could thus influence the sustainability of the pharmaceutical industry in the next decade. The major competitors will be the big pharmaceutical companies that are interested in increasing their profit through high prices; therefore, discounted prices of biosimilars compared to originators are likely to be less than desirable (Pasina et al., 2016).

Economic Implications of Biosimilars

Cost-efficacy studies are crucial to compare the costs and outcomes of a biosimilar with those of a relevant comparator. These economic evaluations help guide the introduction of safe and cost-effective medicines (Drummond et al., 2005) and are used by scientists and industry to set up future biosimilar research and development plans. This methodology of evidence-based decision-making in health care is an effective tool as it fits within the criteria of cost-effectiveness.

In the United States, health-care spending is increasing largely due to the high cost of biological medicines. Biological medicines are the standard care for several debilitating chronic diseases such as cancer, diabetes, multiple sclerosis, and rheumatoid arthritis (Khraishi et al., 2016). While their significance in treating these diseases continues to increase, accessibility to these sometimes lifesaving medicines is denied because health systems cannot manage their high cost. In this context, biosimilars would play an important role in improving access and affordability of medicines (Singh and Bagnato, 2015).

Biological medicines are the most rapidly growing segment of health care in the United States constituting more than US $100 billion in annual spending and expected to exceed US$250 billion by 2019 (Biosimilars Council, 2017). However, as these drugs lose their patents, biosimilar medicines will grow rapidly and provide significant savings in health care. Increased market competition from biosimilars can help lower the cost of expensive drugs. Research has shown that 60% of Americans would be receptive to accepting a biosimilar drug if it would be cheaper (Moriarty, 2018). The US can, therefore, really benefit from biosimilars.

One of the biggest advantages of biosimilars in comparison to their reference medicines is their low market price and subsequent low cost for the health-care system. The low cost of biosimilars is partly due to a tailored development program that avoids repetitive nonclinical and clinical studies, which have already been carried out on reference medicines and also due to market competition (Rader, 2017).

Several stakeholders can benefit from the advent of new biosimilars, such as, patients, hospitals and care facilities, taxpayers, employers, insurers, and state and federal governments. Equitable and improved access to more affordable biosimilar medicines will, in turn, improve patient quality of life and reduce financial pressures on regional, national, and global levels (IMS Health, 2016). Increasing access to biosimilars will also help drive down the cost of originator brand biologics and allow access to biosimilar medications of proven efficacy for many patients who are unable to access the high-priced brand biologics for their treatment. For example, many rheumatoid arthritis patients in countries such as Japan, the United States, and the Europe do not have access to medicines for their treatment (NCBI Resources, "Biologic Monotherapy in the Treatment of Rheumatoid Arthritis," 2015). However, in countries where biosimilar alternatives have been introduced, patient access has increased by 100% due to their lower cost (IMS Health, 2016).

The "high out-of-pocket" treatment cost for patients is acknowledged as a barrier to the use of biologics in the neoadjuvant or adjuvant interventional therapies. Moreover, issues related to treatment costs, drug funding, and reimbursement have led to a significant impact on the management of cancer, quality of life, and long-term survival rates. Out-of-pocket expenses to patients have contributed to personal financial distress and/or a lack of realistic access of treatment options, thereby increasing the demand for low cost but equally effective alternatives (Cherny et al., 2016). Access to the market for biosimilars for diseases, such as cancer, diabetes, and rheumatoid arthritis, would also be economically beneficial as it is believed that biosimilars would be around 10%–40% less expensive than their reference biological products, which would be sufficient ground for adoption of biosimilars in hospital settings as replacement therapy for specific biological reference products (Rumore et al., 2016).

Table 4 Biological reference products with market price reduced as a result of biosimilar products

Biologics innovators	*Price reduction (%)*	*Country*
Erythropoietin	33	Germany
Infliximab	70	Norway

Biosimilars have also been reported to positively influence the reduction in market price of some biological reference products (Table 4) as competition among biosimilars and reference biologics drives down the market price of innovator biologics leading to improved patient access.

The Biologics Price Competition and Innovation Act, which is included in the Patient Protection and Affordable Care Act, creates an approval pathway for biosimilar and interchangeable biological products and is also responsible for providing affordable access to biological products and biosimilars (Rumore et al., 2016). Price control regulations of biosimilars help monitor biosimilar costs, increasing their affordability, and patient access. An independent analysis in 2014 predicted that the availability of biosimilars would result in a US$44.2 billion reduction in biologic spending between 2014 and 2024, or approximately 4% of total biologic spending over the period (Surya and Karen, 2015).

Access to Biosimilars in the EU vs US

It is important to note that there are significant differences between availability and hence access to biosimilars between Europe and the United States. Biosimilars have been widely used across Europe and are being approved by the EMA to ease their market access, which in turn leads to cost savings in pharmacotherapy related to biologics (Remuzat et al., 2017).

In the first 9 years since the passage of the BPCIA (2009) in [2009] in the US, the FDA approved 11 biosimilars (five of which were approved in 2017), with 60+ more in the pipeline, compared to approximately 35 biosimilars approved in the EU [over the same time period] (Biosimilars Council, 2017). Moreover, patient use of biosimilars in the EU has shown no difference in health outcomes to their originator biologicals for treatment indicating a similar profile of safety, quality, and efficacy in their administration. By 2020, the expected cumulative savings for biosimilars are expected to range from Euros 11.8 to 33.4 billion, which is equivalent of savings of 5.2%–14.6% of the estimated expenditures in 8 European countries. The majority of these savings will be observed in France, Germany, and the United Kingdom, while the lowest will be observed in Sweden due to the country's regulatory procedures for biosimilar approval (Haustein, 2012). It is important to note that considerable differences are and will be observed between the overall savings in different countries and between different classes of drugs.

Although there are several similarities between approval and regulatory processes in the United States and the EU, there is no EU-wide legislation for "interchangeable" biologics in Europe, and each biosimilar medicine is evaluated on a case-by-case basis. Equitable access to biosimilars in the EU and the United States is crucial to reduce global health inequalities and improve health outcomes and economies in the health-care sector (Hirsch and Lyman, 2014). Global biosimilar acceptance and availability will ensure a sustained supply of important, lifesaving medications for patients once biologicals have reached their patent expiry dates.

The WHO Prequalification of Medicines Program ensures that medicines purchased by international procurement agencies (e.g., UNICEF) for the purpose of distribution in low-income countries meet acceptable standards of quality, safety, and efficacy. The Lancet Commission on Essential Medicines recommends that the prequalification program should expand the range of essential medicines, including biosimilars. The incentive for governments to embrace biosimilars is to reduce health care economic burden, which in turn should increase access and improve population health-care outcomes (Lancet, 2017). WHO prequalification will hopefully increase competition in the biosimilar market to further reduce costs and increase access to these medicines in low-income countries (Babar, 2018).

Barriers to Access to Biosimilars

Over the past decade, the subject of biosimilar access and affordability has become increasingly significant. Different regulatory and evolutionary pathways play a pivotal role in determining the uptake of biosimilars in the global market. The role of biosimilars in providing access to more affordable medications and increasing competition has come into greater focus. Despite their evolution and growth in the global market, the development of biosimilars continues to be an expensive and time-consuming process, as they need to meet several stringent technical, manufacturing, and analytical challenges. In addition to this, biosimilars also face several regulatory, clinical, and commercialization challenges (Bui et al., 2015; Rathore, 2009). Biosimilar developers will need to continuously adapt to the regulatory criteria that will continue to evolve as biosimilars increase their market share. Thus, there are concerns and doubts regarding the ability of biosimilars to be commercially successful, especially in developed countries where

biosimilars must go through stringent and evolving regulatory processes (Konara et al., 2016). To this end, there are several barriers to access to biosimilars in the ever competitive global market. Pending expiry dates of patents for originator biologicals between 2012 and 2019, coupled with intellectual property rights, opens opportunities for biosimilars to compete in the market, but there are ***barriers*** to their access in health care.

High Expenditure for Development of Biosimilars

Although biosimilars are considered to be low-cost substitutions for pricy biologics, they must comply with the same quality, safety, and efficacy as their reference biologics. Manufacturing of biosimilars, therefore, requires complicated procedures compared to their small molecule reference compounds involving creating structures similar to the reference molecule. This is turn leads to several challenges for manufacturers who have to deal with failure rates and operational costs. Small molecule generics are synthesized using the same Active Pharmaceutical Ingredient (API) as originator molecules and are therefore chemically identical to these molecules and their manufacture involves only one-fifth of in-process tests to meet Good Manufacturing Practice compared to a biological which requires 50–250 tests comprising of complex quality assessment and stringent environmental control (Bui et al., 2015; Surya and Karen, 2015). Minor changes in manufacturing procedure may lead to significant variations of the cellular systems used for biologic production, and may affect stability, and biology of the end product. Manufacturing large molecule biosimilars is, therefore, a complex and expensive process where the end product must be similar to the original molecule in terms of its structure, mechanism of action, and biological activity (EMA, 2017). Furthermore, drug regulatory authorities require that there should be no clinically significant difference between the biosimilar and the reference drug in terms of safety and potency which again warrants the development of validated analytical studies to demonstrate biosimilarity. The development of biosimilars also involves expensive clinical studies that are conducted by using the relevant study populations and endpoints to demonstrate similarity between the proposed biosimilar and originator products in terms of their safety, immunogenicity, and efficacy profiles (CHMP, 2014; FDA, 2015b; WHO, 2009). It must be noted, however, that with standardizing the manufacturing process and the technology required, production costs have been significantly reduced.

It is important to note that before establishment of stringent guidelines and policies by the EMA, several copies of biologicals were sold in unregulated markets. To this end, products in lesser and unregulated international markets are generally classified as "biogenerics." Such products are generally not manufactured in compliance with Good Manufacturing Practice (GMP) standards and lack detailed analytical studies and comparative clinical trials. Now, however, these markets are targeting regulatory processes, procedures, and adopting strategies to comply with the guidelines of regulated markets.

Regulatory Pathways, Legislation of Biosimilars, and Entry to Market

Although the European market accounts for 80% of global spending on biosimilars, access across Europe varies greatly due to different national and local guidelines, funding, and approaches to health-care management Generics and Biosimilars Initiative (GaBI Online, 2017). Data collated from 46 European countries [2017] showed discrepancies in access to biologicals where 22% were not reimbursed for a biological for rheumatoid arthritis (GaBI Online, 2017), thus creating severe restrictions to their access. Non-EU states tend to have stricter eligibility criteria for access to biologicals leading to further barriers to equitable access. EU prescribing practices and regulatory pathways thus needs to be revised and standardized to ensure harmonious treatment strategies across the EU.

Similarly, in the United States, despite advances in biosimilar research and development, regulatory processes have not kept up with this increased development. This has been further complicated as a result of litigation between drug companies leading to a knock on effect on lowering market competition and hence biosimilar pricing. As in the EU, a clearer more cohesive regulatory pathway to FDA approval is required to improve access to biosimilars in the United States.

Requirement for Distinguishing Nomenclature for Generic and Originator Brands

Specific nomenclature is required to distinguish biosimilars from their originator reference compounds and from each other to ensure accurate prescribing and avoid confusion (Dörner and Kay, 2015). To achieve this goal, it would be more appropriate to use the brand name, the International Nonproprietary Names (INNs) plus the brand name, or some other unique identifier (Corrado et al., 2017). Alternatively, WHO has proposed a 4-digit code for a biologic qualifier that could be used to distinguish originators from biosimilars (WHO, 2012).

The European Commission issued the Directive 2012/52/EU, which requires the use of brand names "to ensure clear identification of biological medicinal products (EC, 2012)," a requirement that also applies to biosimilars. In addition, the batch number is required to be notified to the respective regulatory authority to ensure proper traceability because there is a risk of product drift (unintentional changes during manufacturing of biosimilars from the original product or previous batch of biosimilar). The US FDA regulations have created confusion regarding nomenclature for biosimilars (Rumore et al., 2016). According to these regulations nonproprietary (generic) names of biosimilars should contain a unique suffix identifier (e.g., filgrastim-sndz). This may cause confusion among prescribers, pharmacists, and patients and may also result in patent litigation that adversely influences the delay in biosimilars entering the US market (e.g., filgrastim-sndz vs. filgrastim) (Rumore et al., 2016).

The International Non-proprietary Name (INN) is the official generic name given to a pharmaceutical's active ingredient by the World Health Organization. Thus, irrespective of country, products with the same active ingredients share the same INN. This system also applies to biosimilars approved in the EU and elsewhere. Consistencies in scientific properties, efficacy, and patient safety to the reference compounds necessitate biosimilars possessing the same INN as the original drug. Moreover, WHO INN experts believe this INN system should not be altered as different INNs for biosimilars would disregard important scientific knowledge and safety information for health-care professionals who prescribe the medications. INNs assigned to biosimilars already used and circulated in the EU, Japan, and other strictly regulated markets match those of their respective reference compounds. With a different INN, a prescriber would legitimately conclude that the active ingredients in the biosimilar are different to the original reference compound—this in turn would cause confusion in terms of drug dosage, formulation, and package size. In addition to this, different INNs for two highly similar products with the same chemical properties, patient safety profiles, and efficacy would result in unnecessary burden on physicians and pharmacists when making important treatment decisions (WHO, 2012).

Biobetters and Next-Generation Biologics

Although biosimilars have been a success story since their approval in 2006, they face competition from "biobetters." The performance of biosimilars has also been affected by the fact that competition is limited to the first-generation reference products. The term "biobetter" refers to a recombinant protein drug that is in the same class as an existing biopharmaceutical but is not identical, and it is an improved version of the original and produces its effects on the target for a longer period of time. Biobetters build on the success of existing, approved biologics but are considered less of a commercial risk than developing a brand new class of biologics. Moreover, biobetters are being developed using protein or glyco-engineering, which reduces the risk of immunogenicity, makes the drug safer and more effective, and requires lower dosing (Dolinar and Reilly, 2014). Being new drugs, biobetters will possess 12 years of market protection in the United States and have lower research and development costs. Companies interested in the development of biobetter drugs are Novo Nordisk, Merck & Co, Roche Group, Biogen Idec, Amgen, Sanofi-Aventis, Eli Lilly, and GlaxoSmithKline.

The market entry of biobetters and next-generation biologics is thus an important consideration in evaluating the impact of biosimilars and their potential savings for the health-care system. This difference between the biosimilars and biobetters has a significant regulatory impact because unlike biosimilars, biobetters will be registered as innovator drugs. Similarly next-generation biologics have alterations in their molecules to improve their immune function, half-life, or capability of triggering other mechanisms of action (Beck, 2011). If biosimilars gain a substantial share of sales from their referenced products (of a previous generation), their share of overall patient treatments may be limited if physicians and patients prefer biobetters or the next generation of biological products (Grabowski et al., 2014).

Prescriber and Patient Concern's

Uhlig and Goll (2017) reviewed evidence from the administration of biosimilars and concluded that, for biosimilars to be used more widely, both prescribers and patients needed to have more confidence in their benefits and characteristics (Uhlig and Goll, 2017). Their statistical survey carried out via the European Crohn's and Colitis Organization (ECCO) indicated a high level of awareness of biosimilar attributes and warranted support for switching from infliximab to its biosimilar. The authors, however, also highlighted that in order for biosimilars to be adopted widely, both prescribers and patients need to be fully aware of their benefits and attributes. In total, 61% of responders highlighted their lack of confidence in using biosimilars due to a lack of awareness and education in their use (Uhlig and Goll, 2017). Moreover, a recent survey carried out in the United States and Europe highlighted that 47% of respondents thought the agents were sufficiently safe and effective to prescribe, whereas 43% said they required more information on biosimilars (Uhlig and Goll, 2017).

Patients also show concerns with regard to the fact that the low cost of biosimilars compared to their originator counterparts may bias prescribers and health insurers in prescribing them without patient consent and objectively assessing quality. The UK National Rheumatoid Arthritis Society has welcomed the entry of biosimilars into the market but has also highlighted the importance of prescribing biosimilars on the basis of their clinical attributes and not merely as cost-saving alternatives (Corrado et al., 2017).

There is a definite need for health-care professionals to have comprehensive and objective information on the key characteristics of biosimilars before their introduction into clinical practice. Limited literature is available on the opinions of health-care professionals with regard to biosimilars and their use, including US their biosimilarity, interchangeability, risk management, and switchability. Pharmacists and other health-care professionals must, therefore, remain vigilant and ensure they gain regular, continued knowledge and awareness of biosimilars to provide safe and optimal use of biologic products and biosimilars in their clinical practice (Adé et al., 2017). Moreover, a clear specific nomenclature and full transparency of labelling may be helpful in increasing the confidence of both physicians and patients. Health-care professionals and patients can truly benefit from widening their understanding of biosimilars by keeping up with evidence-based informative research that is being carried out on emerging biosimilars (Adé et al., 2017; Rumore et al., 2016). Patients also need to receive clear, concise, and informative information on biosimilars from their health-care professionals to feel included, engaged, and informed about the choices and options available to them.

Patent Litigation Barriers to Patient Access

Another important factor affecting biosimilar entry into the global market is a complex and multistep process called the biosimilar "patent dance." Along with creating the approval pathway for biosimilars, the Biologics Price Competition and Innovation Act (BPCIA) also created a mechanism by which patent disputes between brand companies can be resolved. Original biologic manufacturers have been using the patent dance litigation to keep competition from biosimilar manufacturers at bay. The "litigation backlog" created by brand companies, however, has resulted in the FDA approving only six biosimilars for use in the United States with only three marketed to patients (Chemistry World, "Biosimilars Battleground," May 15, 2017). In June 2017, the Supreme Court issued a unanimous ruling that under Federal law, biosimilar applicants can opt out of this patent dance giving them more control to choose how and when to resolve patent disputes with a brand company (Supreme Court of the United States, "SANDOZ INC. v. AMGEN INC", 2017)

Conclusion

Although biosimilars are effective alternatives to their reference medicines, there are still several challenges to access and use by health-care professionals. Equitable access to biosimilars in the global market is crucial to reduce global health inequalities and improve health outcomes and the economy in the health-care sector. Moreover, pharmacists, physicians, and patients should be knowledgeable about the specifics and issues associated with the administration of biosimilars as they are key players in the implementation of biosimilars in the global market. Biosimilars also face competition from next-generation biologicals and biobetters as they offer an improved version of existing originators and are considered less of a commercial risk than developing a new brand of biologic. It, therefore, remains to be seen how competition will evolve for the more complex biological products with patent expirations as well as biosimilars and biobetters on the horizon in the European and US markets.

In conclusion, based on clinical evidence and scientific studies, although biosimilars provide an attractive cost-effective option to the global market, more steps need to be taken to ensure health-care professionals are knowledgeable and confident in prescribing biosimilar drugs. Additionally, steps need to be taken to ensure a globally uniform regulatory and approval process so that access is equitable and timely.

Glossary

Biological A product derived from a living organism (from animal products or other biological sources) that is used in the diagnosis, prevention, or treatment of diseases. Examples of biological medicines include recombinant proteins, allergy shots, vaccines, and hematopoietic growth factors.
Biosimilarity Demonstration of high similarity to a reference biological medicine in terms of chemical structure, biological activity and efficacy, safety and immunogenicity profile, mainly based on comprehensive comparability studies.
Biotechnology Technology that relies on biological systems, living organisms, or components from living organisms (such as genes or enzymes) to make a specific product. A medicine obtained by biotechnology often has been produced by inserting a gene into cells so that they can produce the desired protein.
Clinical study or trial Study with the objective of determining how a (new) medicine is handled by, and affects, humans. Clinical studies or trials are conducted in healthy volunteers or in patients. Clinical studies routinely involve the use of a control group of patients that is given an inactive substance (placebo) that looks like the test product. Pivotal clinical studies involving a larger group of patients provide evidence on whether the medicine can be considered both safe and effective in a real clinical setting.
Comparability Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function. This scientific principle is routinely used when a change is introduced to the manufacturing process of medicines made by biotechnology, to ensure that the change does not alter safety and efficacy.
Compound annual growth rate (CAGR) The compound annual growth rate (CAGR) is the year-over-year growth rate of an investment over a specified period of time.
EMA (European Medicines Agency) The European Medicines Agency. EMA is responsible for evaluating marketing applications for medicinal products to be approved in the European Union.
Extrapolation Extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication approved for the reference medicine.
Generics A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. A generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the brand name product.
INN International nonproprietary name, a unique name that identifies active substances. The list of INNs, which is globally recognized and public property, is maintained by WHO.

Interchangeability Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.
Originator medicinal product A medicine that has been developed and produced by an originator company and that has been approved by the national regulatory authorities or the European Commission on the basis of a full registration dossier.
Patent A patent is a legal mechanism granted by a State (national government), which allows the discoverer of a medicine the exclusive right to make and sell the product for a set period of time to recover the development costs, in exchange for public disclosure of their invention. Typically, however, a patent application must include one or more claims defining the invention, which must be new, nonobvious, and useful or industrially applicable.
Reference medicine A biological medicine approved in the EU, which is chosen by a company developing a biosimilar as a reference for the head-to-head comparison of quality, safety, and efficacy.
Specifications Acceptance limits for important quality standards, which an active substance or a finished medicine must meet.
US Food and Drug administration (FDA) The federal agency responsible for evaluating marketing applications and/or otherwise regulating the US marketing of medicinal products, medical devices, food, and cosmetics to be approved in the United States. This agency is responsible for approving all medicines before they are made available to doctors and patients in the United States.
Vaccine A biological preparation that is used to establish or improve immunity to a particular disease.

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High-Cost Medicines: Access, Affordability, and Prices

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Introduction to the Concept of High-Cost Medicines

The concept of "high-cost medicine" has gained popularity in recent years. In general, the definition includes mostly new, specialized medicines for complex conditions such as cancers and inflammatory autoimmune diseases (Lu et al., 2008). These medicines include, but are not limited to, biological agents; they selectively target specific molecular sites and therefore are effective (Rader, 2008). In addition, some high-cost medicines are designed to treat rare diseases that affect only a handful of people; they are more commonly termed as orphan drugs. Access to high-cost medicines, regardless of public or private healthcare systems, is gaining attention (de Leon, 1989; Lu et al., 2004). By definition, high-cost medicines are much more expensive than conventional medicines, and therefore have limited patient access in most cases (Mayor, 2010). This in fact may negatively affect patient outcomes (Wong et al., 2010). The World Health Organization (WHO) Regional Office for Europe has defined a medicine as "high-cost" if the therapy for one patient exceeds €10,000 per year to be reimbursed by a public payer (World Health Organization, 2015).

Access to High-Cost Medicines in the European Region

Geographically, Europe is often divided into regions including Central Europe, Eastern Europe, Northern Europe, Southern Europe, and Western Europe. Although access to medicines at affordable prices is one of the key aims of the European Health Policy, it is far from being achieved, especially in the context where there are many life-saving high-cost medicines being introduced into the market (Zaprutko et al., 2017).

Access to High-Cost Disease-Modifying Therapies

Rheumatoid arthritis (RA) is one condition where the introduction of high-cost biologic disease-modifying antirheumatic drug (DMARDs) for the treatment of the disease has improved the control of the disease activity tremendously. According to clinical practice guidelines by the European League Against Rheumatism (EULAR), biologic DMARDs should be initiated in patients who are intolerant of or nonresponsive to conventional DMARDs, in the presence of adverse prognostic factors such as early joint damage (Smolen et al., 2014). Nonetheless, owing to high direct costs of biologic DMARDs in the context of limited healthcare budgets, patient access to reimbursed biologic DMARDs varies across the European region.

Kaló et al. (2017) examined the RA patient population having access to reimbursed biologic DMARDs according to European League Against Rheumatism (EULAR) criteria and national reimbursement criteria in 39 European countries (Kaló et al., 2017). By referring to published RA epidemiological data, they developed a population model to estimate the population size of the RA patient eligible for biologic DMARD treatment. This is according to clinical criteria defined in 2013 EULAR recommendations and national reimbursement criteria defined in a study of the 39 European countries. A composite eligibility score ranging from 1 to 5 was assigned to each country, with a higher score indicating less restrictive access to biologic DMARDs based on national reimbursement criteria and was subsequently categorized into low-access, moderate-access, and high-access clusters. In line with the developed model, 32% of RA patients in the European region were eligible for treatment with biologic DMARDs according to clinical criteria defined in 2013 EULAR recommendations. There were 86%, 68%, and 13% of the EULAR-defined patient populations eligible for biological DMARD treatment according to national reimbursement criteria in high-access, moderate-access, and low-access clusters. Only 59% of the EULAR-defined patient, on average, was eligible for biologic DMARD treatment. The findings highlighted that access to reimbursed biologic DMARDs varies across the European region, with RA patients in the majority of European countries having moderate access to the biologic agents (Putrik et al., 2014b; Smolen et al., 2014).

High priced biologic medicines have transformed the treatment of Crohn's disease (CD). Evidence from clinical trials has demonstrated the efficacy of biological drugs for the treatment of CD. The drugs such as infliximab, adalimumab, vedolizumab, and ustekinumab substantially improve disease remission rate, slow disease progression, and increase work participation and improve quality of life (Gulácsi, 2014). Since biologic drugs are more expensive than standard treatment, most countries have regulated the access to reimbursed biologic drug treatment (Péntek et al., 2017). Péntek et al. (2017) investigated access to biologic agents for the treatment of CD among 10 European countries (Czech Republic, France, Germany, Hungary, Latvia, Poland, Romania, Slovakia, Spain, and Sweden) (Péntek et al., 2017). The authors found that infliximab and adalimumab were reimbursed in all 10 countries, while vedolizumab was reimbursed in only five countries (France, Germany, Latvia, Slovakia, and Sweden). The availability score, which was developed by the researchers to examine the restrictiveness of clinical eligibility and administrative requirements to access biologics among patients with CD, was highest in Hungary, Poland, and Slovakia (most restrictive), but lowest in Germany and Sweden (least restrictive). Treatment with biologic drugs was most affordable in Sweden (26% of the gross domestic product per capita on average) and least affordable in the Eastern European countries such as Hungary (106% of the gross domestic product per capita on average) and Romania (198% of the gross domestic product per capita on average). Important barriers to access to the biologics cited by the gastroenterologists included limited availability and physicians' preferences. The observed inequalities in access to biologic drugs could be partly explained by differences in gross domestic product per capita in which the number of patients with CD on biologics per 100,000 population was positively correlated (0.91) with gross domestic product per capita (Péntek et al., 2017).

Access to High-Cost Anticancer Medicines

The list of high-cost anticancer drugs is growing, as are the challenges in providing equitable access to them for countries within European region. Patient access to 30 innovative anticancer drugs with the highest sales value among 13 European countries was analyzed in a 2015 report and presented in three perspectives.

These three perspectives include expenditure on innovative anticancer drugs, availability of innovative cancer drugs through reimbursement systems, and the waiting time for patients to gain access to the cancer drugs upon marketing approval (Poland, 2015). The highest and lowest expenditure on the 30 innovative anticancer drugs was recorded in Switzerland and Poland, respectively, in which the expenditure amounted to 94% and 24%, respectively, of the mean expenditure for the 13 investigated European countries. The expenditure incurred on innovative anticancer drugs was higher in highly developed European countries (Austria, France, Germany, Italy, Spain, Switzerland, the Netherlands, and the United Kingdom) than the other European countries (Hungary, Poland, Romania, Slovakia, and the Czech Republic), where the mean expenditure incurred in these highly developed countries was 15% higher than the mean expenditure incurred for all investigated European countries. The mean expenditure of the five countries (Hungary, Poland, Romania, Slovakia, and the Czech Republic) accounted for only 38% of expenditure for all other European countries.

Highest availability of anticancer drugs through the reimbursement system without restrictions was noted in the Netherlands (30), followed by Italy (26), and Switzerland (25). The country with the least availability of cancer drugs through the reimbursement system without restriction was Poland (2). In terms of the time elapsed (in quarters) until patients gain access to the included innovative anticancer drugs upon marketing approval, analysis was performed in two measures, namely, the mean time to the first sale and the mean time to achieve significant utilization level. The mean time to the first sale was the shortest in Switzerland (mean: 0.3 quarter after authorization by European Medicines Agency), followed by Germany (0.6), and the United Kingdom (0.6) (Poland, 2015).

Access to High-Cost Orphan Medicines

Alone marketing approval for certain pharmaceuticals does not ensure patient access, but there are some other factors which influence too and which include price, co-payments, and reimbursement policies. This is especially true for orphan drugs, in which usual cost-utility threshold values may not be applied during reimbursement decisions due to ethical considerations surrounding

the use of orphan drugs. Blankart et al. (2011) examined patient access to orphan drugs for the treatment of four rare diseases (pulmonary arterial hypertension, Fabry disease, hereditary angioedema, and chronic myeloid leukemia) in eight European countries (England, France, Germany, Hungary, Poland, Slovakia, Switzerland, and the Netherlands) (Blankart et al., 2011). Three indicators, the outcomes of technology appraisals, the extent of coverage provided by healthcare payers, and the price of the orphan drugs in each country, were used to determine the extent of patient access to these drugs. The authors noted that healthcare payers in five countries (France, Hungary, Poland, Slovakia, and the Netherlands) had issued recommendations for almost all orphan drugs included in the study, while only one drug (imatinib for the treatment of chronic myeloid leukemia) was appraised by the National Institute for Health and Care Excellence (NICE) in England. Germany had not assessed any of the included orphan drugs. Data were not available for Switzerland since Eidgenössische Arzneimittel Kommission (Federal Drug Commission) in the country did not publish its recommendations.

Every orphan drugs included in the study that had been appraised gained positive recommendations in the countries where they were analyzed. Exception was the agalsidase beta for the treatment of Fabry disease in Poland. The majority of the orphan drugs included in the study were being reimbursed in the countries analyzed, with slight variation in the extent of reimbursement owing to differences in co-payment regulations. It is worth noting that all of the orphan drugs included in this study were covered in Switzerland.

In Poland, for covered orphan drugs, no co-payment was needed from the patients. There were large differences in the prices of orphan drugs among the countries analyzed. When the prices were converted into USD, it was observed that Germany paid the most for the included orphan drugs. When the prices were adjusted for relative purchasing power parity, it was observed that the prices for the studied orphan drugs were highest in Slovakia and Poland. Although there were variations to patient access to orphan drugs among European countries, almost all studied orphan drugs were accessible to the patients in these countries (Blankart et al., 2011).

Access to High-Cost Medicines in the Asia-Pacific Region

Accessibility of high-cost medicines poses a major problem to the Asia-Pacific region, which comprises many low- and middle-income countries. Also, there are challenges related to low healthcare budgets and absence or minimal coverage of high-cost medicines under public health insurance schemes in this region (Mandal and Mandal, 2017). The prices of anticancer medicines are highly variable in the South-East Asian, Western Pacific, and Eastern Mediterranean regions (Salmasi et al., 2017).

Access to High-Cost Disease-Modifying Therapies in New Zealand and Malaysia

Increased understanding of the immune pathogenesis of RA has led to the introduction of biologic DMARDs. While the side-effect profile of biologic DMARDs restricted their use only for patients intolerant of or nonresponding to traditional DMARDs, recent findings suggest using these drugs as early as possible in the course of RA to avoid disabilities. However, the widespread use of biologic DMARDs is still limited due to their high-costs.

A study investigated patients' access to four biologic DMARDs (three tumor necrosis factor inhibitors and rituximab) in New Zealand, with comparisons performed between New Zealand and Australia as well as between New Zealand and 13 European countries (Kobelt et al., 2010). Patient access to biologic DMARDs was examined by estimating the proportion of patients treated with biologic DMARDs and the mean annual sales of biologic DMARDs per RA patient. The prevalence of RA was first used to estimate the proportion of patients treated in each of the included countries, to subsequently estimate the mean annual sales per RA patient (Kobelt et al., 2010). The study utilized two prevalence estimates to serve as sensitivity comparators: one estimate was an average of the Nordic region and the United Kingdom (upper prevalence estimate), while the other estimate was based on an average including all remaining European countries (lower prevalence estimate). The results of the analysis demonstrated very low utilization of biologic DMARDs for treatment of RA in New Zealand, where the estimated proportion of patients treated with biological DMARDs was the lowest when compared to the 13 European countries and Australia, in both upper and lower prevalence estimates. This was reflected in the mean annual sales per RA patient, where the figures were also trailing behind those of 13 European countries and Australia (Kobelt et al., 2010).

Like many middle-income countries, health systems in Malaysia operate on a multi-payer system, which includes public and private healthcare payers as well as out-of-pocket payment from individual patients. Due to over dependence on out-of-pocket spending, medicines are sometimes unaffordable. This is particularly true for patients who require long-term use of high priced disease-modifying therapy (DMT) for the management of chronic diseases such as multiple sclerosis (MS), where they frequently meet difficulties in obtaining continued access to these medicines (Kishore et al., 2015). Some of the first- and second-line disease-modifying therapies, which are commonly prescribed cost around MYR3200 to MYR6000 (USD695 to USD1390) per month, which exceeds the national mean monthly salary of about MYR2312 (USD522) (Vijayasingham et al., 2017). The situation is complicated by the fact that MS is considered one of the critical medical conditions by private health insurance providers in Malaysia. This restricts eligibility of patients to apply for new health insurance policies (Vijayasingham et al., 2017).

Vijayasingham et al. (2017) present case experiences of working individuals with MS in navigating access to high-cost DMTs through various public and private health care payers in Malaysia. All participants included had relatively high socioeconomic status were white-collar workers and the majority of them had received tertiary-level education. However, each of them

encountered challenges to sustainably finance continued access to DMTs. One patient, who gained access to DMT through the public healthcare system initially after having his or her socioeconomic background, thoroughly vetted only to be denied access later because of a salary increment. Furthermore, a patient had been forced to resign from his job after seeking reimbursement on DMTs from his employer. These experiences illustrate the challenges for Malaysia in the provision of access to high-cost medicines.

Access to High-Cost Anticancer Medicines in Australia

Anticancer drugs are often expensive, especially those that are newly developed, which contribute to the growing cost of cancer care. In Australia, patient access to expensive drugs often depends on listing of the drugs on the Pharmaceutical Benefits Scheme (PBS) for reimbursement. Nevertheless, to be eligible for listing, drugs must have favorable cost-effectiveness assessment, and this is not forthcoming for every new anticancer drug. It would pose many difficulties for patients to access new anticancer drugs that are not listed on the PBS (Karikios et al., 2014). Wilson and Cohen examined patients' access to newer anticancer drugs approved by the United States Food and Drug Administration (USFDA) between 2000 and 2009 among publicly insured beneficiaries in Australia (Wilson and Cohen, 2011). Three subdimensions of patient access were analyzed, namely market availability, insurer coverage and conditions of reimbursement, and patient out-of-pocket costs (Wilson and Cohen, 2011).

There were a total of 34 new chemical entities and biologics approved by USFDA for cancer treatment between 2000 and 2009. However, only 19 of these new anticancer drugs were granted marketing approval in Australia. In addition, only 12 of the 19 approved new anticancer drugs were listed on the PBS for reimbursement, while Medicare in United States covered 18 of the 19 approved new anticancer drugs. All 12 listed new anticancer drugs were designated as authority required items in Australia, where initiation requirements were assigned to six of the new drugs. Also, nine of these new anticancer drugs were subject to treatment continuation rule based on evidence of treatment response, and seven of these new drugs had step therapy requirements. All new anticancer drugs except bevacizumab had quantity limits (maximum quantity that can be marketed/prescribed/dispensed over a given period of time) placed on them (Wilson and Cohen, 2011). On average, the time elapsed between marketing approval and reimbursement was 23.8 months, ranging from 6 to 53 months, while in the United States, it was 16.3 months, ranging from 11 to 21 months. Generally, anticancer medicines were priced 24%–41% lower in Australia compared to the United States, and cost sharing per prescription was greater among the Medicare population in the United States than the publicly insured beneficiaries in Australia. The analysis suggested that although there was a higher number of new anticancer drugs available in the United States, the evidence-based approach to the reimbursement decision adopted by Australia had contributed to the reduced prices compared to the United States, which may positively influence the affordability of new anticancer drugs (Wilson and Cohen, 2011).

Access to High-Cost Medicines in Thailand

A well-designed and well-executed public access scheme has the potential to improve access to high-cost medicines. For instance, the Thai government implemented a multipronged strategy known as the high-cost medicines E2 access program (E2 Program), including different health insurance schemes to cover selected high-priced specialty medicines (Yoongthong et al., 2012). The scheme aims to address the challenges of increasing healthcare expenditures while enabling access to high-cost medicines.

Sruamsiri et al. (2016) assessed if the E2 Program has achieved its goals of improving access to high-cost specialty medicines. The utilization rate of the selected high-cost medicines (intravenous immunoglobulin, leuprorelin, liposomal amphotericin B, verteporfin, and botulinum A toxin) was used as a proxy measure for patient access to the medicines. It was observed that at baseline, about two-thirds of eligible patients received the selected high-cost medicines. The utilization rate of the selected high-cost medicines among eligible patients increased significantly immediately after the implementation of the E2 program [rate of increment = 9.8% (95% confidence interval (CI) = 6.8%–12.8%)]. The estimated rates of increment in the utilization of the selected high-cost medicines at 1 year and 2 years after the E2 program implementation were 12.7% (95% CI = 4.4%–21.0%) and 11.5% (95% CI = 0.3%–22.7%), respectively. In conclusion, the study demonstrated E2 access program as a successful means to facilitate patient access to high-cost specialty medicines (Sruamsiri et al., 2016).

Access to High-Cost Medicines in the American Region

Access to High-Cost Disease-Modifying Therapies in Brazil

High prices of new disease-modifying therapies play an important role in pushing countries toward fair and transparent pharmaceutical access schemes. For example, in Brazil, access to biologic drugs is achieved through the judicial system or via administrative means (Lopes et al., 2014). While the legal route provides easy access to these medicines, it may also encourage the financing of health technologies that may not have a concrete proof of efficacy and safety.

Lopes et al. (2014) conducted a descriptive cross-sectional study to examine the access and utilization profile of biologic medications for psoriasis treatment provided by the judicial system in Brazil (Lopes et al., 2014). A total of 190 lawsuits filed between 2004 and 2010 to obtain biologic drugs for psoriasis treatment were analyzed. It was observed that the Infliximab (57.4%)

had the highest request rate followed by efalizumab (21.6%), etanercept (16.3%), and adalimumab (4.7%). The authors noted that the prescription of a biologic medicine in the majority of the analyzed lawsuits was not explicitly justified, with the absence of information concerning patient's previous treatment, progression of the disease, supplementary examination, or clinical diagnoses. In fact, none of the analyzed prescriptions for biologic drugs fulfilled the legal prescribing requirements. In addition, it was also observed that the applicants were treated with biologic medicines for periods of more than 13 months, with some patients being treated for more than 49 months. Additionally, more than two-thirds (70.3%) of the patients did not undergo laboratory tests for drug therapy monitoring (Lopes et al., 2014).

Access to High-Cost Anticancer Medicines in Canada and the United States

In Canada, many patients depend on drug access programs to get access to high-cost anticancer drugs. These access programs are independently administered by the provincial governments, with each provincial government deciding on the arrangement and eligibility requirements for their programs (Morgan et al., 2014). Therefore, concerns have been raised regarding equitable access to these high-cost anticancer drugs among patients from different provinces (Morgan et al., 2014). Chafe et al. (2011) surveyed eight provincial drug program managers about top 10 highest expenditure intravenous and oral anticancer drugs (Chafe et al., 2011). They then compared the number of top 10 intravenous and oral drugs that each program had in common with programs in other provinces. Provinces were categorized as having "fair," "moderate," "substantial," and "perfect" agreement when there were five, six or seven, eight or nine, and ten drugs in common, respectively. Furthermore, the utilization rates per 100,000 population for the five intravenous and four oral anticancer drugs for which complete data were available were compared across the provincial programs (Chafe et al., 2011). For intravenous anticancer drugs, there were about seven drugs in common on average, indicating "moderate" to "substantial" agreement among the provinces in terms of the highest expenditure on intravenous anticancer drugs. In case of oral anticancer drugs, the results indicate "fair" to "moderate" agreement across the provincial programs. The authors also noted that the coefficient of variation of utilization rates for nine intravenous and oral anticancer drugs across the provincial programs ranged from 8.4% to 55.3%. The study demonstrated that there were important variations in Canadians' publicly funded access to anticancer drugs despite approval for public coverage (Chafe et al., 2011).

Trastuzumab, a recombinant humanized monoclonal antibody that selectively targets the human epidermal growth factor receptor 2 (HER2), was approved by USFDA as the targeted therapy for HER2-positive metastatic breast cancer and as adjuvant treatment for HER2-positive breast cancer. Ades et al. (2017) evaluated patient access to trastuzumab in the United States by determining whether its use was proportional to patients' needs between the years 2001 and 2013 and compared the results with European countries (Ades et al., 2017). Since HER2-positive breast cancer cases ranged from 15% to 20% of the new breast cancer cases, the authors considered both scenarios (15% and 20%) in their analyses (Ades et al., 2017). The study highlighted that there was insufficient access to trastuzumab for all patients in need in the United States after the approval of trastuzumab as adjuvant treatment of HER2-positive breast cancer in 2006 despite complete coverage earlier (Ades et al., 2017).

Access to High-Cost Orphan Medicines in the United States

The advent of the Orphan Drug Act in the United States in 1983 fostered the development of treatments for rare diseases affecting fewer than 200,000 individuals, also known as orphan drugs (Cohen and Awatin, 2017). Since the targeted population is limited, orphan drugs have relatively high unit costs. Therefore, regulatory approval by USFDA for more than 600 orphan products does not ensure a sufficient condition for reimbursement or patient access.

Cohen and Awatin (2017) examined patient access to orphan drugs by analyzing payer coverage of 138 orphan drugs approved between 2000 and 2016 in the United States (Cohen and Awatin, 2017). Payer coverage rate for a particular orphan drug was presented as the percentage of 20 leading commercial payers that cover the drug. The 20 payers were selected based on their numbers of covered lives and data accessibility. It was reported that the payer coverage rate was between 75% and 100% for 80% of the orphan drugs, with more than one-third (n = 46) of the orphan drugs achieving complete coverage.

Affordability of High-Cost Medicines

The wealth of a country, or more specifically the affordability in a health system, is an important determinant of the access to high-cost medicines. The affordable high-cost medicines could be crucial for those who are suffering from curable form of any disease but cannot afford high priced medicines. A number of studies within the published literature have demonstrated that affordability as measured by gross domestic product per capita correlates with patient access to high-cost medicines.

Affordability of Cancer Drugs

Goldstein et al. (2017) compared the patterns of affordability of cancer drugs in Australia, China, India, Israel, South Africa, the United Kingdom, and the United States. They found that anticancer medicines are significantly less affordable in India, China, and South Africa than in high-income countries, including the United States where prices are considerably higher (Goldstein et al., 2017). In 2008, Kos et al. compared the access to nine new targeted oncology drugs in eight selected European countries

(Austria, France, Germany, Italy, Slovenia, Sweden, Switzerland, the United Kingdom) (Kos et al., 2008). The utilization rate of bevacizumab, bortezomib, cetuximab, erlotinib, imatinib mesylate, and rituximab was much lower than the average utilization rate in the eight selected European countries (Kos et al., 2008).

The differences in utilization of oncology drugs in Slovenia compared to the selected European countries are attributed to factors such as purchasing power, incidence rate of the cancer types considered in the analysis, and the allocation of resources for health. Slovenia had the lowest gross domestic product per capita according to purchasing power compared to the other selected European countries. Due to the low gross domestic product per capita of Slovenia, the country had a lower rate of utilization of the targeted oncology drugs in most cases.

Affordability of Disease-Modifying Therapies

Putrik et al. (2014a) investigated three dimensions of patient access (availability, affordability, and acceptability) to biologic DMARDs among patients with RA in all European countries (n = 46) (Putrik et al., 2014a). One proxy variable was chosen for each dimension of patient access, namely, the number of reimbursed biologic DMARDs for the dimension of availability, average annual price of biologic DMARDs for the dimension of affordability, and average score on the barriers to access to treatment with biologic DMARDs for the dimension of acceptability (Putrik et al., 2014a). The researchers developed a simple scoring system to evaluate the level of patient access to biologic DMARDs across the countries. For each of the dimensions, a score ranging from 0 to 3 was given to a country based on either an absolute number of biologic DMARDs for the dimension of availability or on the position in the quartile distribution of the variable for the dimensions of affordability and acceptability. Upon analysis, the overall access score to biologic DMARDs was reported to vary between 0 and 9 (9 indicating the best patient access), and it was observed to correlate strongly and positively (correlation coefficient = 0.86) with gross domestic product per capita (Putrik et al., 2014a).

Similarly, Péntek et al. (2017) explored the associations between patient access to biologics for the treatment of Crohn's Disease (CD) (in terms of both the dimensions of availability and affordability) with gross domestic product per capita, among 10 selected European countries. Affordability was defined as the annual cost of treatment as a percentage of gross domestic product per capita. It was observed in the correlation analysis that both the availability score (correlation coefficient = -0.88) and the affordability (correlation coefficient = -0.75) of biologics were strongly and negatively correlated with gross domestic product per capita. The authors also concluded that the wealth of a country influenced patient access to biologics for the treatment of Crohn's Disease (Péntek et al., 2017).

Strategies to Improve Access to High-Cost Medicines

High-cost medicines pose both health and economic challenges for healthcare systems. Some of the major challenges include affordability, decision-making related to the evaluation of high-cost medicines for coverage, and reimbursement and the difficulties associated with defining value for money. Health technology assessment has also become the key health policy instrument for decision-making and managing the introduction and use of high-cost medications. With well-performed health technology assessment, patients' access to cost-effectiveness can be made possible. Nevertheless, there exist disparities in health technology assessment processes among countries as illustrated in a review within Europe (Akehurst et al., 2017). The review illustrates the differences that include availability of published guidelines to support submission, timelines for decisions, and the price negotiations as part of the decision-making process. There are also differences in the health technology assessment process; some countries emphasize on disease severity and drug efficacy, whereas others focus on cost-effectiveness (Akehurst et al., 2017).

As decision makers have a significant role to allocate funds for the purchase of valuable targeted therapies, managed entry agreement like value-based pricing is a good strategy to adopt. Value-based pricing or value-optimized pricing is essentially a pricing strategy that dictates prices according to the perceived value of a product or service to a customer as opposed to the cost of the product (Shapiro and Varian, 1998). Currently, almost all targeted therapies have adopted cost-plus pricing model or cost-based pricing model, which considers the total cost involved in developing the drug and adding some amount to ensure the ability of the manufacturer to make a profit (Department for Business Innovation and Skills, 2012). Value-based pricing is gaining traction because the prices can be determined solely by patient outcomes, which include a reduction in hospitalization and associated medical care. In this context, the drug can be priced much higher than its counterparts in other classes as it lowers overall medical costs, hence providing better value for money (Gilmore, 2017).

Conclusion

Healthcare systems are under significant pressure to provide sustained access to affordable high-cost medicines. Health technology assessment and value-based pricing have the potential to improve medicine pricing regulation and accessibility to high-cost medicines. Improvements in the decision-making processes in regions like Europe have played a central role in increasing acceptance to prioritize access to high-cost medicines.

List of Abbreviations

CD	Crohn's disease
DMARD	Disease-modifying antirheumatic drug
DMT	Disease-modifying therapy
EMA	European Medicines Agency
E2 program	High-cost medicines E2 access program
EULAR	European League Against Rheumatism
HER2	Human epidermal growth factor receptor 2
PBS	Pharmaceutical Benefits Scheme
RA	Rheumatoid arthritis
USFDA	United States Food and Drug Administration

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Medication Adherence

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The World Population Prospects report that the number of older persons has increased significantly in recent years and is projected to grow by 56% between 2015 and 2030 (United Nations, 2015). Studies over a period of years have shown that age is a powerful predictor of health and the incidence of chronic diseases (United Nations, 2015). Chronic diseases are defined as "diseases which have one or more of the following characteristics: they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training for the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care" (Dictionary of Health Services Management, 1982). Chronic diseases account for 60% of all deaths in the world and the World Health Organization reports that the prevalence of chronic diseases will increase by 57% by 2020 (World Health Organization, 2002). An increase in the prevalence of chronic diseases can be translated to an increase in the number of medicines taken by individuals for a long period of time, with some patients on lifelong medicines. With the advances in medicine, many of these chronic diseases can be controlled by medicines, if the medicines are prescribed optimally, and if they are taken by the patients as prescribed.

What Is Medication Adherence?

> "Not only be prepared to do what is right himself, but also to make the patient . . . cooperate"
>
> —Hippocrates

The World Health Organization defined medication adherence as the "degree to which the person's behavior corresponds with the agreed recommendations from a healthcare provider" (World Health Organization, 2003). The US National Library of Medicine defines medication adherence as the "voluntary cooperation of the patient in taking drugs or medicines as prescribed. This includes timing, dosage, and frequency" (Definitions & Translations, 2017). Meichenbaum and Turk defined medication adherence as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result (Meichenbaum and Turk, 1987). As evidenced by all the definitions of medication adherence, it is apparent that the patient plays an active role in medication adherence. The patient has to take medicines as "agreed upon," "voluntarily," and with "collaborative involvement." These words define the ultimate drive for medication adherence. The term "medication adherence" is also called "medication compliance" and is defined as taking a medicine as prescribed by a physician. This definition takes a paternalistic attitude and puts the blame on the patient for not taking the medicine. For this reason, the word "compliance" is now replaced by "adherence," which displays more shared decision making between the patient and the provider.

For patients with chronic conditions, where the medicines have to be taken for a long period of time, the healthcare providers have to develop a collaborative relationship with patients, so that the patients take an active role in their treatment and agree to take the medicines as prescribed. To conclude, when patients do not take their medicines as prescribed based on agreed recommendations with the provider, it is called medication non-adherence.

How Common Is Medication Non-Adherence?

> "Noncompliance, the invisible epidemic"
>
> —Clepper

The World Health Organization reported that among patients with chronic diseases, in developed countries approximately 50% do not take medicines as prescribed and the adherence rate is even lower in developing countries (World Health Organization, 2003). The rate of non-adherence varies among diseases and populations and is reported anywhere between 10% and 92% (Grahame-Smith and Aronson, 2002). For example, non-adherence to cardiovascular medicines was 67.53% in Asia, 54.53% in Latin America, 48.48% in Eastern Europe, 47.44% in Western Europe, 46.45% in North America, and 35.02% in Middle East (Rodriguez et al., 2013). For type 2 diabetes, the prevalence varies between 36% and 93% and for asthma it is between 40% in the United States and 78% in Iceland (Cerveri et al., 1999; Cramer, 2004). African Americans are often found to be more non-adherent than Whites among the older people in the United States (Gerber et al., 2010). Another study conducted in a large integrated healthcare system in the United States found that older people and men were better adherent (Rolnick et al., 2013). Among older adults, the rate of non-adherence varies between 38% and 57% (Sackett and Snow, 1979). In the United Kingdom, one in five patients does not take all their medicines as prescribed (Hagan, 2015). Approximately 50%–90% of patients stop taking their medicines by the end of the first year of treatment. This is observed across various diseases such as hyperlipidemia, type 2 diabetes, obesity, hypertension, and depression. As can be seen, the prevalence of medication non-adherence is large enough to warrant attention from clinicians, researchers, payers, and health policy regulators.

Why Is Medication Adherence Important?

> "Drugs don't work if patients don't take them"
>
> —Former US Surgeon General Everett Coop

There are several and varied consequences of not taking medicines as prescribed, the most significant among them being the lack of optimal clinical benefits. If the prescription is optimal and based on a chronic care plan from the healthcare provider, not taking the medicine as prescribed can result in suboptimal clinical outcomes. On one hand, this can result in an increased medication dose, which can result in increased treatment cost and potential risk of adverse effects. On the other hand, non-adherence can result in exacerbations of the symptoms which can result in increased healthcare utilization such as emergency room and hospitalization visits, in addition to lost productivity for both patients and/or caregivers. Additionally, medication non-adherence can result in disease progression and overall lower quality of life. Literature has reported that medication non-adherence has resulted in approximately 125,000 deaths per year in the United States and is responsible for 33%–69% of the medication-related hospital admissions (McCarthy, 1998; Osterberg and Blaschke, 2005). In the European Union, approximately 190,000 people die every year as a result of medication non-adherence (Cordis, 2011). A study conducted among 493,609 older people in the United States demonstrated that patients with diabetes who were non-adherent to oral hypoglycemic agents, ACEIs/ ARBs, and statins were 44.6% more likely to be hospitalized for any cause, 32.8% more likely to visit the emergency room, and 22.6% more likely to die during the follow-up period (Yang et al., 2009). The same study also demonstrated that for each class of medicine, adherence resulted in an 11.8% reduction in all-cause hospitalizations, 9.7% reduction in emergency room visits, and 6% reduction in mortality.

What Is the Financial Impact of Medication Non-Adherence?

> "Medicine is most expensive when it's not taken at all"
>
> —John Lechleiter

In the United States, medication non-adherence is called the $289 billion problem, while in the United Kingdom, it is called the £500 million problem (New England Health Care Institute, 2009; Hagan, 2015). In Canada, the total annual cost due to medication non-adherence is estimated between $687 million and $1.633 billion dollars (Iskedjian et al., 2002). The World Health Organization reports that for every additional dollar spent on adhering to a prescribed medication, medical costs would be reduced by $7 for people with diabetes, $5.10 for people with high cholesterol, and $3.98 for people with high blood pressure (Sabatte and De Geest, 2003). In the United States, the total direct cost of non-adherence for patients diagnosed with diabetes, hypertension, and dyslipidemia is $105.8 billion or $453 per adult (Nasseh et al., 2012). A study conducted among 3260 diabetes patients showed that the total medical costs were $4000 when the adherence is greater than 80% compared to $9000 when the adherence is less than 20% (Ansell, 2008). Among older adults in the United States, non-adherence to medicines associated with diabetes, heart failure, and pulmonary disease costs between $49 and $840 per patient per month (Stuart et al., 2013). The United States Congressional Budget Office reported that a 1% increase in the number of prescriptions filled by older adults results in a 0.2% decrease in overall medical spending (Congressional Budget Office, 2012). As can be seen from the literature, medication non-adherence poses a heavy economic burden to the healthcare system.

Why Are Patients Non-Adherent With Their Medications?

> "Keep a watch . . . on the faults of the patients, which often make them lie about the taking of things prescribed . . . "
>
> —Hippocrates, Decorum

Table 1 Determinants of patient adherence

Categories of reasons for medication non-adherence as identified by the World Health Organization	*Factors that determine medication non-adherence under each category*
Social/economic factors	• Family support • Family/caregiver • Social support • Social stigma of a disease • Cost of drugs/treatment • Prescription coverage from insurance/employer • Socioeconomic status • Employment status
Therapy-related factors	• Adverse effects • Patient-friendliness of the regimen • Effectiveness of the drug (objective and perceived) • Duration of the treatment • Type of drug • Organized treatment (setting, treatment plan, psychotherapy, etc.)
Patient-related factors	• Age • Gender • Marital status • Education • Ethnicity • Housing • Cognitive function • Forgetfulness • Patient's knowledge of disease and treatment • Health beliefs to both drugs and illnesses • Psychological profile • Co-morbidities and patient history (such as non-adherence in the past, past treatment failure, etc.) • Alcohol or substance abuse • Patient related barriers (such as transportation)
Condition-related factors	• Presence (or absence) of disease symptoms • Severity of disease • Clinical improvement (feeling better or disappearance of symptoms) • Psychiatric disorders • Specific disease conditions • Duration of the disease
Health system-related factors	• Barriers to healthcare access • Poor drug supply • Prescription from a specialist • Receiving unclear, multiple and conflicting information about drug administration • Provider-patient communication and relationship • Lack of efficient follow-up with patients

(Modified from Kardas, P., Lewek, P., Matyjaszczyk, M., 2013. Determinants of patient adherence: a review of systematic reviews. Front. Pharmacol. 4, 91.)

Patients do not take their medicines for a multitude of reasons. The past four decades of research on medication adherence has identified the various reasons that contribute toward medication non-adherence. With the multitude of factors that influence medication adherence and to ensure that the blame for non-adherence is not completely placed on the patient, the World Health Organization organized the reasons for medication non-adherence into five categories: (1) Social/economic factors, (2) Therapy-related factors, (3) Patient-related factors, (4) Condition-related factors, and (5) Health system-related factors (World Health Organization, 2003). Kardas et al. (2013) conducted a review of systematic reviews to identify the various factors that can be included in each of the five categories defined by the World Health Organization report (Kardas et al., 2013). The team identified 771 individual factors that influence medication adherence and **Table 1** describes the results from this review.

Several studies have taken effort to determine the effect of the individual factors on medication adherence. However, there is no evidence as to the hierarchical nature of these factors. All these factors are important and vary depending on the patient, disease, and treatment. While some of these factors can have a direct and relatively easy intervention, certain others will need more coordinated care between the providers such as physicians, pharmacists, and nurses to improve medication adherence. For example, factors such as adverse effects or regimen complexity can be addressed effectively in a time-efficient way to improve adherence. Other factors,

such as affordability of medication or transportation issues, can also be addressed in a timely manner. However, factors that are related to beliefs of patients about the drug, disease, healthcare system, provider, etc. can be more difficult to be addressed and need more time and resources to be resolved.

Another important factor to keep in mind while addressing non-adherence is comorbidity and the way adherence varies across different disease conditions and treatments for the same patient. Also, the reasons for non-adherence can differ for the same patient across different disease conditions and across time. In other words, a patient can be adherent to one medication and be non-adherent with another medication. For example, while being adherent with asthma medicines due to the symptomatic nature of the disease, can be non-adherent with diabetes insulin injections due to fear of needles. Yeaw et al assessed persistence and adherence to drug therapy in six chronic conditions using a claims database and reported varying rates of adherence for the same patient (Yeaw et al., 2009). Thus, a healthcare provider's role is to understand the patient as a whole so that the factors that trigger non-adherence at various situations can be assessed and appropriate interventions can be implemented.

Lack of adequate communication between patients and healthcare providers, especially physicians, is a major factor that can lead to medication non-adherence. Studies have reported that either patients do not understand what they are expected to do or they misunderstand what they have been asked to do. This issue adds up when the patient does not have adequate health literacy, the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (Ratzan and Parker, 2000). While 35% of adults do not have adequate health literacy in the United States, the rate of inadequate health literacy is 42% in England, and 47% in the European Union (Kutner et al., 2006; Department for Business Innovation and Skills, 2012; Sorensen et al., 2015). Additionally, recent studies have shown the moderator effect of health literacy in the relationship between patient beliefs and medication adherence (Unni and Shiyanbola, 2016). In other words, while the relationship between patient beliefs and medication adherence was strong in patients with adequate health literacy, it was almost non-existent in patients with inadequate health literacy. Thus, assessing patients' health literacy, then communicating and developing interventions based on their health literacy can be a step toward better medication adherence.

Efforts have been taken to simplify and understand the complex medication non-adherence behavior by developing various taxonomies. A recent effort by the "Ascertaining Barriers for Compliance (ABC) project by the European Consensus meeting on the taxonomy and terminology of patient compliance" mainly classified adherence on a treatment timeline as adherence happening at initiation, implementation, and discontinuation (Vrijens et al., 2012). Initiation is defined as the moment at which the patient takes the first dose of the prescribed medicine; implementation is the extent to which a patient's actual dosing corresponds with the prescribed dosing regimen; and discontinuation occurs when the patient stops taking the prescribed dosing regimen. Between the prescription initiation and discontinuation, steps have to be taken to promote and manage adherence and it includes patients, social support (including family and caregivers), providers, community, and healthcare settings. Persistence is the length of time between initiation and discontinuation; the time between discontinuation and end of prescribing time denotes the non-persistence to therapy (Vrijens et al., 2012). Non-adherence at initiation is often referred to as primary medication non-adherence. Primary medication non-adherence occurs when a new medication is prescribed for a patient, but the patient does not obtain the medication or an appropriate alternative within an acceptable period of time after it was prescribed (Adams and Stople, 2016). A recent literature review reported that primary medication non-adherence ranges from 1.94% to 75% with a non-weighted average of 20.3% (Adams and Stople, 2016). This rate is often higher at 28% for new prescriptions, especially for chronic diseases such as hypertension, hyperlipidemia, and diabetes (Fischer et al., 2010). While continuous efforts are in place to increase the adherence at the stages of implementation and discontinuation, it is imperative to keep an eye on the stage of initiation too.

An earlier classification of adherence was based on the reasons for non-adherence as intentional and unintentional non-adherence. When non-adherence happens due to missing or altering doses to suit one's needs, it is known as intentional non-adherence; when non-adherence happens due to forgetfulness or cost issues it is known as unintentional non-adherence (Cooper et al., 1982). Examples of intentional non-adherence include stopping medicines due to side effects, thinking medication is not effective, omitting medicines if not feeling well, altering dosing for convenience, stopping medicine to see if it is still needed, and being careless about taking medicines as prescribed. Examples of unintentional medication non-adherence include forgetfulness, trouble opening containers, trouble swallowing pills, trouble reading labels, inability to afford medicines, and running out of medicines (Vik et al., 2005). Wroe discussed how intentional non-adherence is an active process whereby the patient weighs the various pros and cons of taking medicines (as suggested by Donovan and Blake) and decides whether or not to adhere with the medicines (Wroe, 2002; Donovan and Blake, 1992). Horne et al., in their beliefs about medicines theoretical framework explained how patient's beliefs in the necessity of medicines and their concerns about their medicines can influence this value proposition in the mind of patients (Horne et al., 1999). When the necessity beliefs about medicines outweigh the concern beliefs about medicines, the patient will be adherent and when the reverse occurs, the patient will be non-adherent. The necessity beliefs are statements such as "My health, at present, depends on my medicines" and concern beliefs are statement such as "I sometimes worry about the long-term effects of medicines." These beliefs often arise from patients' experiences about both medicines and illnesses, either personal or what they have observed in other patients. Unintentional non-adherence, on the other hand, is a more passive process where the patient wants to take medicines but does not due to reasons such as forgetfulness.

Forgetfulness is one of the reasons that is commonly attributed to non-adherence and is considered as unintentional non-adherence. Approximately 24% of patients who are non-adherent report forgetfulness as the reason for non-adherence (Boston Consulting Group, 2003). A recent survey in the United Kingdom reported 65% of the patients reporting forgetfulness as the reason for non-adherence (Hagan, 2015). Several interventions such as pill boxes and reminders were developed to address this reason for non-adherence. However, some recent studies have cast doubt on the unintentional nature of forgetfulness (Unni and Farris, 2011;

Gadkari and McHorney, 2012). These studies have shown a significant relationship between concern beliefs about medicines and unintentional non-adherence, concluding the possibility of overestimation of forgetfulness as unintentional non-adherence. In a study of breast cancer patients, Atkins and Fallowfield commented that "based on the veracity of responses given by patients, there was a possibility that patients found it easier to report 'forgetting' to take tablets than the less socially desirable admission that they chose not to take them" (Atkins and Fallowfield, 2006). Thus, when patients without any evident cognitive issues report forgetfulness as the reason for non-adherence, asking them about their underlying concerns about medicines can be a proactive way to promote medication adherence.

What Are the Theoretical Models That Explain Medication Adherence?

> "Theories without facts may be barren, but facts without theories are meaningless"
>
> —Kenneth Boulding

Medication adherence is a complex phenomenon with several interwoven factors that determine adherence. The patient, the disease, the treatment, society, the environment, and the healthcare system (including the providers), all play a major role in defining medication adherence. Thus, understanding the theoretical models that explain medication adherence becomes significant. Several models have been developed to explain medication adherence. The most commonly used theoretical models for improving medication adherence are Social Cognitive Theory, Health Belief Model, Transtheoretical Model, and Common Sense Model of Self-Regulation. A brief summary of the frequently used models is provided below. Though the models were originally developed for explaining health behavior, not necessarily medication adherence, the model descriptions below will use medication adherence as the healthcare behavior.

Health Belief Model (HBM): The HBM (Rosenstock, 1990) is based on the value expectancy theory where a health behavior, such as adherence, will be based on the balance between the desire to get well (value) and the belief that taking medicines will help in getting well (expectancy). The various components of the model are; perceived susceptibility (patient's perception of their risk of contracting the condition), perceived severity of the condition, perceived benefits of taking the medicines, and perceived barriers in taking the medicines (such as cost). Patients often balance all these perceptions in their mind to determine whether they want to adhere with medicines. These perceptions are also influenced by the cues to action such as symptom exacerbation and other demographic and sociopsychological variables such as age, gender, personality, knowledge, etc.

Theory of Reasoned Action (TRA) and Theory of Planned Behavior (TPB): According to the TRA (Ajzen and Fishbein, 1980), the proximal determinant of a behavior such as adherence is the "intention to adherence." The intention in turn is determined by the attitude to the behavior (beliefs about the outcomes from the behavior) and subjective norm (how important is this behavior to significant people in the patient's life and the patient's motivation to comply with those people). The TPB (Fishbein and Ajzen, 1975) was a modification of the TRA which added perceived behavioral control (the patient thinks they can actually do the behavior) to the model as a determinant of both intention and behavior.

Self-Efficacy Theory: The Self-Efficacy Theory (Bandura, 1997) postulates that a patient's decision to adhere with the medicines will depend on the patient's beliefs in their ability to take the medicines as prescribed by the healthcare provider. These beliefs are further influenced by their previous experiences in adhering with medicines, the success of the previous experiences, urging by significant others in adhering, and how the patient infers outcomes from the adherence behavior.

Social Cognitive Theory (SCT): The SCT includes a range of theoretical concepts and serves as a framework for understanding and implementing both organization and individual approaches to behavior change (Bandura, 1998). The theory incorporates cognitive, emotional, and behavioral understanding of behavior change. The major constructs in the SCT are environment (factors physically external to the patient), situation (patient's perception of the environment), behavioral capability (knowledge and skill to perform a behavior), expectations (expected outcomes from a behavior), expectancies (value of the expected outcome), self-control (how well the patient can regulate his goal-directed behavior), observational learning (learning a behavior by watching the actions and outcomes from another person's behavior), reinforcements (responses to a behavior that will either facilitate or impede the reoccurrence of that behavior), self-efficacy (patient's confidence in performing a behavior), emotional coping responses (how a patient deals with emotional stimuli), and reciprocal determinism (the dynamic interaction between the patient, the behavior, and the environment in which the behavior is performed). The SCT explains the dynamics of individual behavior which is quite significant in medication adherence. Each construct in this theory is quite dynamic when it comes to medication adherence. Thus, understanding the desired behavioral outcome, which is medication adherence, and then identifying the various constructs from the theory that is relevant to the patient at each point of time in their life should be considered while communicating with the patients and developing interventions. For example, while behavioral capability is essential when diagnosed with a new condition, self-control may be important later in the diagnosis.

Transtheoretical Model (TTM): The TTM conceptualizes the process of intentional behavior change, or in this case, intentional medication adherence (Prochaska and Diclemente, 1983). The model defines the various stages of change, with each stage having a temporal dimension, and the processes of change. The first stage, pre-contemplation, is the stage when the patient is not ready to adhere with their medicines in the next six months. At this stage, patients are either uninformed or under-informed about the consequences of non-adherence, or did not have positive previous experiences with medication adherence. The second stage, contemplation, is the stage when the patient is getting ready to be adherent with their medicines in the next six months. In this

stage, they are aware of the pros and cons of being adherent with the medicines. In the third stage, preparation, the patient is ready to be adherent with their medicines in the immediate future (within a month). The fourth stage, action, is when the patient is actually taking the medicines for the past six months. The fifth and last stage, maintenance, is when the patient has been taking medicines for more than six months. The processes of change are the activities that patients use to progress through these stages. The various processes are: consciousness raising (increasing awareness to encourage medication adherence), dramatic relief (experiencing the negative emotions that go with the consequences of medication non-adherence), self-reevaluation (realizing that medication adherence will help in creating a better self-identity), environmental reevaluation (realizing the positive impact that adherence can create in the patient's proximal social and physical environment), self-liberation (making a firm commitment to be adherent), helping relationships (social support), counterconditioning (learning to be adherent with medicines), contingency management (giving either rewards for adherence or consequences for non-adherence), stimulus control (removing cues for unhealthy behavior such as non-adherence), and social liberation (change in social norms to support medication adherence).

Common-Sense Model of Self-Regulation (CSM): According to this model, patients use their "lay" beliefs about their illnesses to guide their decisions on coping with the illness, in this case, being adherent with medicines (Leventhal et al., 1980). The model describes various components of the illness representations, both cognitive and emotional: (1) identity—the label of the symptoms that the patient believes are related to the illness; (2) cause—personal ideas about the etiology of the illness; (3) timeline—how long the patient believes the illness will last; (4) consequences—beliefs about the expected effects and outcomes of the illness; (5) cure/control—expectations about the course and treatment efficacy; (6) illness coherence—understanding the meaning of the illness; and (7) emotional representation—emotional response to the illness such as worry, depression, anger, anxiety, and fear. Based on the illness representations, patients will decide to either take or not take the medicines.

Horne's Extended Self-Regulatory Model (ESRM): The ESRM is an extension of the Common Sense Model, wherein the cognitive and emotional responses to the treatment by patients were added to their illness perceptions to determine the adherence behavior of the patient (Horne and Weinman, 2002). Similar to patient's perceptions about their illness, they also have cognitive and emotional responses to treatment. The cognitive responses to treatment are often classified as necessity beliefs in treatment (perceptions of personal need for treatment) and concern beliefs in treatment (concerns about a range of potential adverse consequences). Thus, when there is a health threat in the form of symptoms, patients use their illness perceptions, beliefs about medicines, and their emotional responses to both medicines and illnesses to appraise the situation. Based on the appraisal, they will decide on the coping procedure, which is medication adherence.

Information-Motivation-Behavior Skills Model: The Information-Motivation-Behavior Skills Model has three major constructs to guide complex health behaviors such as medication adherence (Fisher and Fisher, 1992). This includes information (basic knowledge about the disease and the effective strategies including medicines for its management), motivation (personal attitudes toward adherence, perceived social support for adherence, and the perception of how others with this condition will behave), and behavioral skills (patient has the specific skills necessary to perform the adherence behavior). According to this model, information, motivation, and behavioral skills have a direct influence on the behavior, which is medication adherence in this case. Additionally, behavioral skills are also influenced by information and motivation.

How Is Medication Adherence Measured?

> "Every line is the perfect length if you don't measure it."
>
> —Marty Rubin

With the high rate of non-adherence and the various factors that lead to medication non-adherence, it is important to measure medication adherence. For clinicians, measuring adherence is important so that effective treatments are not discarded when the reason the treatment was not working was because of non-adherence. Additionally, knowing the level of adherence and the reasons for non-adherence can assist clinicians in implementing interventions to improve medication adherence. However, measuring medication adherence can be quite challenging, depending on the goal for measurement and the definition of medication adherence. With different definitions and measurements, comparing adherence across different studies, diseases, and populations is also difficult. Thus, the clinician and/or researcher should have a clear goal for the measurement so that appropriate measurements can be used.

The measurements are mainly divided into two categories: objective and subjective (Vik et al., 2004). Objective measures include measures such as direct biochemical measures, electronic monitoring, pill counts, and secondary database analysis. While some of these measures will objectively evaluate whether the patient actually consumed the medicines (such as direct biochemical measures and electronic monitoring), other measures, such as pill counts and secondary database analysis will measure whether the medicines were picked up by the patient either from the pharmacy or the pill bottle. The major disadvantages with the direct biochemical and electronic measures are the clinical intrusion, cost, and the difficulty in doing it in a regular clinical setting. Using pill counts and secondary database analyses are rather inexpensive and easy to use, however the clinician or researcher cannot determine whether the medicine was actually consumed or not. Additionally, while objective measures quantify the level of medication adherence, they cannot determine the reasons for non-adherence, making it difficult to implement appropriate interventions to improve adherence. The subjective measures on the other hand can overestimate adherence due to self-reporting bias, but can point to the reasons for non-adherence or barriers to adherence. Though overestimation of adherence can be an issue with subjective measures,

Table 2 List of adherence measurements

Type of measure	*Specific measure*	*How is it measured?*
Objective Measures		
Direct measures	Measurement of the drug or its metabolite concentration in body fluids	
Electronic monitoring	Medication Event Monitoring System	
Secondary database	Medication Possession Ratio (MPR)	Days' supply obtained/refill interval or fixed interval
	Proportion of Days Covered (PDC)	Days' supply obtained/number of days between the first fill of the medication during the measurement period and the end of the measurement period
	Continuous, Multiple Interval Measure of Medication Acquisition (CMA)	Cumulative days' supply obtained over a series of intervals/total days from the beginning to the end of the time period
	Continuous, Multiple Interval Measure of Medication Gaps (CMG)	Cumulative days without any medication over a series of intervals/total days from the beginning to the end of the time period
Pill counts	Pill counts	(Number of dosage units dispensed − number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits)
Subjective Measures		
Patient diaries	Self-reported tool on how patients follow the drug regimen	
Patient interviews	Traditional interview	Clinicians interviewing patients to assess the level of adherence and the reasons for non-adherence
	Motivational interviewing	Interviewing techniques to assess the level of adherence, determine the reasons for non-adherence, and make interventions when non-adherence is identified
Self-reported questionnaires/scales	Morisky Medication Adherence Scale (8 items)	Classifies patients as low, medium, and high adherents
	Brief Medications Questionnaire (9 items)	Medication taking behavior and barriers to medication adherence
	Self-Efficacy for Appropriate Medication Use Scale (SEAMS, 13 items)	Self-efficacy in chronic disease management
	Medication Adherence Reasons Scale (MAR-Scale, 20 items)	One global item of medication adherence and 19 specific reasons for non-adherence in the past seven days
	Adherence Estimator (3 items)	Screening instrument for predicting medication non-adherence

interventions can be implemented to improve the adherence of patients who self-report as non-adherent. A list of the most commonly used adherence measures is described in **Table 2**.

Since every measure has its own advantages and disadvantages, defining the goal of the measurement can aid in selecting the appropriate measurement. For example, if the goal of the measurement is to quantify adherence after the implementation of a new treatment protocol, objective measures such as secondary database analysis can be adequate. However, if the goal of the measurement is to develop a tailored intervention program to improve adherence, a subjective measure can be more useful. If the clinician is trying to evaluate the level and reasons for non-adherence, a patient interview will be sufficient. However, if the goal is to understand how patients are taking medicines and what the barriers are in taking medicines, a self-reported questionnaire will be appropriate. Additionally, when needed, it is apt to use multiple measures such as a pill count followed by a self-reported questionnaire.

How Can Medication Adherence Be Improved?

> "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments"
>
> —Haynes et al.

Being a complex phenomenon with significant clinical consequences and enormous financial impact, several interventions are available to improve medication adherence. For a patient to be adherent with medications, especially the medicines for chronic conditions, the patient has to acquire new coping strategies including new behaviors, new routines, and learning to live with a chronic illness. Therefore, most patients will require some kind of intervention to improve their adherence with medicines. The World Health Organization recommends the use of multimodal, targeted, and tailored interventions for efficiency and effectiveness (World Health Organization, 2003). A comparative effectiveness review of the various interventions reported that interventions range from low-cost, low-intensity telephone, and mail interventions to intense interventions such as care coordination, case management, and care collaboration (Viswanathan et al., 2012). The often-reported interventions are: blister

Table 3 Interventions often used in improving medication adherence

Type of intervention	*Strategies used for each interventions*
Behavioral intervention—to change the patient's behavior toward treatment	• Cognitive behavioral interventions including telephone follow-ups and home visits • Medication management programs—providing planning and support such as discharge interventions • Employing prompts or cues for medication taking and linking patient's daily routines with medication taking
Educational interventions—to increase patient's knowledge and beliefs about medicines and illnesses	• Education programs about the disease or treatment • Self-management skills training • Managing side effects from the treatment
Integrated care interventions (case management)—collaboration within and between healthcare providers to improve adherence, especially in patients with complex health problems	• Collaboration between physicians, pharmacists, nurses, case managers, and payers • Often can reduce the risk of hospitalization and length of stay in hospitals
Self-management interventions—enabling the patient to manage symptoms, treatments, lifestyles, and psychosocial, cultural, and spiritual consequences of chronic diseases	• Goal-setting • Self-monitoring for symptoms, lifestyle, adherence, etc. • Access to own health records • Stimulus control and corrective feedback • Creating social support • Commitment enhancement, reinforcement, and relapse prevention • Support via technology such as telemedicine, web-based interventions, and cellphones/text messaging
Risk communication interventions—to address the patient's perceptions about the risk associated with taking the medicines as prescribed	• Decision aids—education tools that will present the risk information to enable the patient in shared clinical decision making • Often recommended to be used as part of a complex intervention
Packaging and daily reminders—to remind patients to take their medicines as prescribed	• Reminder phone calls • Text messages, pagers • Interactive Voice Responses (IVR) system • Video telephone calls • Pill boxes • Blister packaging

packaging; reminders; risk communication; case management; counseling using a software-based telephone; collaborative care by telephone or telephone and in-person; decision aids; face-to-face education with a pharmacist; education and behavioral support by telephone, mail, and/or video; education and social support; health coaching; pharmacist-led multi-component interventions; patient access to medical records; provider access to patient adherence data; self-management; shared clinical decision making; telemonitoring, and using a virtual clinic. While 50% of interventions were targeted at multiple agents (such as patients, caregivers, providers, and health system), 40% were targeted only the patient. Also, half of the interventions were delivered by a pharmacist, physician, or nurse, and also had some type of face-to-face interaction. **Table 3** provides a snapshot of the various interventions used to improve medication adherence.

Of the various interventions, the most consistent for the most improved medication adherence are educational interventions and case management approaches (Viswanathan et al., 2012). However, these approaches were not the best for hypertension, hyperlipidemia, myocardial infarction, and diabetes. Other interventions that are promising are reminders and a pharmacist-led multicomponent approach (Viswanathan et al., 2012). For clinical conditions such as depression and diabetes, collaborative care was the most effective (Viswanathan et al., 2012). Reducing out-of-pocket expenses can improve medication adherence at a moderate level, especially in cardiovascular conditions (Viswanathan et al., 2012). Evidence has shown that targeting interventions at patients and at the healthcare team can be more effective (DeBusk et al., 1994). Shared decision making between a patient and a non-physician clinician had better improvement in adherence, and the adherence lasted up to two years (Wilson et al., 2010). Similarly, patients given a decision aid to help them decide whether to take statins to lower the risk of cardiovascular diseases had better adherence than patients given the usual care. Incorporating patient preferences through shared decision making can have a positive impact in increasing medication adherence (Viswanathan et al., 2012).

A meta-analysis of the interventions to improve medication adherence reported a statistically significant moderate effect size of 0.301 for treatment versus control comparisons, 0.533 (statistically significant) for treatment group pre- vs. post-intervention comparison, and 0.011 (statistically insignificant) for control group pre- vs. post-intervention comparison. The effect size of adherence interventions was 0.211 for underrepresented racial/ethnic groups and 0.33 for older adults (Conn et al., 2016). An effect size of 0.2 or less is often considered as a small effect from the interventions, 0.5 and higher as a moderate effect and 0.8 and above as a strong effect. However, the translation of this improvement in medication adherence to clinical outcomes and quality

of life outcomes is not very evident. The meta-analysis reported that the face-to-face delivery of interventions was more effective, especially when the goal is to change the patient's knowledge, attitudes, or beliefs about medicines. Other effective interventions reported by the meta-analysis are behavior-based interventions such as employing prompts or cues for medication taking and linking the patient's daily routines with medication taking. The authors postulate that, as they are ongoing, behavior-based interventions are more successful compared to educational interventions, which happen less frequently. The unsuccessful interventions reported by the meta-analysis include asking patients to self-monitor their symptoms and medicine taking behaviors, teaching patients about managing side effects, giving patients' feedback about their adherence, goal-setting, and increased provider communication. Finally, the effectiveness of the interventions was not related to demographics such as age, gender, or racial/ethnic composition.

Who Are the Stakeholders in Improving Adherence?

"If you think about how healthcare is delivered, it's on an ad hoc basis. Someone comes into a hospital, someone comes into a pharmacy, someone comes into a doctor. But beyond those touchpoints, the patients are on their own. There's no real continuity of care."

—Christopher A. Viehbacher.

Patients are an important stakeholder in the world of medication adherence. They are the ones experiencing the illness, having their routines altered, being subjected to the side effects from the medicines, and having emotional responses to all these situations. Family and caregivers along with society also play an important role in adherence. Providing adequate social support and providing the right social and physical environment is equally important in improving medication adherence. Patient support groups and patient organizations can also work alongside patients to ensure that the voices of patients are heard. Physicians who work with patients from the moment of diagnosis play a significant role in medication adherence. Communication between the physician and patient, developing a trusted relationship, encouraging patients to be a part of the shared clinical decision making, and developing an integrated care network for the patient will all work toward improved medication adherence. Pharmacists, with their knowledge of medicines and developing medication management plan for optimized clinical outcomes, are also significant stakeholders. Additionally, due to their accessibility to patients and being the last point of contact before patients go home with medicines, pharmacists should counsel and encourage patients for improved medication adherence. Nurses with their clinician role, and opportunity to interact with patients before and after their physician appointment, can be in the ideal place to assess the levels of medication adherence and to determine the reasons for non-adherence, if non-adherence exists. They can also play a significant role in educating patients about their illness, medicines, side effects from medicines, and encouraging them to ask questions. Psychologists can also play a significant role in adherence improvement. Since medication adherence can be considered as a behavior that needs modification, psychologists can assist in developing tailored intervention programs for each patient depending on their social context, personality, and needs. Finally, pharmaceutical industries can play a significant role in the overall improvement of adherence. Developing drugs with fewer side effects, less complex regimens, and with easier administration can promote adherence. Additionally, offering patient assistance programs for those patients who cannot afford their medicines can also improve medication adherence.

What Are Some Practical Strategies to Improve Medication Adherence at the Patient Level?

"We have to be very careful not to blame the patients. A lot of the conversation [around patient engagement] has been, how do we get them to do stuff? To me, that's not engagement. "

—Victor Montori.

Consider medication non-adherence as a possibility with each patient. With the rate of non-adherence varying between 10% and 92% and with 50% and 90% of patients stopping medicines within the first year of treatment, even after a cardiovascular event, non-adherence should be in the mind of every provider. Even when the patient is adherent with one medicine, they may be non-adherent with another medicine. When a therapy is not working, thinking about non-adherence before changing the drug/dose can be the right step.

Communicate with the patient about non-adherence and document the level of adherence and reasons for non-adherence in their records. The physician or pharmacist can ask these questions directly, use a self-reported scale before the visit, or they can ask the patient to keep a diary, especially with new medicines and those with too many side effects/fear of side effects. Clinicians can use empathetic communication styles to allow patients to open up about their medicine taking habits. Once non-adherence is identified, clinicians should investigate the patient's reasons for non-adherence. A scale such as the Medication Adherence Reasons Scale can be a comprehensive tool to identify the reasons for non-adherence (Unni et al., 2014). While identifying the reasons, clinicians need to put themselves in patient's shoes and be receptive to the answers from them. If a patient is non-adherent due to lack of beliefs in the medicine (in spite of a clinician spending an hour explaining about the medicines), the clinician needs to remain empathic. The patient's environment with their families, colleagues, and friends, and their experiences all play a major role when they decide not to be adherent.

Identify a solution that is targeted and tailored for the patient based on their situation, beliefs, and experiences. Take input from patients in developing these solutions so that they are co-authors in the prescribed treatment regimen. If needed, include the patient's family and caregivers in the process as social support can increase medication adherence. Develop a system to communicate with patients in between clinic visits. This can encourage patients to ask questions and have their concerns taken care of by a healthcare professional. Additionally, this can also increase the self-efficacy of patients in following the treatment regimen as planned.

Develop an integrated care network of healthcare providers for each patient that can include the primary care physician, pharmacist, nurse, social worker, psychologist, and any specialist as needed. With increased communication and reinforcement from each provider about the illness, medicines, and the need for medication adherence, a safe environment can be created for patients to adhere with their medicines.

Conclusion

Medication adherence or non-adherence is a complex behavior. Non-adherence behavior is not black and white or right and wrong. A patient is making a decision based on many factors about initiating and continuing medicines. As a result, patients, especially when taking medicines for chronic conditions, need to be supported and not blamed. In other words, we need to reengineer the healthcare system to meet these challenges. The current system does not allow adequate time for providers to encourage communication with patients. Patients with complex conditions and low health literacy need more time with their providers. Also, adherence behavior is not static; it changes and evolves over time based on the needs and beliefs of the patient. For example, a forty-year-old woman diagnosed with high cholesterol may be non-adherent due to her busy schedule and strong "I can manage it with lifestyle change" attitude. However, the same patient in her fifties may have different beliefs and may be ready for adherence, but may also need coaching on the illness as well as the medicines. Moving into her sixties, with other comorbidities and retirement, her beliefs and adherence patterns can change again. Thus, healthcare practitioners have to develop a system to capture the beliefs and adherence patterns of patients over the years to better understand patients and assist them with adherence. In spite of the best prescription, the best discharge plan, and the best packaging, if a patient decides not to take their medicines, it is a waste of healthcare resources and a source of frustration to providers. Thus, every provider should consider their patients' adherence as the top priority in every visit and communication.

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Aging Populations and Medicine Use: A Sociological Approach

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Background

The world's graying population is growing steadily. Declining fertility rates and significant improvements in life expectancy are the major causes of this phenomenon. Globally, life expectancy at birth has risen from 67.2 to 70.8 years between 2000–05 and 2010–15 (UN, 2017). It is projected to rise by 6 years (from 71 to 77 years) between 2010–15 and 2045–50.

In 2017, the number of people aged 60 or above was 962 million. This is expected to be more than double by 2050 and more than triple by 2100, rising from 2.1 billion in 2050 to 3.1 billion in 2100. The number of people aged 80 or over is expected to be triple by 2050, from 137 million in 2017 to 425 million in 2050. By 2100, it is expected to increase to 909 million, nearly seven times it's value in 2017 (UN, 2017). In spite of decline in fertility rates and higher life expectancy, the increasing number of older people in developed countries is also partly due to the improvements in curative medicine.

Longer life provides the opportunity to reconsider what the life of older people might consist of and people are rethinking ways to spend these extra years. A remarkable event occurred in Malaysia in May 2018: a 93-year-old became the seventh prime minister and is considered to be the oldest prime minister in the world. This sets an example of what an older person above the age of 80 years can achieve. The ability to carry on with these extra years of life; however, heavily depends on their health status and does not necessarily mean that older people are living healthy lives. People are living longer but with more disease.

Aging is commonly associated with an increased risk of multimorbidity. The increasing prevalence of medical conditions associated with old age is a major challenge. Although this is also prevalent in other age groups, it is much higher in older age groups, affecting 65% of people aged 65–84 years and 82% of people aged at least 85 years (Barnett et al., 2012).

In 2010, the Global Burden of Disease (GBD) estimated 23.1% of the total disease burden [574 million of the 2490 million disability-adjusted life years (DALYs)] is attributable to disorders in people aged 60 years and older (Prince et al., 2015), the leading causes being cardiovascular diseases, malignant neoplasms, chronic respiratory diseases, musculoskeletal diseases, mental and neurological disorders, infectious and parasitic diseases, unintentional injuries, diabetes mellitus, digestive diseases, respiratory infections, and sense organ diseases. Globally, in 2016, three disorders dominated mortality in this age group: ischemic heart disease, stroke, and chronic obstructive pulmonary disease (WHO).

The GBD in older people is projected to increase more or less in line with the increase in the older population, consistent with population aging being the most important driver of the chronic disease epidemic (Mathers and Loncar, 2006). The largest increases in disease burden will occur for those disorders that are strongly age-associated (dementia, stroke, COPD, and diabetes).

The number of people with dementia worldwide will increase sharply, driven by worldwide patterns of population aging; 44.4 million people had dementia in 2013, with numbers nearly doubling every 20 years to 75.6 million in 2030 and 135.5 million in 2050 (ADI). People with dementia have the highest multimorbidity. In Scotland, people with dementia have 4.6 additional chronic illnesses (Guthrie et al., 2012). In the United States (US) primary care, people with dementia on an average had four additional chronic medical disorders—82% had hypertension while 39% had diabetes mellitus—and were prescribed about five drugs (Schubert et al., 2006).

The Health of Older Adults

The health of older adults can be conceptualized in four categories on a population health continuum (Tkatch et al., 2016):

Healthy and Active

These older adults have no chronic health conditions or disease and therefore staying healthy and active is critical to them.

At Risk but Healthy

Older adults in an "at risk" but healthy group are managing a chronic condition (such as hypertension) and their focus is to stay healthy, prevent the progression of their condition, and prevent future chronic conditions.

Coping with Disease

Older adults who have multiple conditions or diseases and their focus is on slowing the progression of these conditions and/or reversing the damage.

Very Ill

Older adults who have severe medical episodes and are in need of constant or regular medical interventions.

Tkatch and team suggested a holistic perspective on health that includes a more objective construct such as physical functioning and the more subjective constructs of psychological well-being, social well-being, and self-rated successful aging to provide a more accurate health description and a comprehensive perspective on the quality of life of older adults (Tkatch et al., 2016).

Physical Functioning

Physical functioning relies primarily on objective determinants and outcomes as it relates to issues that result as a function of a combination of age, illness, and mobility. The objective measures of age and chronic illness are particularly relevant as physical decline occurs. For example, some physical limitations of older adults are characterized by the inability to walk a quarter of a mile, stand for 2 h, stoop, bend or kneel, and lift or carry something more than 10 pounds (equal to bags of groceries). Reduced physical functioning also includes activities of daily living (ADLs), for example, bathing, dressing, etc., and risk of a fall. Age, minority status, being female, lower education, depressive symptoms, and illnesses such as diabetes, arthritis, and heart failure are examples of the characteristics of those with physical decline. Outcomes of poor physical functioning include continued decline, falls, worse mental health, and increased mortality. Sensory impairment is another aspect of physical functioning limitations. For older adults, the decline of hearing and vision has a significant impact on their well-being and could increase risk of falls, depression, cognitive impairment, and loneliness (Tkatch et al., 2016).

Psychological Well-being

Psychological well-being is a multidimensional construct that personifies the human capacity to continue to grow, adapt to our environment, and evolve throughout the aging process. For older adults in particular, psychological well-being is characterized as the ability to deal with life situations, to have and maintain positive and close relationships, self-acceptance of both self and others, and autonomy. Predictors of high psychological well-being for older adults include social support, physical activity, spirituality, and higher socioeconomic status. Conversely, depression, stress, and anxiety are predictors of low psychological well-being. Outcomes of high psychological well-being include lower rates of cognitive decline, higher levels of resilience, and greater life satisfaction. Notably, high psychological well-being is a key factor in successful aging and reduced mortality rates for both physically healthy and unhealthy older adults (Tkatch et al., 2016).

Social Well-being

Social well-being has been defined as the relative ability to deal with social challenges and how well one functions in the social world. Social integration, social contribution, social coherence, social actualization, and social acceptance are the five major

components of social well-being. Social well-being has a significant impact on the health of older adults, with higher levels of social well-being related to lower levels of cortisol and inflammatory factors that contribute to a number of diseases including cardiovascular disease. Aging has an implication on one's social networks and social roles whereby some of these changes enhance one's social well-being and some detract from it.

Social relationships are an important indicator of quality of life, with those who have negative social relationships reporting worse quality of life independent of disease status. Close knit family ties have particular relevance for the well-being of older adults. Negative social factors that reduce the social well-being of older adults include loneliness and social isolation. Loneliness can result from a feeling a loss of meaning in life, lack of independence, and loss of loved ones. Social support is also a key influence on the social well-being of older adults. Among older adults, high levels of social support are associated with lower stress and better mental and physical well-being (Tkatch et al., 2016).

Medicine Use

Aging is often associated with a decline in organ function. Physiological changes that occur while aging affect pharmacokinetics (what the body does to a drug) and pharmacodynamics (what a drug does to the body). Changes that occur in absorption, distribution, metabolism, and elimination of drugs cause reduced volume of distribution for some drugs, slower drug metabolism, reduced renal clearance of many drugs, and slower gastric emptying. Additionally, sensitivity to drugs also increases and necessitates dose reduction of many medicines to avoid toxicity (Lucas, 2011).

Older people, however, consume more medications than any other age group. In the US, approximately 36% of patients aged 65 years or older are prescribed five or more drugs (Qato et al., 2016). Population-based studies conducted in the United Kingdom (UK) revealed that people aged more than 65 had a dramatic increase in the total amount of medication within 20 years (Gao et al., 2018). The type of medications commonly used by older people and seen to be increasing are statins, antiplatelets, NSAIDs, antihypertensives and proton pump inhibitors, particularly simvastatin, aspirin, lisinopril, and omeprazole (Qato et al., 2016). Additionally, multivitamin or mineral supplements, especially omega-3 fish oils, vitamin D, and coenzyme Q10; and calcium were the most commonly used supplements.

There has also been a global upsurge in the use of complementary and alternative medicine (CAM) among those aged 50 years and above (NIH, 2011). It has been claimed that CAM offers a safer approach to common health conditions for the elderly, strengthening their body's own defensive and healing abilities (Eliopoulos, 2006). CAM use among patients with several chronic conditions such as cancer, osteoarthritis, cardiovascular, and neurodegenerative disorders has been widely studied. For osteoarthritis patients, acupuncture and glucosamine together with conventional care has been reported to provide a safer option in improving mobility and reducing pain than conventional care alone (Maa et al., 2008). Biofeedback and mind body therapies have been reported to reduce systolic blood pressure among hypertensive patients (Greenhalgh et al., 2010; Oberg, 2009). Similarly, mindful therapies such as meditation, Tai chi, spiritual therapies, and prayer are reported to improve health-related quality of life of elderly patients with neurodegenerative diseases (Lavretsky, 2009). Integrating CAM into geriatric care might remove communication barriers among patients and their health care providers, improving cost-effective therapeutic options with fewer side effects. Furthermore, the holistic approach of CAM therapies might provide elderly patients a chance to take charge of their own health creating treatment options that reflect their own health and cultural believes. Geriatric care in old people's homes is another challenge faced by their caregivers. In this context, a number of CAM therapies such as Qi Gong, Tai chi, dancing, and yoga can be offered in groups and might help people to socialize, thereby reducing symptoms of depression and stress which are commonly seen among residents. Such rehabilitation techniques can assist old people to improve mobility and physical dependence which is commonly seen in many chronic conditions.

Polypharmacy

The top most issue related to medicine in older people is polypharmacy. Polypharmacy is associated with poorer clinical outcomes, increased risk of adverse drug reactions (ADRs), nonadherence, drug–drug interactions, and higher health care costs. The prevalence and incidence of polypharmacy are high among older adults (Morin et al., 2018). In the UK, the proportion of older people taking five or more medications increased four times from 12% to 49% between 1991 and 2011 (Gao et al., 2018). The most common definition of polypharmacy is the concomitant use of "five-or-more-medications" (Gnjidic et al., 2012). Many people can benefit from polypharmacy but the higher the number of medications the higher the risk of adverse events (Gnjidic et al., 2012) and nonadherence (Pasina et al., 2014). In Sweden, a nationwide cross-sectional study found that 16%–24% of all older adults (≥65 years) were exposed to medications whose risks overweigh the expected benefits (Morin et al., 2018).

Polypharmacy often reflects the magnitude of chronic multimorbidities. The number of medicines a patient takes strongly correlates with the number of chronic conditions the patient has (Morin et al., 2018). For each additional chronic disease, at least one additional drug was introduced. Additionally, the rise in polypharmacy was also due to older people being treated with preventive medicines to reduce the rate of mortality and morbidity, particularly in cardiovascular disease (Force et al., 2016) and stroke prevention (Alhusban and Fagan, 2011). Another cause of polypharmacy is the development of clinical practice guidelines focusing only on the management of a single disease and absence of guidance on how to tackle older patients with multimorbidity (Vitry and Zhang, 2008). If clinical guidelines are to be followed for all medical conditions, an older person might be expected to take

more than 10 medicines. This calls for development of combined guidelines for most common patterns of multimorbidity. On top of that, another possible reason for polypharmacy is a prescribing cascade (David et al., 2016). This occurs when a new medicine is started to treat an adverse effect of another medicine which has been misinterpreted as a new medical condition (Kalisch et al., 2011; Nguyen and Spinelli, 2016).

Polypharmacy is seen as a threat to patients but underutilization of medicine may also be hazardous. A study in Belgium observed a high prevalence of polypharmacy (58%), concurrent with a high prevalence of underuse (67%), and misuse (56%) among a cohort of community-dwelling patients aged 80 years and above (Wauters et al., 2016). The study found that underuse of medicines was associated with increased rates of mortality and hospitalization, after controlling for polypharmacy and misuse. Deprescribing is one means of possibly overcoming polypharmacy. It is the process of tapering or stopping drugs, aimed at minimizing polypharmacy and improving patient outcomes. Caution needs to be taken; however, when limiting the number of medicines prescribed, as when beneficial medicines are stopped patients are at risk of worsening medical conditions.

Nonadherence

Adherence is "*the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*" (WHO, 2003). Adherence to medication has always been an issue, especially in older patients. Poor adherence could lead to decreased therapeutic benefits for the patient, frequent hospital visits and increased health care costs and even lead to death (Yap et al., 2016).

A study classified the reasons for nonadherence into patient factors, medication factors, health care provider factors, health care system factors, and socioeconomic factors (Yap et al., 2016). Some of the patient factors that might affect adherence to medications are education level, patient's mental state, physical health, behaviors and attitudes, knowledge and beliefs about medications, and past medical history. Medication factors which might influence adherence among older people are types of drug formulation, packaging, storage issues, drug regimen such as polypharmacy or complex dosing regimen, drug handling such as necessity to cut tablet or difficulty opening containers, presence of ADRs, drug–drug interactions, poor labeling instruction, and lack of immediate consequences of missed doses (Yap et al., 2016).

Health care provider–patient relationship is important in achieving the therapeutic goals of a treatment. Some of the health care provider factors that could hinder adherence in older people are poor communication between the provider and patient, lack of patient involvement, lack of confidence in health care providers, and lack of trust by the patients. Among the health care system, factors that could lead to nonadherence are lack of patient education and follow-up. Finally, lack of caregiver and increased caregiver burden are the socioeconomic factors associated with poor adherence (Yap et al., 2016). Similarly, a cross-sectional study conducted in Korea found that thorough explanation of medication and patients' satisfaction with counseling were the strongest predictors of higher adherence. Whereas, the use of multiple pharmacies, frequent dosing interval and low level of education were associated with poor adherence (Jin et al., 2016).

Adverse Drug Reactions

The number of medications that a patient takes is the strongest risk factor for harm (Steinman et al., 2014). Up to 6.5% of hospital admissions are due to ADRs and patients on multiple medications are more likely to suffer from an ADR (Pirmohamed et al., 2004). Among older adults, ADR prevalence rates are as high as 26% (Hamilton et al., 2011) and incidence of ADR rates are as high as 21%–22% (Lavan et al., 2018; O'Connor et al., 2016) have been reported. Additionally, it was found that 12% of patients aged 70 and above were admitted to hospital due to ADRs (Mannesse et al., 2000). The majority of ADRs in older people are Type A reactions involving commonly prescribed medications and are usually preventable (Davies and O'Mahony, 2015). The most common ADRs were acute kidney injury and electrolyte disturbance secondary to diuretics; falls secondary to benzodiazepines and opiates; orthostatic hypotension/symptomatic bradycardia secondary to anti-hypertensives; and upper gastrointestinal bleeding, gastritis and acute kidney injury secondary to nonsteroidal antiinflammatories (O'Connor et al., 2016). Factors such as changes in pharmacokinetics and pharmacodynamics could have contributed to ADRs; however, the main independent risk factor is the number of medications that older people take (Davies and O'Mahony, 2015).

A Sociological Approach toward Medicine Use

Sociology is the study of the relationship between the individual and society. It seeks to understand how an individual's thoughts, actions and behaviors are influenced by the society. Besides, it also seeks to understand how individuals actively structure their society through their own actions. Sociology deals with real-world issues (research on and with people) and these issues are forever bound to be in transition and change (Paul et al., 2001). The following quotation from Nettleton clearly illustrates the role of sociology in health and illness as well as health services.

Our birth may be mediated by technology and controlled by health professionals. The beliefs about health and illness held by our peers and by those with whom we live will shape our experiences of illness and understandings. Our contact with health professionals (dentists, doctors, pharmacists, opticians, health promoters, practice nurses, etc.) is likely to be a routine fact of our lives. Our self-identity may be shaped by our experiences of illness and our interactions with both formal and informal institutions of health care. Our attitudes toward our bodies will be

influenced by our socio-cultural context. We may come into contact with new technologies of health care, either through our own illness or through having children. We may have to face the ethical and moral dilemmas central to the blurring of the beginning and ending of life (Nettleton, 2013, p.1).

Health and illness are social phenomena. Morbidity and mortality might change according to social differences in social class, age, gender, and ethnicity. Within the context of aging, sociology is concerned about the lives of older people and the context of their existence, about how they live, the social forces that operate upon them, and how those individuals contribute to and change those social forces (Paul et al., 2001).

Being healthy or successfully aging depends on the degree of health independence, family, financial security, life adaptation, personal growth, friends' and relatives' relationships, emotional care from family and friends, satisfaction with life, regular social activities, high level of psychological and social well-being, learning new things, physical appearance, sense of humor and spirituality, leisure activity, happiness, and independence (Tobiasz-Adamczyk, 2015). The concept of healthy aging of older people; however, differs based on norms, traditions, religious beliefs, and the system of values.

For example, for older Japanese people the main components of successful aging were: remaining in good health, being able to take care of oneself, having family and friends, "good genes", being free of chronic diseases, satisfied with life, and adjusted to age-related changes. For older Australians, except for good genes, similar concepts to the Japanese were shared and other concepts that emerged were feeling good about oneself, being able to make choices about things that affect aging, staying involved with the world and people, being able to act according to ones' own inner standards and values, not feeling lonely or isolated, being able to cope with the challenges of later years, and being able to meet all of their needs (Tobiasz-Adamczyk, 2015).

As far as illness is concerned, it is socially patterned and an older person's social position as well as their individual health will have an important influence on their life experiences especially when it comes to medicine taking. Nettleton clearly illustrated that health care does not happen in isolation but is within a specific organizational context. For example, when an older person gets ill, he or she might visit a doctor, a pharmacist, a nurse or a traditional or complementary practitioner. These services might be funded or require direct payment from patients, which might have an implication on the provision of service and the use of such services by patients. The maintenance of health and the management of illness among the older population happen through interactions with health care workers and these interactions help to sustain their lives and the society that they live in. Being ill can be detrimental to older persons' lives and their relationships with other people and society (family, friends, colleagues, and health workers) and might impact on their ability to perform daily activities and how they choose to present themselves to others. An elderly person being ill will have an impact on the caregivers at the same time. This interactional element is one component of sociological analysis in relation to the understanding of health and illness.

Sociology deals with the nature of the social structure, the relationship between self and society and the historical development of society (Paul et al., 2001). Different kin-ship, religious, economic, political, and other institutions of a society frame a social structure. The power of individuals to operate independently from the constraints of the social structure is called agency. A deeper understanding through the exploration of the relationship between the social structure and agency provides a sociological approach for understanding medicine use in older adults.

Sociology of Aging

The evolution of the sociology of aging can be divided into three phases. The first phase perceived aging as a "role less roles", whereby older citizens withdrew from social roles and social interactions, in relation to diminishing biological, psychological, and social dimensions. The second phase replaced the concept of withdrawal by a new approach to aging, focusing on the continuation of activity in the older stage of life in order to develop a concept of successful aging. The third, and current, phase is focused on promoting older stages of life as active (activity theory), concentrated on the social participation of older citizens, physical activity, diet and other behaviors promoting health, and reducing the risk of disease (Tobiasz-Adamczyk, 2015). Structural functionalism, symbolic interactionism and conflict theory are three main theoretical frameworks that can be applied to the sociology of aging.

Functionalism

Talcott Parsons (1902–1979) is one of the founding fathers of sociology and theorized the relationship between patients and health professionals. Parsons was well known for introducing the concept of the "sick role". Sick role theory refers to the notion that an individual's response to illness is governed by a set of social expectations and responsibilities (Paul et al., 2001).

Parsons theorized that a person who experiences illness is deviating from normal social roles and responsibilities and is forced to rely on others. He argued that as long as individuals conformed to the conditions of the sick role then they were seen to be legitimately deviant. His famous four components of the sick role are:

1. Ill people are exempt from their normal social responsibilities such as work or domestic labor. This exemption requires some form of legitimation from doctors or those in medical authority.
2. They are not held responsible for their condition and cannot be expected to recover by an act of will.
3. Ill people must want to try to get well, if not, they can by accused of malingering.
4. Ill people are obliged to seek and cooperate with medical practitioners to help make themselves well again.

With regard to medicine taking, it can be assumed that pharmacists represent an important link by reinforcing the doctor's instructions through the supply of medicines and maintaining the ideology and values of the sick role (Van Der Geest and Whyte, 1989).

As conceived by Talcott Parsons, the functionalist perspective on health and medicine emphasizes that good health and effective medical care are essential for a society's ability to function. Poor medical care is likewise dysfunctional for society, as people who are ill face greater difficulty in becoming healthy and people who are healthy are more likely to become ill.

Parsons emphasized the importance of individuals' good health for society's health but his perspective has been criticized for several reasons. First, his idea of the sick role applies more to acute (short-term) illness than to chronic (long-term) illness. Although much of his discussion implies that a person temporarily enters a sick role and leaves it soon after following adequate medical care, older people with chronic illness can be locked into a sick role for a very long time or even permanently.

Although, the prominent theories of aging emphasize the involvement of older people in social activities and engagement in society, functionalists find that people with better resources who stay active in other roles adjust better to old age (Crosnoe and Elder, 2002). Older people, however, go through a period during which relationships can be affected due to retirement, decreased community involvement, and reduced social networks. Disengagement theory suggests that withdrawing from society and social relationships is a natural part of growing old. Older people are benefited because disengagement allows them to focus on the next era of their lives and society is benefited because it allows the next generation to take over societal roles, which supports societal stability. In this view, older adults become increasingly disengaged from society, have reduced social roles, and become socially isolated. Activity theory shows that older people who remain active are the happiest. This theory posits that society benefits from older people who continue to contribute and are accepted as valued members of society. From activity theory and the symbolic interactionist perspective, older people need to continue to be active, although their social roles may change. As opposed to being socially isolated, this view sees older people as continuing to be involved with others and often creating new networks. Critics of this theory point out that access to social opportunities and activity are not equally available to all and not all older people find fulfillment in the presence of others or in participating in activities.

Conflict Theory

Neither disengagement theory nor activity theory explain why the level or type of social interaction needs to change in old age. Critics of these theories say they fail to take into account the effects of social stratification and class on elderly people. Conflicts of interest and class divisions are key elements of conflict theory (Paul et al., 2002a). Research has found that individuals from the upper classes tend to have better health and be less likely to be dependent in their later years than are individuals from the lower classes. More affluent people typically have better or even greater access to health care, consistent access to food and medication, and can afford to have the help they need for necessary everyday activities than less affluent people. Conflict theorists also take a note of the age stratification that can be observed in society. Older people are often the victims of agism and unable to get jobs with the same income level as they had in their youth or are forced to live on a fixed income from social security or a pension. As a result, they are reduced in terms of social status. In general, conflict theorists see elders as victims of social stratification and capitalism.

Illness, diagnostics, and treatment are conceptualized as expressions of relations of power in society and unequal distribution of resources. The concept of professional dominance describes the superior power exercised by physicians in relation to other professions in the health services, a power that stems from the physician's legitimized right to define medical reality (Freidson, 1970). Freidson's conflict theory assumes that the doctor and the patient come from different social and cultural worlds.

Modernization theory suggests that the primary causes of elders losing power and influence in society are the result of industrialization and modernization (Cowgill and Homes, 1972). As the status of older people decreases, they are increasingly likely to experience social exclusion. Before industrialization, strong social norms bound the younger generation to care for their elders. As societies industrialize, however, the extended family is replaced by the nuclear family. As societies become increasingly individualistic, the norms regarding the care of older people change accordingly. Thus, the (voluntary) obligation of caring for an elderly family member is diminishing in both developed and developing nations. The presence of chronic illness, loss of a spouse and lack of income in the elderly can be seen as triple jeopardy. This theory suggests that as people age, family support, and care giving will eventually become a huge burden.

When asked about intergenerational relationships and family solidarity, parents usually rated their relationship as warmer and more cohesive than did their children (generational bias). The model of intergenerational solidarity in families identifies six dimensions of solidarity: affectual, associational, structural, consensual, functional, and normative. In addition, conflict, ambivalence in family relationships, and the role of stress have been used to provide a multidimensional theoretical explanation for the mistreatment of older people. Dependency, caused by health status and disability in older people associated with expected help, care and social support (like a "hospital at home"), triggers problems related to issues such as abusive behavior of carers (Tobiasz-Adamczyk, 2015).

The conflict approach also critiques the degree to which physicians try to control the practice of medicine and to define various social problems as medical conditions. On one hand, it is believed that physicians are the most qualified professionals to diagnose problems and determine treatment. On the other hand, it has also been recognized that physician's financial status will also improve if they succeed in characterizing social problems as medical problems and in monopolizing the treatment of these problems. This leads to the concept of medicalization. Once certain problems become "medicalized," possible social causes and the potential solutions are neglected.

Medicalization of Aging

Medicalization describes a process by which nonmedical problems become defined and treated as medical problems in terms of illness and disorders (Gabe et al., 2004). It can occur conceptually when medical vocabulary is used to define a problem, institutionally, when organizations adopt a medical approach to treating a problem in which they specialize, and at the level of practitioner–client interaction when a problem is defined as medical and medical treatment occurs (Conrad and Schneider, 1980). Medicalization causes an increase in the (1) consumption of pharmaceuticals, (2) use of new medical technologies, (3) frequency of visits to medical settings, (4) range and extent of medical services, (5) risk of iatrogenic disease, (6) influence of medicine in previously nonmedical domains, (7) level of health surveillance, and (8) media coverage of health and medical matters (Russel, 2009).

Pharmaceuticalization or the "translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention," often works in tandem with medicalization but it has potential to reach beyond it (Williams et al., 2011). The pharmaceutical industry is crucial to the creation and definition of disease through its dominance in clinical research and scholarly knowledge, direct-to-consumer advertising and lobbying power. The pharmaceuticalization of old age occurs through various mechanisms, including conditions such as osteoporosis, expanding the terrain covered by cognitive enhancement, the creation of completely new pathologies such as erectile dysfunction and by transforming normal life experiences into "undesirable" but "manageable" states, for example the menopause (Twigg, 2015).

The increasing medicalization of society is often viewed negatively (Moynihan et al., 2002). For Marxists, medicalization is seen as catering to the interests of the ruling capitalist class, whereby people are made dependent on medicine which is categorized as a consumer good propagated by that class (Gabe et al., 2004). Nevertheless, medicalization can be positive if it means some form of treatment can be offered. Redefining a condition as appropriate for medical attention opens up opportunities for the alleviation of symptoms or a cure and also legitimates the condition. It also helps to reduce the stigma associated with a particular condition (Gabe et al., 2004).

The expansion of the role of pharmaceuticals in defining life's problems has also been alternatively viewed as a "culture of liberation," in which individuals liberate themselves from undesirable social or biological forces (Twigg, 2015). This ultimately leads to a "culture of perfectibility" where people have the freedom and responsibility to pursue solutions to health problems, including the spiritual, emotional, and physical dynamics of life (Twigg, 2015). The growing population of affluent older people leads to greater expectations of medical care, fueled both by greater consumerism and the promotion of new medical technologies by doctors and the pharmaceutical industry. Aging individuals are bombarded with messages about how to use pharmaceuticals to alleviate disease, to manage risk and to function well. It is a trend for older people to demand cures for wrinkles, baldness, yellow teeth, and relief from symptoms of the menopause and andropause. Growing treatment options, such as botulinum toxin for the treatment of wrinkles, minoxidil for male pattern baldness, tooth whitening treatments, and hormone replacement therapy for women, are some of the examples of medicalization in the aging population (Ebrahim, 2002). Since these new pharmaceutical interventions are changing the norms of old age, it could be empowering to some people to be expected to live up to new expectations of virility and youth, while some might feel guilty for not managing their old age in the 'right" way. Hence, pharmaceuticalization of old age may make pharmaceutical consumption a "personal health responsibility." This particular "pharmaceutical imagination" views the world from a certain race, class, gender, sexuality, and age perspective, which could be oppressive to those who are marginalized.

In favor of the medicalization theory, it is argued that although aging is a natural process, it does not mean that the diseases that accompany it are also natural and should be excluded from medical attention. The aging process varies from one individual to another and it could cover a wide range of conditions and needs, from the fit to the frail. Various trials have shown the benefits of treating older people rather than ignoring their health problems. For example, evidence from trials of blood pressure lowering and statins show that older people are no different from younger people in their response to treatment but, because of their higher levels of risk, they might gain greater benefits from effective treatments. The availability of effective treatments for cataracts, hearing impairments, angina, osteoarthritis, impotence, depression, and other conditions should be an opportunity for the older population to enjoy better health care (Ebrahim, 2002).

Medicalization can also be seen as risky when legitimate concerns exist about the risks of infection during hospitalization, overprescribing, inappropriate use of tranquillisers for restraint, and the hazards of pressure sores. It has also been argued that hazards associated with medical care exist at any age: poor standards of practice and medical injuries can be prevented (Rothschild et al., 2000). Based on the potential benefits of treatment, attempts to ration medical care on the grounds of chronological age are unethical, as medicalization of aging can mean greater access to health care for older people, which could translate to reductions in mortality and disability (Ebrahim, 2002).

Symbolic Interactionism

Interactionists believe that social life can only be understood by exploring the "real-life" situations that people experience and which they believe to be meaningful (Paul et al., 2002b). The interactionist approach emphasizes that health and illness are merely social constructions whereby various physical and mental conditions have little or no objective reality but will be considered as healthy or unhealthy conditions if they are defined as such by society (Buckser, 2009).

Theories within the symbolic interactionist perspective focus on how society is created through the day-to-day interaction of individuals, as well as the way people perceive themselves and others based on cultural symbols. It assumes that if people develop a sense of identity through their social interactions, their sense of self is dependent on those interactions.

With regard to aging, symbolic interactionists stress that the changes associated with old age have no inherent meaning; however, the attitudes displayed toward the elderly are rooted in society. The symbolic interactionist approach is commonly used to study interactions between patients and health care professionals.

Symbolic interactionist, Erving Goffman, extensively studied the behavior of staff and patients in mental institutions. He noted that a mental hospital was not intrinsically a therapeutic environment: it was custodial, centered on eradicating the self-image and self-respect of residents. He argued that to understand the behavior of residents, it was better to construe them as psychologically normal rather than mentally ill. He blamed their behavior on the lack of privacy and the level of surveillance that they experienced. Goffman noticed the various techniques used by residents to maintain their self-respect, for example, they appeared to be obsessive about trivial objects. He tried to make sense of their behavior from the point of view of the residents under the conditions in which they were forced to live. He explained that residents were typically not allowed to have any access to trivial things such as string, tin foil, and toilet paper. In these circumstances, any trivial item becomes a desirable possession, and they are the items that other residents would steal, thus, the only safe place is to put them in their pocket. Goffman felt that rather than being irrational, the resident's behavior appeared to be rational in the circumstances. He concluded that when one attempts to see behavior sympathetically from the point of view of the individual displaying that behavior, then the assumptions of the observer can be questioned and such behavior can be seen as rational (Goffman, 1968).

Goffman's theory encouraged many researchers to explain how the structure of institutions for the elderly affects service-provider/resident interactions. For example, elders often experience negative effects in institutionalized settings, such as being infantilized. Research showed that a marked improvement in elderly people's verbal responses were seen when a competent caregiver left and was replaced by a social worker who used a different approach with the residents. Residents seemed more alert and less cognitively impaired in their interactions with staff and visitors. The only explanation was the difference in the caregivers' communication styles, since both were competent and caring staff members. The first caregiver spoke to the residents in a slow, sing-song voice using a child-like vocabulary in her attempt to be nurturing and comforting, whilst the caregiver who replaced her spoke to the residents with the same adult speech patterns she used with staff. It was surprising when some residents who had previously spoken very little or who had seemed to show signs of dementia started speaking and interacting in more normal ways. This observation sparked the interest to investigate whether infantilization can alter the responses of elders to their caregivers and, in turn, increase the risk of residents being labeled as cognitively incompetent (Marson and Powell, 2014).

Other issues within the scope of symbolic interactionism include the study of health beliefs, labeling, the role of culture in defining health and illness, and stigma, as well as compliance and concordance model which are also related to the domain of pharmacy practice (Paul et al., 2002b).

Conclusion

This chapter addresses issues pertaining to medicine use in older people from a sociological perspective. The growing aging population poses various challenges to the health care system due to the projected increase in the GBD. To improve the quality of life of older people, a holistic approach that integrates physical functioning, psychological well-being, and social well-being is crucial. Polypharmacy, adverse drug reactions, and nonadherence are common drug-related problem amongst older people with multi-morbidity. Nevertheless, medicine use is a social phenomenon that deals with real-world issues which are continuously changing and evolving. Functionalism, symbolic interactionism, conflict theory, medicalization and pharmaceuticalization of aging are examples of sociological theories that can inform pharmacy practice beyond the biomedical perspective.

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Who Are We?—The Evolving Professional Role and Identity of Pharmacists in the 21st Century

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Introduction

Pharmacy is in the midst of significant professional transformation. The profession once responsible for compounding and dispensing medication is looking to reposition itself as clinicians within the health-care system (Adamcik et al., 1986). A crucial element to the success of this transformation will be the ability of the profession to clearly form a clinician identity or way of "being," which can be clearly internalized by pharmacists and subsequently role modeled to pharmacy trainees in both classroom and workplace environments. Identity formation is a crucial part of becoming a professional (Cruess et al., 2016a; Goldie, 2012). According to Irby, it involves "expanding one's knowledge, understanding, and skilled performance; through engagement with other members of the professional community and by deepening one's commitment to the values and aspirations of the profession" (Irby, 2011).

Also identity formation is not static. It is a dynamic process, which occurs over time, often relying on student immersion into a community of practice (Cruess et al., 2016a; Irby, 2011). Much work has been done in the area of professional identity formation in the health professions arena, specifically in medicine. Moreover, medical educators have gone so far as to propose that identity formation should be the foundation of all medical curricula (Cruess et al., 2016a). A paper by Monrouxe suggests that the goal of medical education is as much about the development of a professional identity, as it is about gaining knowledge and skills (Monrouxe, 2010).

This increased attention to professional identity formation as a mandate for medical education has led to a significant increase in research and publications over the last several years. Pharmacy, on the other hand, has been under-studied in this domain, which is surprising considering it is an ancient profession (Beales and Austin, 2006). One reason that might contribute to the lack of research in this area in pharmacy is the ongoing questioning of its professional status (Denzin and Mettlin, 1968; Dingwall and Wilson, 1995). On the one hand, if pharmacy is not a profession, then why would one study its identity or how it is formed?

On the other hand, the lack of research might be because pharmacy is a relatively small, allied health profession, thus not as attractive to sociologists, compared to doctors, who draw more interest, prestige, and funding (Dingwall and Wilson, 1995). Regardless of the reason, there currently exists a paucity of literature in the area of professional identity in pharmacy. This chapter

will provide an overview of the evolving professional role of the pharmacist over the last century. It will explore the aforementioned professional status debate surrounding pharmacy and will look at the work that has been done in the area of professional identity formation and professional socialization to date. In addition, it will explore some of the key conversations and accompanying research on professional identity formation currently taking place in medicine, which may inform future research directions and curriculum design in pharmacy. This chapter will also explore the construct of professional identity in both pharmacy education and pharmacy practice—as one's professional identity formation begins during the education process, but is enacted and continues to evolve in practice settings over the course of one's career.

What Is a Profession?

What defines a profession has been a topic of interest for sociologists for close to a century (Bader et al., 2017). No single definition exists, yet most would agree professionals are afforded significant status in society, thus, they are interesting to study. Much of the early academic work on professions was uncritical, focusing on the role that professions played in society and the traits, which would allow professions to be discriminated from other occupations (Dingwall and Wilson, 1995; Traulsen and Bissell, 2004). Over time, the line of thinking shifted to a more critical lens, with a focus on how professions competed for status, wealth, and power within the market (Dingwall and Wilson, 1995). A paper by Traulsen and Bissell reviews some key theories of professions and the impact on the pharmacist (Traulsen and Bissell, 2004). The table below highlights some key individuals and theories noted in their paper, as well as others noted in the works of Bader et al. and MacDonald (Bader et al., 2017; MacDonald, 1995; Traulsen and Bissell, 2004). A complete review of the sociology of professions is beyond the scope of this chapter; however, some key references in this area are listed at the end of the chapter for those with a specific interest in this area.

The Professionalization of Pharmacy

The History of Pharmacy

The notion of pharmacy as an invisible profession, lacking an identity, seems incomprehensible, given the ancient origins and elite standing it once held (Beales and Austin, 2006; Charters et al., 1927; Kronus, 1976a,b). In the introduction to the *Basic Material for a Pharmaceutical Curriculum*, Charters states:

> Pharmacy is an ancient and honourable profession. Its beginnings are lost in the mists of antiquity and its history replete with substantial accomplishments. Pharmacy is the mother of medicine and the original source of many forms of research (Charters et al., 1927; p. 1).

The practice of pharmacy dates back to ancient Egypt, where evidence of the first prescriptions and "recipe" books are documented (Kronus, 1976a). Over centuries, the profession evolved, alongside medicine, with a clear role, identity, and professional status. It has been said that before the turn of the 20th century, "druggists in North America were closer to the public ear than the doctor and were increasingly sought for advice in therapeutic matters" (Muzzin et al., 1993, p. 381). Similar stories exist in Europe and other parts of the world. As time passed, however, and medicine became more formalized, the role of the pharmacist changed and pharmacists began to lose professional ground. During this time, the status of pharmacy relative to medicine began its decline (Kronus, 1976a). Societal changes in industrialization and health-care organization provide some explanation for this shift. The professionalization of pharmacy is set within the historical constructs that govern various practice models at different periods of time (Bader et al., 2017). In the 19th century, manufacturing, compounding, and distributing medications were key activities of practice (Bader et al., 2017; Hepler, 1987). By the early 1900s, however, pharmacy practice was essentially restricted to compounding and dispensing medications (Adamcik et al., 1986; Denzin and Mettlin, 1968). Then, with the advent of industrialization and large-scale manufacturing of medicines, pharmacists soon lost their social purpose as both compounders and distributors, leaving dispensing functions as their predominant role (Buereki, 1999; Hepler, 1987). Both internally and externally, this was viewed as another downgrading of the professional status (Adamcik et al., 1986; Bader et al., 2017; Beales and Austin, 2006). Despite pharmacists having complete occupational control over the activity of dispensing medications, it has always been seen as a "lesser" activity. Hepler notes in a 1987 paper, that as early as 1858, William Proctor was noted to have said:

> If the preparation of medicines is taken from the apothecary and he becomes merely the dispenser of them, his business is shorn of half its dignity and importance, and he relapses into a simple shopkeeper (Hepler, 1987, p. 370).

Because of the loss of jurisdiction over the majority of their professional roles over time, pharmacists have been in continuous search of new responsibilities and functions. As such, their professional status has been constantly questioned by pharmacists themselves and by other professions and members of the public. The debate continues today, and the search for legitimacy as professionals is currently embedded in the construct of pharmacist clinicians and the pharmaceutical care paradigm. The continuous shifting in professional roles contributes to role ambiguity and impacts the process of identity formation.

Is Pharmacy Really a Profession?

In a public address in 1915, Abraham Flexner challenged the professional status of pharmacy. Flexner, the man associated with medical education reform, gave a keynote address at a social work conference during which he asked the following question "Is pharmacy a profession?" He answered his own question as follows:

> The pharmacist compounds the physician's prescription, for which task he requires a considerable degree of expertness, a knowledge of certain sciences—especially chemistry and a high degree of caution, since either the slightest error on the part of the physician, whether due to ignorance or to carelessness, may have very serious consequences. Recurring to our criteria, I should say that pharmacy has definiteness of purpose, possesses a communicable technique, and derives at least part of its essential material from science.
>
> On the other hand, the activity is not predominantly intellectual in character and the responsibility is not original or primary. The physician thinks, decides, and orders; the pharmacist obeys—obeys, of course, with discretion, intelligence, and skill—yet in the end obeys and does not originate. Pharmacy, therefore, is an arm added to the medical profession, a special and distinctly higher form of handicraft, not a profession (Flexner, 1915, p. 582).

Sociologist, Harold Wilensky, later echoed this sentiment in a landmark paper entitled *The Professionalization of Everyone?* (Wilensky, 1964). In this paper, Wilensky describes the struggles that numerous occupations embark on, to achieve the authority and recognition of established professions such as medicine and law, noting that very few will be successful in achieving such authority and status. Wilensky classifies pharmacy as a marginal profession, auxiliary to medicine. In spite of pharmacy's heroic attempts to expand their professional status, they remain in the shadow of medicine based on power structures that are reinforced by both formal and informal societal structures (Wilensky, 1964).

Medical sociologists Denzin and Mettlin further explored this notion of pharmacy as a marginal or quasi-profession in their 1968 paper entitled *Incomplete Professionalization: The Case of Pharmacy* (Denzin and Mettlin, 1968). In contrast to Wilensky, however, they focused their work completely on pharmacy, dismissing it as a profession (Bader et al., 2017; Denzin and Mettlin, 1968; Muzzin et al., 1993). This paper is important, as it has provided much of the framework within which pharmacy has been examined as a sociological phenomenon over the last 50 years, in spite of the numerous ways in which the theories of professions have evolved since its publication (Dingwall and Wilson, 1955). It has had significant impact, as it contributes to the perpetuation of the discourse of pharmacy as an inferior profession.

In this paper, Denzin and Mettlin argued that pharmacy is an example of an ancient occupation, which has failed to maintain its prestigious title and is now commonly labeled as a quasi-profession. In essence, pharmacy has achieved "incomplete professionalization." That is, pharmacists have taken on a number of characteristics of a profession (trait theory), but they failed to overcome the marginality associated with professions, which still contain elements of an occupation (Denzin and Mettlin, 1968). The authors noted that although pharmacy took on many professional elements, such as the development of formalized institutions to transmit knowledge, codes of ethics, professional organizations, and the ability to self-govern, they never actually reached full professional status (Denzin and Mettlin, 1968). In their opinion, pharmacy lost its ability to maintain its status in many domains. Specifically, pharmacy failed to abide by the requirement of a profession that "you do not advertise." Similarly, they noted that pharmacists have failed to recruit truly committed persons who commit their lives to the altruistic goals and values of the profession. They have likewise failed to engage in long-term activities, which ensure their control over the social object around which their activities are organized—the drug. Furthermore, they have failed to accumulate a systematic body of scientific knowledge which can only be learned by socialization in their own institutions, and which is needed for the enactment of their professional role. Finally, due to the proliferation of subspecialties within the profession, pharmacy has failed to hold together a cohesive social organization, which exercises strict control over its members and ensures its perpetuation through time (Denzin and Mettlin, 1968). Denzin and Mettlin felt that the business aspect of retail pharmacy kept the profession caught between two dominant value orientations: business versus profession (Denzin and Mettlin, 1968; Kronus, 1975). This is important as business and service professions are commonly conceptualized as relying on different core values to attract and motivate members (Friedson, 1970; Kronus, 1975). Business offers more to individuals who value financial reward, whereas professions offer more to those who value altruism as the reward (Friedson, 1970). This tension creates a potential conflict when selecting individuals into pharmacy schools, designing pharmacy curricula and ultimately impacts on how pharmacists form their professional identity.

As noted, the Denzin and Mettlin paper is one of the most detailed sociological accounts of the professional status of pharmacy; however, it may no longer sufficiently explain the professional role of the pharmacist, since sociological theories have changed, as has the work of the pharmacist. In 1995, Robert Dingwall and Eileen Wilson undertook a study to explore whether pharmacy was really an incomplete profession (Dingwall and Wilson, 1995). Their paper challenged Denzin and Mettlin's claim of incomplete professionalization and went on to present the results of an ethnographic case study of a neighborhood pharmacist's work. This was an initial attempt to develop new theories around the role of the pharmacist and the nature of medicines. Dingwall and Wilson argued that Denzin and Mettlin's dismissal of pharmacy's claim to full professional status rested on two main grounds. First, it was the failure of pharmacy to meet criteria of the trait theory of professions (i.e., advertising, failure to recruit altruistic people, loss of control over the drug, failure to develop a unique body of knowledge, and failure to maintain occupational cohesion). Second, it was the failure of pharmacists to gain control of the social object of their work—the drug (Dingwall and Wilson, 1995).

Dingwall and Wilson challenged these grounds by comparing pharmacists to doctors and lawyers, the gold standards when discussing established professional status (Wilensky, 1964). They noted that lawyers advertise on a large scale without compromising their professional status. In a similar vein, service orientation is not necessarily in tension with the desire to maximize income, as

most self-employed doctors and lawyers are also concerned with marketing their services and making a profit. They suggested the comment that pharmacy fails to recruit students of altruistic nature is difficult to substantiate, as there is no comparative data to support or refute this claim. Of final note, although pharmacists do not have complete control over the social object of their work, it is not clear as to what extent other professions actually control this either and there is no evidence to suggest controlling the social object is a requirement of being a profession. As an example, lawyers do not control the creation of the law, but they have considerable influence over its interpretation and use. Much the same can be said for pharmacists. They do not control all aspects of the drug, but they have significant influence over its use. These criticisms overall reflected the general weaknesses of a trait-based approach to understanding professions. Overall, a key problem that Denzin and Mettlin faced is ultimately their lack of data on the everyday work of a pharmacist. Their analysis was based predominantly on surveys, attitude studies, and occupational propaganda, which did not provide a complete picture of the work pharmacists do (Dingwall and Wilson, 1995). Dingwall and Wilson set out to improve upon Denzin and Mettlin's conclusions by developing a program of ethnographic study of the different organizational conditions under which pharmaceutical services are delivered to examine their general propositions about the status and meaning of the social object and its control (Dingwall and Wilson, 1995).

Dingwall and Wilson carried out a study of participant observation over a six-week period in an independent retail pharmacy in the Southern United States in 1992. Over the course of their study, they found that a significant dimension of the pharmacist's work was related to the control and use of information. They observed that it was not the drug itself that was the social object but rather the passage of information around the drug that constituted it as a social object. From here, Dingwall and Wilson identified three aspects related to the use of information by pharmacists: (1) their knowledge about patients; (2) the advice given to patients about the use of drugs; and (3) their understanding of drug interactions and other adverse effects (Dingwall and Wilson, 1995). Dingwall and Wilson noted that pharmacists use information about patients, obtained from consultations and information in pharmacy computer systems to assess the nature of the patients' conduct with respect to medication use. The pharmacist mobilizes data to facilitate appropriate medication use. Patient counseling involves the giving of information to patients and this was noted as a significant area of autonomy in pharmacy work, as much counseling is patient initiated. This is in contrast to work that suggests pharmacists are just mediators between physicians and patients.

Lay people recognize pharmacists as an independent and authoritative source of expertise. Finally, there are cases where pharmacists take the initiative around information giving and most of these are around drug interactions and allergies, which the physicians were unaware of or overlooked in the course of prescribing. This role is important—the pharmacist is looking into the future and warns of hazards to come. Therefore, Dingwall and Wilson challenged Denzin and Mettlin's notion that the social object of pharmacy is the drug. Dingwall suggested that the social object of pharmacy is "the symbolic transformation of the inert chemical into the drug, which is itself a focus of actions designed to restore or limit the impact of disordered human biology on the order of society and everyday life" (Dingwall and Wilson, 1995, p. 125). In this respect, pharmacy plays a distinctive part in health care in modern society. All this being said, Dingwall and Wilson did not conclude that pharmacy is a profession because they have a distinct social object, but clearly, they refute the notion that it is incomplete. They suggested maybe we are asking the wrong questions—maybe a better question is what kind of occupation is pharmacy? This line of inquiry might lead to a deeper understanding of the profession.

Other Work in Professionalization of Pharmacy

Other research that has looked at the professional work of pharmacy includes that done by Carol Kronus. She took a specific look at the dominant value-orientation concept associated with professional status. She used pharmacy practice to test the theoretical model that business is based on pecuniary and extrinsic values, while service professions are predicated on altruistic values (Kronus, 1975). Kronus compared pharmacists with business role orientations (retail pharmacists) versus those favoring a professional role orientation (hospital pharmacists). The results of this paper were compelling, as they did not support the aforementioned theory that community pharmacists were business oriented and thus less altruistic. In fact, Kronus found that pharmacists, regardless of role orientation, were equally motivated by service and income values (Kronus, 1975). In addition, after controlling for work setting, altruism actually predominated in the business setting (Kronus, 1975). This paper was the first of its kind to challenge the notion that pharmacists working in retail settings are merely "entrepreneurs" thus not professionally oriented. This noteworthy outcome further complicates current notions of pharmacists' professional identities, as there is still significant stigma associated with being a retail pharmacist due to the business element of the role.

Another theory that has been explored in the professionalization of pharmacy is the concept of reprofessionalization. According to Birenbaum, the effort to upgrade the status of pharmacy in the health-care delivery system can be viewed as reprofessionalization (Birenbaum, 1982). Birenbaum claims this movement in pharmacy was a reaction to developments in technology, social organization, the division of labor, and financing of health-care services and pharmaceuticals (Birenbaum, 1982). It involved upgrading pharmacy into a clinical profession (Adamcik et al., 1986; Birenbaum, 1982). The clinical pharmacy movement was looking to change the knowledge, skill, and motivation of pharmacists and convince outsiders that pharmacists should be able to consult with patients and physicians. Reprofessionalization in pharmacy practice has been encouraged by structural changes in the organization and delivery of pharmaceutical services. Reprofessionalization can be seen as a collective response to occupational displacement. Structural changes driving the reprofessionalization include (1) the decline of the community pharmacy, (2) automation, (3) development of physician extenders, namely physician assistants and nurse practitioners, (4) new patterns of recruitment into pharmacy schools, and (5) communication among pharmacists. Although this reprofessionalization sounds attractive, it is unclear

how successful it has been since the professional status of pharmacy is still being challenged, and the clinical role has not been fully realized by the profession.

Is a New Conceptual Framework the Future?

Building on the notion of "reprofessionalization" and the need for health-care providers to evolve their professions, Bader and colleagues proposed the application of a conceptual framework composed of three interrelated professional sectors to uncover challenges in the advancement of the profession of pharmacy: education, regulation, and practice (Bader et al., 2017). The authors suggested that no unified approach currently exists as to what constitutes professionalization—or the process of becoming a profession and a framework could help identify current challenges or gaps in the process (Bader et al., 2017). The study was conducted in Jordan and used the Jordanian pharmacy environment as a case example. The original framework used in the study was developed by Rouse in his work with the Accreditation Council for Pharmacy Education (ACPE). The framework has been used for quality improvement purposes and to support the development of the pharmacy profession. It depicts the dynamic nature between education, regulation, and practice. A slight tension between the three sectors is desired to drive change and advancement. It is important, however, that the separation between the three sectors does not get too wide, as this creates a disconnect, which might lead to dissatisfaction or frustration within the profession. A proper push-pull fit between these professional domains is crucial not only to maintaining the integrity of the profession but also to advancing it (Bader et al., 2017).

In the study, Bader et al. conducted semi-structured interviews and focus groups with 53 key pharmacy informants in Jordan. First, interviews were conducted to identify challenges facing pharmacy in Jordan. This was followed by focus groups in which the same participants validated the interview findings and mapped the challenges against the conceptual framework designed by Rouse (Bader et al., 2017). The study identified eight major challenges spanning education, regulation, and practice: graduate preparedness for practice, the quality assurance and accreditation of pharmacy education, pharmacy preregistration requirements, workforce development, workforce planning, pharmacist remuneration, pharmacy assistants, and PharmD-trained pharmacists. These challenges were mapped to the conceptual framework to identify the sectorial disconnects, which could help to explain each challenge and lead to the identification of potential solutions. The authors concluded that the challenges identified were complex and could often be tracked to all sectors of the framework. The use of the framework highlighted the importance of multisector engagement from across the professional sectors when looking to design and implement solutions, as without collaboration, the gaps between the sectors get too wide, which can negatively affect the professional advancement of pharmacy. The findings of this study are interesting and could be applicable beyond Jordan, thus further work in this domain is warranted.

What Is Professional Identity?

In its simplest form, an identity is who we are and who we are seen to be (Monrouxe, 2010). A professional identity, therefore, is who we are in the context of our chosen profession. Professional identities develop alongside our personal identities, incorporating experiences from our personal, private, public, and professional selves into a meaningful whole (Cruess et al., 2016a,b). According to Monrouxe, these identities are rooted in language and interaction and are not fixed but rather are dynamic and constantly transforming (Monrouxe, 2010). Currently, there exists no universal definition of professional identity. From a medical lens, Cruess and colleagues define a physician's professional identity as a "representation of self, achieved in stages over time, during which the characteristics, values, and norms of the medical profession are internalized, resulting in an individual thinking, acting, and feeling like a physician" (Cruess et al., 2016a; p. 8).

This definition, although specific to physicians, highlights the dynamic nature of identity and can be applied to other health professions as well. A professional identity is important, as it is thought to facilitate the internal regulation of professionals, as well enabling confidence to practice (Monrouxe, 2010).

Identity Theory

The concept of identity has been an area of interest within social sciences for decades, but is relatively new in health professions, particularly pharmacy. Numerous theories, from a broad range of paradigms exist, which can be used to understand professional identity (Monrouxe, 2010). A detailed explanation of all theories is beyond the scope of this chapter; however, some key theoretical underpinnings are presented here.

Identities are complex and can be conceptualized in a number of ways. In *Teaching Medical Professionalism*, Monrouxe explored professional identities from various perspectives including individual theories, interactional theories, and institutional theories (Monrouxe, 2016). Individual identity theory is focused around the notion that identity is situated within an individual, constructed in one's mind. In these models, identity encompasses the embodied individual and their psychological-cognitive worlds (Monrouxe, 2016). Erik Erikson is a key theorist in this paradigm. Using a psychoanalytic approach, he proposed eight stages (psychosocial crisis) in which we pass from infancy to adulthood (Erikson, 1968). In contrast, interactional theories are rooted in social constructionism. Meaning that from this perspective, professional identities are coconstructed through language, artefacts, and action and are continuously renegotiated. This paradigm encourages one to understand the impact of discourse and role modeling on the development of professional identities. Institutional identity theories encompass how identities are located or

formed through institutions, often organizations in which we work and learn. These theories explore how organizational culture impacts identity. Therefore, identities can be understood from various perspectives, which can all help inform how we form professional identities.

Professional Identity Formation

Now that we have developed an understanding of what professional identities are, we can begin to explore how they are formed. Not surprisingly, this is a complex process, with no step-by-step guide available for use. In addition, there is no consensus around a definition across professions. In the medical arena, Jarvis-Selinger and colleagues describe the process of professional identity formation "as an adaptive developmental process that happens simultaneously at two levels: (1) at the level of the individual, which involves the psychological development of the person and (2) at the collective level, which involves the socialization of the person into appropriate roles and forms of participation in the community's work" (Jarvis-Selinger et al., 2012, p. 1185). This definition implies that when thinking about identity formation, one must consider the role of both individual and interactional theories of identity. At the individual level, there are distinct stages that one moves through to become a professional. In medicine, practitioners move from medical student to clerk to resident to physician. Each of these stages is associated with a new identity; therefore, individuals must move through a process of constructing and abandoning identities as they transition (Jarvis-Selinger et al., 2012). This is complicated, thus it is essential that educators understand these transitions to help students navigate the process successfully. In addition, social interaction is another key component of identify formation. Individuals, enroute to becoming professionals, join communities of practice in which their identities are forming based on participation in the work of the community. This interaction provides opportunity for strong socialization into these professional communities of practice, including its ways of being and acting (Jarvis-Selinger et al., 2012).

In the pharmacy arena, the American Association of Colleges of Pharmacy (AACP) Taskforce on Professional Identity Formation defined the process as "a transformative process of identifying and internalizing the ways of being and relating within a professional role" (AACP, 2014). The council went on to identify 10 factors or traits that play a role in this transformation/socialization and they are as follows:

1. Knowledge and skills of a profession
2. Commitment to self-improvement of skills and knowledge
3. Service orientation
4. Pride in the profession
5. Covenantal relationship with the client
6. Creativity and innovation
7. Conscience and trustworthiness
8. Accountability for his/her work
9. Ethically sound decision making
10. Leadership

Overall, the definition proposed by AACP reflected the dynamic nature of professional identity formation and the importance of "being" a professional, as opposed to merely acting professionally. That said, the identification of factors (with no clear definitions) seemed to be an attempt to reduce the complexity of professional identity into a checklist exercise that can be implemented in curricula and observed for assessment purposes. The list of factors seemed to be better aligned with the notion of professionalism versus professional identity (Von Hoff, 2017). Professionalism is a term used to describe the behaviors of a professional, thus, "what one does" (Cruess et al., 2016a). Professional identity on the other hand is "what one is" and includes many dimensions beyond behaviors. Pharmacy might benefit from the work occurring in medicine, to further refine professional identity, and the process of formation in pharmacy education and practice. Overall, forming a professional identity is important, as it has been shown to provide a sense of worth, belonging, or purpose (Dawodu and Rutter, 2016); hence, further research in this area is needed to better understand it in the context of health professions, and specifically pharmacy.

Professional Identity—The Role of Higher Education

As previously noted, to be a professional requires one to construct an identity to fit into the desired professional world or community of practice. The role of professional education then, is to help students or novice practitioners to construct these identities (Ronfeldt and Grossman, 2008). During the educational process, students negotiate images of themselves as professionals, based on input and images reflected to them during their programs (Ronfeldt and Grossman, 2008). This is a complex process, as alongside professional identity formation, students must also negotiate their personal identity within the context of their developing professional role (Ronfeldt and Grossman, 2008; Von Hoff, 2017). Currently, there is pressure for universities to produce graduates who are 'work-ready'. What this actually means, is that universities need to generate students who display mastery of knowledge and skill; competency in applying such knowledge and skill in complex work environments; and professional temperaments that nurture

ethical and reflective practice (Trede et al., 2012). Going a step further into health professional education specifically, this means students must graduate with an understanding of their professional roles, clinical responsibilities, workplace culture and societal role. This is no small undertaking for universities and professional programs. It reinforces the need for professional faculties to have a clear understanding of the identities they want to foster in their learners and how they will do so through both the formal and informal curricula.

A recent literature review on the development of professional identities in the higher education literature illustrates that forming a professional identity is a multifaceted process that goes beyond technical skills and interpersonal skills alone (Trede et al., 2012). Identity development must also include professional judgment, self-reflection, and self-directed learning (Trede et al., 2012). This illustrates the importance of research in this area, specific to pharmacy, to better understand what is required to form patient-centered clinical identities. The ability to generate pharmacy specific data will enable informed curriculum design and professional training in the future. The transition from student to novice to expert is difficult and, if left to occur naturally, might lead to disillusionment and issues with retention in the profession (Ronfeldt and Grossman, 2008). In addition to the above, professional socialization processes during education and training are critically important to identity development, as is workplace placements (Trede et al., 2012). Therefore, there is little doubt that universities and professional programs play a significant role in identity formation, though how much is intentionally designed versus being left to chance is debatable. What is clear though is that numerous opportunities exist for professional education to contribute to the formation of professional identities.

Professional Identity—Pharmacy Education

There has been a significant philosophical shift in health professional education recently: a shift from teaching professionalism to supporting professional identity formation (Cruess et al., 2016a). The idea of professional identity, however, is not new. According to Cruess et al., Merton published one of the first studies of the sociology of medical education in 1957 (Cruess et al., 2016a). In this work, Merton stated that "medical education has a dual purpose: to shape the novice into the effective practitioner of medicine, to give him the best available knowledge and skills, and to provide him with a professional identity so that he comes to think, act, and feel like a physician" (Merton, 1957, p. 5). In addition, Cruess and colleagues stated that, "if medical education is to be reframed around the concept of professional identity formation, the definitions of identity, professional identity, and professional identity formation become foundational elements of any education program" (Cruess et al., 2016a, p. 7). This is of particular importance to all health professions, including pharmacy whose professional practice is currently undergoing significant change. Having clear definitions of the concepts of professional identity in pharmacy education is crucial, as they are the cornerstones of contemporary curriculum design and student socialization processes.

The formation of professional identities is important to enable students to transition from university life to work life (Noble et al., 2014a). It plays an important role in helping novice practitioners cope with uncertainty and build confidence, in addition to providing frameworks for professional work (Noble et al., 2014a). Currently, there is a paucity of literature on professional identity and professional identity formation in pharmacy education and practice (Dawodu and Rutter, 2016; Noble et al., 2014a). It is difficult to articulate the identity of contemporary pharmacists, which contributes to role ambiguity for both the profession and society. A commentary by Dawodu and Rutter argued that the change to mass production of medicines by the pharmaceutical industry has eroded the status that was once afforded to the profession (Dawodu and Rutter, 2016). Because of this change of function, pharmacists have been searching for new roles that go beyond the dispensing of medications.

> Current pharmacy leaders are advocating for the pharmacist as medication expert, a clinical role committed to maximizing the use of medications for individual patients, thus contributing to improving patients' health outcomes (Dawodu and Rutter, 2016, AFPC Educational Outcomes, 2017). This lack of identity creates problems in education and practice, as pharmacists do not have a clear sense of who they are and what they stand for. There is currently a lack of consensus to clearly articulate the professional identity of a pharmacist. Dawodu and Rutter state: Incoherent, confused and mixed messages conveyed by the profession (about what we are) are hindering professional socialisation and consequently the ability of future pharmacists and qualified pharmacists to gain a sense of true professional identity (Dawodu and Rutter, 2016, p. 2).

A thought-provoking piece by Morison and O'Boyle reinforced this professional identity crisis. It compared first-year nursing, medical, dental, and pharmacy students' perceptions of the professional identity of their respective discipline (Morison and O'Boyle, 2007). The results illustrated that medicine and nursing students had a strong belief and commitment to their professional identity at the outset of training and high intrinsic motivation to join their professional group. Pharmacy and dental students, on the other hand, were motivated in terms of less personal factors such as good working conditions and good salaries (Morison and O'Boyle, 2007). Pharmacy students actually struggled to identify roles that made their profession distinct. Also of note in this study was that nursing and medical students had clear ideas about what it means to belong to their profession but pharmacy and dental students struggled to describe this, resorting instead to explaining their identities by how they differed from medicine. Pharmacy and dental students had a stronger grasp of a doctor's role, than of their own respective future professional role. This is problematic as evidence suggests that pharmacy students enter working life without a strong sense of professional identity and hold negative opinions of the profession. Overall, this literature reinforces the need for pharmacy educators to revise curriculum to include clear attempts to facilitate 21st century pharmacist identity formation. There is a significant role for pharmacy educators to shape student views on what it is to be a pharmacist, and this should not be taken lightly.

Professional Identity—The Role of the Curriculum

If the goal of health professions education in the 21st century is professional identity formation, then the curriculum must support this process. This has major implications for curricular design such as the creation of new educational outcomes, methods to engage and support students through the process, development of educational activities that promote professional identity formation, methods to assess progress toward a professional identity, and faculty development (Cruess et al., 2016a). Currently, there is a lack of literature outlining how professional identity can be supported throughout the continuum of professional education; however, there are studies, including some specific to pharmacy, that explore various curricular activities and their impact on identity formation.

In professional education programs, some key factors influencing students' professional identity are (1) opportunities for imagination, (2) observation, (3) experimentation, and (4) evaluation (Noble et al., 2014a). Taking this into account, pharmacy curriculum then needs to include learning opportunities where connections are made for students between what is being taught and the implications for future practice, so they can imagine their future selves. In addition, curriculum needs to provide opportunities for students to observe role models in action and to experiment with being a professional themselves through activities that are authentic approximations of practice. Finally, there needs to be opportunities for students to evaluate their learning experiences (Noble et al., 2014a).

With these factors in mind, Noble and colleagues undertook an ethnographic study to examine the student experience of the formal pharmacy curriculum at a large research focused Australian university. The study used sociocultural learning theory as a theoretical framework to understand how the formal curriculum experience supports students' professional identity formation. The researchers examined a typical week for a pharmacy student in each year of study. All of the formal curricular experiences were examined, as it has been found that all aspects of professional education, not just the practice related aspects contribute to students' formation of their professional identities (Noble et al., 2014a). The study data were analyzed for themes based on an a priori framework for student professional identity formation (1) opportunities to imagine being a pharmacist; (2) observing what it might be like to be a pharmacist; (3) experimenting with being a pharmacist; and (4) evaluating the experience of being a pharmacist. Overall, there were significant opportunities for students to imagine being pharmacists in the curriculum; however, there were few observed instances where explicit connections between the content being presented and practice were made. This presented challenges to the students who indicated they struggled to establish meaning from the presented content.

During the study, students tended to observe academics and tutors in educator roles rather than enacting pharmacist roles, which meant students had to imagine for themselves what the pharmacist's role might be like or how the educator may actually practice. This is problematic, as for successful identity formation, expert role models are needed.

The key opportunities for students to experiment with their professional identities occurred during tutorials and laboratory practicums. Despite the intended patient-centeredness of these activities, there was an absence of patients and when the students role-played being patients they lacked authenticity. This approach encouraged information provision rather than patient engagement, and there was a focus on the assessment checklist. As such, students were not afforded opportunities to develop their own way of doing things. As a result, the observed ways that students engaged with the counseling and dispensing tutorials tended to mechanistic. Rather than presenting the curricular experience as an opportunity to experiment with provisional pharmacist identities, the direction toward assessment seemed to reinforce student identities and provided limited opportunities to experiment with being pharmacists.

Finally, students were rarely prompted to examine how their learning experiences related to their future pharmacist selves. In other words, they were not asked to consider what types of pharmacists they would like to be. In a number of instances, students were upset that they could not see how what they were learning related to their future roles.

This study begins to address an important gap in pharmacy practice and education research. Overall, from the perspective of professional identity formation, the curriculum may not be enabling students to construct strong patient-centered professional identities. This creates opportunities for pharmacy educators to consider how the curriculum promotes professional identity formation and redesign it with more emphasis on patient-centeredness, making connections to practice, pharmacist role modeling, and opportunities to experiment and a curriculum that supports feedback.

In addition to the above study, Noble and colleagues also used focus groups comprising 82 students representing each year of the 4-year curriculum at the same Australian university (Noble et al., 2014b). The study explored students' perceptions of their overall curricular experience and examined how these experiences influenced the construction of their professional identities. Overall, the authors found that the students struggled with professional identity formation. Many were entering the degree with little understanding of what being a pharmacist entailed and many did not actually desire to become a pharmacist. Many students saw pharmacy as a gateway to other professions, such as medicine, which contributed to a lack of a sense of professional identity (Noble et al., 2014b). Once in the curriculum, the role of the pharmacist became clearer, but it was very idealistic, and the students felt that it was not enacted. Students experienced a disconnect between the idealistic notion of pharmacy practice shared in the curriculum with the realities of practice experienced during experiential rotations and work placements. The struggle left the students feeling that the role of the pharmacist was constrained and limited. Overall, this study highlights the importance of support of professional identity formation immediately from the point of entry. Students need to be supported through the process of learning to "be" a pharmacist, particularly as they transition through different learning and practice environments. More research in this area is needed to further understand how to support students through the process.

Other Curricular Activities—Teaching Methods

To best support professional identity formation in the curriculum, evidence informed pedagogic strategies and teaching methodologies must be used. There is evidence to support the use of reflection/reflective writing, clinical and professional experiences, mentoring, learning communities, and interprofessional experiences (Holden et al., 2016). There are limited data specifically exploring teaching methodologies; however, there are some studies which have looked at the use of group work and problem-based learning (PBL) and their impact on professional identity formation. A brief review of these studies is provided.

As previously noted, professional identity formation is not static but rather constantly undergoing reformation. This relies significantly on social and relational factors between faculty, students, practice environments, and courses (Bridges, 2018). Group work is a common pedagogical strategy used in pharmacy education, which draws on social aspects of learning and is thought to be a means to develop collaboration, teamwork, leadership and as a way to enhance students' intellectual, personal, and professional development (Bridges, 2018). A recent study aimed to explore the potential of mutual learning through group work to contribute to not only academic knowledge and understanding but also to the development of students' professional values and selves. The study was conducted in the United Kingdom. Overall, the study found that the opportunity for group work and collaboration can positively influence development of students' professional outlook and values; however, careful management of group working is required to create a mutually supportive environment where students feel able to interact, share, and develop together.

Another study by Tan et al. (2016) looked specifically at problem-based learning and how it contributes to students' professional identity development. PBL originated in medical education but has expanded and is used in many other areas of professional education. It has been suggested as a useful strategy to support professional identity formation. For their study, Tan et al. applied a comprehensive professional identity framework (professional identity five-factor scale or PIFF) to PBL pedagogy at a polytechnic in Singapore that prepares students in a wide range of professions. The study aimed to gain insight into how PBL was incorporated into the dimensions of (1) knowledge about professional practices, (2) having the professional as a role model, (3) experience with the profession, (4) preference for a particular profession, and (5) professional self-efficacy (Tan et al., 2016). They obtained data from 709 students and 6 educator-practitioners. The students provided descriptions of significant influences that helped them understand what it meant to work in their chosen professions and the educator-practitioners provided information regarding their preferred teaching approaches that were influenced by their professional journeys. Overall, the authors found that from the student perspective PBL does not feature in the dimension "experience with the profession," but it did impact identity formation in the other four dimensions. From the educators-practitioners perspective, PBL was important in self-efficacy and preference for a particular profession but only in the context of aerospace engineering (Tan et al., 2016). For most educator-practitioners, however, PBL was not their preferred teaching approach to prepare students for work. Overall, the authors found that to comprehensively promote professional identity development, PBL has to include experience with the profession in some way and this can be challenging.

Other Curricular Work—Assessment Practices

Assessment is a central component to education, as emphasized in the age-old statement "assessment drives learning." Assessments are the mechanisms by which educators and professional stakeholders are assured learners have met educational outcomes and minimum standards for professional practice (Norcini and Shea, 2016). For students it offers guidance to areas of strength and weakness in their professional development. There is an abundance of literature on assessment practices in health professional education, specifically aimed at determining what students know and how well they perform (Norcini and Shea, 2016). In contrast, there is much less evidence to support the assessment of what a student "is" (Norcini and Shea, 2016). Debate exists as to how professional identity can be assessed and maybe more importantly, if it should be assessed? Significant challenges exist in the assessment of "being," particularly with respect to the lack of clear definitions of professional identity and how it is formed. Recent work by Cruess et al. proposed amending Miller's Pyramid to include professional identity formation (Cruess et al., 2016b). The author's proposed that a fifth level be added at the apex of the pyramid, to reflect the presence of a professional identity and that this level be named "is" (Cruess et al., 2016b). Recall, each level of Miller's pyramid is associated with structured methods of assessment. The levels are "Knows," "Knows how," "Shows How," "Does," and now potentially "Is". Amending Miller's pyramid will have significant teaching implications, as this new level will require changes in what is being taught to students, as well as the development of appropriate tools to assess identity formation. More work is needed in this area; however, it is important to consider assessment if professional identity formation is a mandate of health professions and more specifically, pharmacy education.

Professional Socialization—Pharmacy Education

Professional socialization is a term used frequently in health professional literature to describe social processes associated with becoming a professional. Similar to professional identity formation, there is no universal theory of socialization; hence, it is used in various ways in the literature and often vaguely (Hafferty, 2016). According to Fred Hafferty, "socialization fundamentally involves training for self-image and identity" (Hafferty, 2016). This implies that the underlying dimension of all socialization processes is personal transformation, not merely changing behaviors and attitudes to align with professional roles—identity transformation is not merely situational adjustment (Hafferty, 2016). The core element of socialization is adopting a collective sense of what it means to be an in-group member versus out-of-group member. The process of socialization is impacted by formal,

informal, and hidden curricula; hence, curricular design must be intentional to reinforce development of the type of health professionals we wish to produce.

Historically, learning how to be a pharmacist involved an apprenticeship model. An aspiring apothecary (pharmacist) would work alongside an established practitioner and learn the skills required to practice (Buereki, 1999). In this way, pharmacists were socialized to their role by a "master" of the profession (Buereki, 1999). Over time, pharmacists came together in formalized colleges and universities for education and training purposes. For example, the first schools of pharmacy in the United States, United Kingdom (UK), and Canada opened in 1821, 1842, and 1882, respectively. By the mid-1940s, baccalaureate degrees in pharmacy were standard. During this time, the pharmacy curriculum was heavily rooted in chemistry, preparing pharmacists to formulate and dispense medications. Over time, however, the basic science and chemistry focus of the curriculum shifted to be more rooted in biology with an emphasis on pharmacology by the 1960s. The 1970s saw the beginning of the clinical pharmacy era and the 1990s marked the birth of the pharmaceutical care era in pharmacy education (Buereki, 1999). With each curriculum shift over the last century, the role of the pharmacist is assumed to have evolved, moving away from that of dispensing and information gathering, toward clinical decision making and the pharmaceutical needs of the patient (Anderson, 2002; Frankel et al., 2014). The most recent significant curricular transition from Bachelor of Science in Pharmacy (BScPhm) programs to entry-level (undergraduate) Doctor of Pharmacy (PharmD) programs across North America, and Master of Pharmacy (MPharm) programs across the United Kingdom and other parts of Europe, is designed to emphasize the evolving roles of the pharmacist, specifically in the patient care domain (Austin and Ensom, 2008; Sosabowski and Gard, 2008; Waite et al., 2006). However, in spite of these changes to the degree designations and curricular content, there is no evidence to suggest that pharmacy educators themselves have internalized the new roles and identities they are expected to teach. Many pharmacy educators and mentors harbor pharmacist identity constructs of the past. Therefore, in spite of curricular changes, pharmacy education continues to socialize students to dispensing and scientist orientations. To be successful in constructing a new identity for pharmacists in the 21st century, new socialization processes must take root. A significant challenge to developing this new clinician identity in pharmacy education and training is the unwillingness of practicing pharmacists to accept increased professional responsibility and accountability for patient care (Frankel et al., 2014; Rosenthal et al., 2010).

The aforementioned challenges infer that additional work is needed to better understand pharmacy identity formation during formal and informal pharmacy education. As previously mentioned, literature suggests that practising pharmacists struggle to articulate a clinical pharmacist identity (Elvey et al., 2013; Frankel and Austin, 2013). This is problematic, as these practising pharmacists become teachers and mentors in the workplace to large numbers of pharmacy students during clinical rotations and work experiences. This practice exposure has significant impact on the pharmacy learner's developing professional identity and might inhibit growth of the clinician identity that was forming during in-class experiences.

A study from Australia specifically examined professional socialization in pharmacy education (Kritikos et al., 2003). The authors set out to explore pharmacy students' perception of their profession relative to 10 other health-care professions. The results revealed that pharmacy students perceived community and hospital pharmacists to be similar in power and status, but significantly lower in status than physicians, dentists, and physiotherapists. This study highlights the notion that pharmacy students' lack a clear identity during pharmacy school but have strong beliefs that they are professionally inferior to other health disciplines, namely, medicine. This is another area that the profession needs to tackle if pharmacists are to be viewed as equally contributing members of the health-care team.

Another paper by van Huyssteen and Bheekie examined professional identity development specifically in first-year students. The authors identified and described first-year pharmacy students' professional identity and explored whether it changed during the first semester "introduction to pharmacy" course.

For this study, the students wrote three sequential reflective reports in which they were expected to identify critical experiences since their enrolment. The authors analyzed student reports for themes. The early reports indicated that students had stereotypical views of pharmacists as medicine suppliers. Subsequent reports, however, showed a shift in perspective, as students articulated a more complex role for the pharmacist and formulated the pharmacists' value for society. The findings showed that students developed an increasing sense of belonging to the pharmacy profession as they moved through the introductory course. It would be interesting to repeat a similar study in subsequent years of the program, to determine if the professional identity of students changes. There is work to suggest that pharmacy students professional identity might shift and become more negative as they move through the program (Knapp and Knapp, 1968) suggesting that informal and hidden curriculum content might impact identity formation in a negative way and more strongly than formal curriculum content. Further work in this area is needed to better understand the evolution of professional identity formation throughout the pharmacy curriculum.

Additional work by Carol Kronus examined the impact of formal education in pharmacy on the formation of professional identity versus workplace impact (Kronus, 1976b). She was curious to know if the roles that pharmacists were socialized to during formal education remained consistent as pharmacists entered the workplace or if pharmacists were resocialized to, different role orientations as work commenced. Pharmacy practice is characterized by diverse values and work settings; however, the education and training process is quite standardized. As such, Kronus rightfully identifies pharmacy as being ideal to test two models of influence: (1) the professional model that posits that occupational members retain a stable identity established via their socialization experience during education versus and (2) the situation model, which emphasizes the resocializing pressures of the work situation (Kronus, 1976b). The results of this study indicate that professional identity formation in pharmacy is more strongly influenced by the work setting compared to the education setting. She suggests that the notion of long-lasting professional identity only works in situations where occupations have more power than other occupations, clients and governments, which is not the case

for pharmacy as it is considered a weak profession, particularly compared to medicine (Kronus, 1976a,b). This study is of particular importance when one begins to think of professional identity and the potential for experiential placements to impact professional socialization. It is very important for pharmacy educators and schools of pharmacy to select the sites for workplace placements very carefully—to ensure the sites are modeling the identity characteristics consistent with the formal, didactic education. Very little literature exists in pharmacy looking at the impact of experiential education and professional identity formation. This topic will be explored in more detail later in this chapter.

Development of professional behavior and attitudes in pharmacy students is an important professional outcome. In spite of this, there seems to be a lack of structure or clear framework in pharmacy curricula related to professional socialization of our pharmacy students (Kelley et al., 2009). A paper by Kelley and colleagues set out to determine if pharmacy educators have the right formula for successful professional socialization. The paper drew on literature in higher education that showed that student engagement leads to positive learning outcomes, as well as character development. With this in mind, Kelley and colleagues compared strategies used by undergraduate first-year experiences (FYE) programs to enhance student engagement with approaches used by professional doctoral programs to improve professionalism (Kelley et al., 2009). The study was conducted in six US universities with pharmacy schools. The study found that both FYE and professional programs used orientation programs, course work, and student codes of conduct to develop character or professionalism, respectively. The FYE programs included more reflective writing activities, peer mentoring, and diversity activities than professional schools. The study concluded that the undergraduate FYE is a useful framework for developing professional attitudes and behaviors in pharmacy students. The authors go on to recommend the following to pharmacy education: (1) incorporating professionalism development into program mission statements; (2) communicating the importance of developing professionalism to students; (3) offering activities aimed at professional development; and (4) engaging students fully in these activities.

Professional Identity and Experiential Learning

Experiential learning is a common component for most modern health professional education programs. Pharmacy is no exception, with many programs expanding the number of weeks students spend learning in workplace environments. With the movement to entry level of doctor of pharmacy programs across North America, students are required to complete experiential rotations after each year of professional study, with the entire fourth year of the program being experiential in nature. In many schools, students are spending upward of 40 weeks in experiential learning environments. This shift in experiential learning is important when it comes to professional identity formation, as students will incorporate these experiences into their developing identities. These rotations have the potential to enhance identity formation or potentially inhibit it. There are numerous definitions of experiential learning; however, a good one by Yardley and colleagues states that experiential learning involves "constructing knowledge and meaning from real life experience" (Yardley et al., 2012). The key to experiential learning is reflection. Similar to other areas, there is limited evidence regarding the impact of experiential learning in pharmacy on professional identity formation. A 2016 paper in the American Journal of Pharmaceutical Education (AJPE) examined the extent to which reflective essays written by graduating students revealed professional identity formation and self-authorship development (Johnson and Chauvin, 2016). After a six-week advanced pharmacy practice experience (APPE) in which the students were exposed to a model of self-authorship development they completed a culminating reflective essay on their rotation experiences and professional identity formation. The essays were then thematically analyzed. The results indicated that a relationship existed between self-authorship and pharmacist professional identity formation. This study suggests that purposeful structuring of experiential rotations can facilitate professional identity formation and is an opportunity for pharmacy educators to impact student growth and development in this domain. More work is needed to further understand how to structure rotations to maximize the potential for professional identity development in students.

Professional Identity—Pharmacy Practice

Currently, the profession of pharmacy is still considered to be in transition, still seeking out professional legitimacy as clinicians. The modern day paradigm of pharmacy practice is pharmaceutical care. Pharmaceutical care is a patient-centered philosophy, in which the focus of attention is optimizing medication outcomes for individual patients (Anderson, 2002; Cipolle et al., 2012). Increasingly, pharmacy curricula across the globe have been revised to incorporate a patient-centered approach as a foundation. Yet, in spite of the strong movement toward the pharmacist clinician, this identity is still not widely accepted by pharmacists themselves nor among other health-care providers. A recent paper by Elvey and colleagues examined how pharmacists in England perceive their professional identity. The study identified the presence of nine separate identities for pharmacists. Of the nine, the strongest identities were that of scientist and medicine maker (Elvey et al., 2013). The identity of clinical practitioner was overshadowed by those of businessperson, manager, and medicine supplier (Elvey et al., 2013). These multiple identities might reflect the continued role ambiguity, inadequate socialization processes during education and training, and lack of clear professional direction (Elvey et al., 2013). The study also reinforces a clear need to understand what should define a pharmacists' identity in the 21st century from the beginning of education and training and into the workplace. As noted, professional identity formation begins during ones' professional education; however, it continues to evolve as individuals begin to practice.

Further to the Elvey et al. study, a Canadian study by Pottie and colleagues explored pharmacist's identity development within multidisciplinary primary health-care teams (Pottie et al., 2009). The study analyzed narrative reports from 63 pharmacists over a 9-month integration period. The study found that pharmacists' integration into team-based primary health care provided both challenges and opportunities. Pharmacists' professional identities evolved in relation to valued role models, emerging practice-level opportunities, and their patient related contributions. Overall, setting, skills, perspectives, and mentorship factored into identity formation. This study is important as it suggests that pharmacists' professional identities require further transformation depending on practice type, thus reinforcing the transforming nature of identities over time.

The Future: Where are we Heading?

Pharmacy is in the midst of yet another professional transformation, to the role of clinician. Trends in pharmacy curricula across the globe suggest an increase in clinical therapeutics courses, pharmacy skills labs, and experiential rotations contrasted against a decrease in basic science courses and dispensing and compounding labs, with the intention of creating clinicians. If pharmacy is going to be truly successful in achieving clinician status; however, it must go beyond curricular content change and make professional identity formation an explicit curricular objective. This means that pharmacy educators must define the desired patient-centered pharmacist identity and purposefully design the curriculum to include teaching and assessment practices that will support the development of the desired identity. The formal curriculum will need to include significant time for reflection so learners can consciously factor patient-centered culture into their way of being. In addition, pharmacy will need to invest in significant faculty development. If the identity of the profession is going to change, it will require strong faculty leadership. Faculty members will need to be educated in professional identity formation and pedagogical practices that support it. In addition to core faculty, pharmacy will also need to work with pharmacist preceptors and role models to ensure they are supporting the formation of the clinician identity. Pharmacists who have responsibilities to mentor and assess students during rotations must provide positive clinical experiences for students. These individuals with teaching responsibilities should receive education and development similar to faculty members and their performance should be assessed regularly with validated tools. If not adequate, they should be remediated and/or removed from teaching. Finally, pharmacy would benefit significantly from more research in this area. The data available currently are sporadic, but the profession needs approaches that are more systematic.

Conclusions

Pharmacy has undergone significant professional transformations over the last century in both practice and education. These changes have impacted how pharmacists and pharmacy educators understand their professional identities. With the current movement in health professional education to make professional identity formation, the main goal of professional programs, pharmacy is well situated to develop a program of research in this area to inform curricular design and future educational reform.

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Counterfeit Medicines: A Quick Review on Crime Against Humanity

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Introduction

People's lives and public health depend on effective and quality legitimate medicines. There are two types in the market: proprietary medicines and generic medicines (Liu and Lundin, 2016). Generic medicines are also known as nonproprietary medicines, while the proprietary medicines are brand-name medicines. The proprietary medicines is produced, marketed, or used under exclusive legal right of the inventor or manufacturer (Law Insider, 2018), while generic medicines are medicines that are no longer under patent protection and may be produced by any manufacturers.

People's healthcare is mainly in need of essential medicines for prevention and treatment of illness, slowing down the disease process, reducing suffering and rehabilitation. Unfortunately, individuals especially in the low- and middle-income countries (LMICs) lack access to effective and quality medicines (Leisinger et al., 2012); most of the reasons for mortality, morbidity, and disability could be prevented or treated with medicines, and individuals are not just neglected and deprived from getting these medicines but are exposed to illegitimate medicines such as counterfeit medicines (also referred to as fake, spurious, or falsified medicines; sometimes the abbreviation SSFFC (substandard/spurious/falsely labeled/falsified/counterfeit) is used.

Definition

The Australian Therapeutic Goods and Administration (TGA) defines counterfeit medicines as imitation goods which are packaged to look like genuine items (TGA, 2015). Products are considered counterfeit if they are falsely manufactured, packaged, or advertised. According to the US FDA (Food & Drug Administration), counterfeit medicine is fake medicine, sometimes called falsified pharmaceutical products or different other terms (US FDA, 2016). The MEDICRIME convention (Council of Europe, 2011: Article 4j) defines the term counterfeit as "a false representation as regards identity and/or source". According to the Pharmaceutical Security Institute (PSI), "counterfeit medicines are products deliberately and fraudulently produced and/or mislabeled with respect to identity and/or source to make it appear to be a genuine product" (PSI, 2018a). In 2017, the term "falsified" was accepted by the members at the Seventieth World Health Assembly as a more acceptable term and clearly understood for future work (WHO, 2017a, 2017c). Different organizations, stakeholders (from lay people to policymakers), and countries have defined the word "counterfeit medicines" differently and this can cause confusion. According to the new term, falsified medical products are defined as "medical products that deliberately/fraudulently misrepresent their identity, composition or source." This chapter will use the term "falsified medicines" throughout. The term "counterfeiting" is meant in its broadest sense of "falsification."

Falsified medicines may be comprised of incorrect ingredient, without active ingredient, with harmful substances, with active ingredient, but with the wrong amount or maybe the product is contaminated. They can have less or more than the required amount of active ingredients. They can also contain the correct amount of active ingredients, but have been manufactured in unhygienic and unsafe environments (PSI, 2018a). PSI reported cases where genuine medicines have been placed in counterfeited packaging to extend the expiry date.

Merck, one of the top multinational pharmaceutical companies defined counterfeiting as: "Unauthorized use of trademark, trade name, other identifying mark, imprint, or device, or any likeness thereof to adulterate, falsely purport, or represent that the product was manufactured or distributed by the identified manufacturer or distributor" (Merck, 2014).

It is important for authorities and researchers to differentiate falsified medicines from substandard medicines defined as "pharmaceutical products that do not meet their quality standards and specifications" (WHO, 2017a). These products are produced by legitimate companies that have limited technical capacity and appropriate facilities to ensure minimum quality standards to manufacture, supply, and distribute the medicines (WHO, 2017b).

Extent of the Problem

According to the World Health Organization (WHO, 2006), it is a worldwide issue, affecting every region and, especially the LMICs. All range of products can be affected, i.e., generic and originator brands; cheap and expensive; and different classes of medicines. Falsified medicines may harm the users with deteriorating patient health and disease conditions. They do not ensure quality, therapeutic efficacy, or safety. Moreover, they also have financial implications for caregivers, healthcare system resources, and healthcare delivery (Sanofi, 2013).

Even though many reports have mentioned the extent of the problem, the accurate prevalence rate is hard to estimate, partly due to non-well-documented reports. Thus, there is lack of reliable data, however, it is worth mentioning estimates provided by various studies and organizations. The volume of falsified medicines is also unclear. According to Cockburn et al. (2005), the prevalence of falsified medicines seems to be growing. Cockburn et al. (2005) and Newton et al. (2006) reported that in areas that are suffering from communicable diseases such as HIV-AIDs, tuberculosis, and malaria, the number of falsified medicines could be more than 50%. Nayyar et al. (2012) reviewed studies on the quality of five classes of anti-malarial medicines from seven countries in Southeast Asia. Thirty-five percent from 1437 samples of medicines failed chemical analysis, 46% of 919 failed packaging analysis, and 36% of 1260 were classified as falsified. Further findings from 21 countries in sub-Saharan Africa, reported that in 21 surveys of medicines from six classes, around 804 (35%) failed chemical analysis, 28 (36%) failed packaging analysis, and 78 (20%) were classified as falsified. The global falsified medicine trade, a billion-dollar industry, is thriving in Africa (Sambira, 2013).

The Pharmaceutical Security Institute has collected data on medicines falsifying worldwide for many years. According to the agency, between 2013 and 2017, total pharmaceutical crime incidents, which include falsifying, increased from 2193 cases (in 2013) to 3509 cases (in 2017). PSI tracked worldwide falsified medicine confiscations and the amounts seized. In 2017, 52% of cases were classified as commercial incidents (i.e., incidents involving the seizure of more than 1000 dosage units), 32% as non-commercial (i.e., incidents involving less than 1000 dosage units were classified as non-commercial), and 16% were unknown cases. Close to six hundred falsifying incidents involved either customs seizures or police/health inspector raids (PSI, 2018b). Mackey et al. (2015) studied the PSI Counterfeit Incident System database and found that in 417 (27.6%) reports, China was the source country of the incident.

According to a 2010 World Health Organization Fact Sheet—IMPACT (AIFA, 2011)—it is difficult to estimate the percentage of falsified medicines in circulation. WHO estimated around 1% of medicines in circulation in industrialized countries are falsified. Moreover, in many African countries, parts of Asia, Latin America, and countries in transition, a much higher percentage of the medicines on sale may be falsely labeled or falsified. The World Bank reported that up to 15% of all medicines sold in developing countries create a threat to patients (World Bank, 2014). In another report, INTERPOL estimated that 30% of medicines in Africa are either falsified or of inferior quality. The issue is more problematic in the poorest countries (INTERPOL, n.d.). INTERPOL's flagship pharmaceutical investigation, Operation Pangea, for example, seized 2.4 million fake and illicit pills in 2011 (INTERPOL, n.d.). During another Operation Pangea VIII in summer 2015 that involved 115 countries, approximately 21 million falsified medicines worth a total value of USD81 million were confiscated in a week (Lundin, 2015). The author further reported that the WorldWide Antimalarial Resistance Network revealed that 35% of all anti-malarial medication was falsified. The figures in Nigeria were as high as 64%. Other medications that are often falsified are those used for HIV/AIDS, TB, and Ebola (Lundin, 2015).

According to the European Union's custom authority, there is an upward trend in Intellectual Property-violating goods crossing the borders: one-tenth of the 43,500 cases of such goods in 2009 were medicines (EU Custom Authority, 2017). Uganda's National Drug Authority reported that cases of medicines failing to meet quality standards at the country's national laboratories have fallen by 15% since the early 2000s (Wilson, 2013). A drug quality project carried out by the Medicines Transparency Alliance (2015) in Uganda found that 55% of cefixime products, 23% of cefuroxime products, and 25% of erythromycin products were suspicious. According to a report by Sari (n.d.), in Indonesia, in terms of financial value, fake medicines constituted 25% of the country's $2 billion pharmaceutical market. Meanwhile, in terms of quantity of goods, the size of falsified pharmaceuticals was 3.8% (versus other products such as food, cosmetics, software, etc.) according to the Indonesian Anti-Counterfeiting Society (MIAP) in 2016. According to the Center for Medicine in the Public Interest in the USA, the global sales of falsified medicines could increase to USD75 billion in 2010, a 90% rise in five years (WHO, 2010).

Who and What Are Affected?

No product is immune from falsification. Both generic and branded (or originator) medicines are affected. Falsified medicines involve both lifesaving and lifestyle medicines (Blackstone et al., 2014). Falsification affects all countries, healthcare systems,

pharmaceutical supply chains, manufacturers of the original medicines, retailers, wholesalers, healthcare institutions, healthcare providers, regulatory agencies and officers, policymakers, publics, and patients.

Based on the PSI (2018c) data, when examining falsifying incidents only, medicines in the genitourinary, anti-infectives, and central nervous system (CNS) therapeutic categories were the most frequently targeted by individuals engaged in pharmaceutical falsifying. The PSI tabulated 1510 falsified incidence reports worldwide (from 2009 to 2011), mostly from health-related government agencies. Slightly more than half (51.3%) reported a falsified medicine without a recognized or verifiable subcategory. Despite the fact, practically all types of pharmaceutical products have been shown to be involved, the prevailing data suggests that anti-infectious agents, mainly antibiotics and antiparasitic agents, are the most falsified products in developing countries (Wondemagegnehu, 1995; Frankish, 2003; WHO, 1999; Pincock, 2003; Scutti, 2015; PSI, 2018b). Others are genitourinary (15%) and cardiovascular (12%) medicines (PSI, 2018b). Even though no one has a clear idea about the statistics, still, it is clear the falsified medicine problem is bigger than in the past and covers widely used medicines, such as anti-malarials, as well as high-demand medicines, and high-value medicines, such as those used to treat cardiovascular disease, cancer, and HIV/AIDS (Mackey et al., 2015).

Economy-wide falsifying undermines innovation, which is key to economic growth. The crime of falsifying medicines affects intellectual property rights. Intellectual property theft decreases incentives to create and innovate, consequently reducing economic output and employment. Falsification affects the income of pharmaceutical and biopharmaceutical industries, reducing the incentive to engage in research, development, and innovation. Besides posing health hazards to patients, including death, falsification wastes consumer income with spending on useless products. In China, about 0.20–0.30 million people die annually because of falsified and substandard pharmaceutical products (Morris and Philip, 2006). Additionally, and more importantly, 28% of the counterfeit reports (from 2009 to 2011) in the Counterfeit Incident System of Pharmaceutical Security Institute indicated China to be the source country of the falsified medicines (PSI, n.d.). The severity of the effects on patients and consumers depends on the contents in the falsified medicine. It can affect the legal medicine supply chain as the raw material and ingredients of the products can pass through the system including storage, transportation, and distribution activities. **Table 1** shows some cases of the effects of falsified medicines on people.

What Are the Roots of the Problem?

There are many diverse reasons for falsified medicines. Political, economic, social, and cultural factors of the country are part of the reason for the emergence and prevalence of falsified medicines. Due to increasing globalization, the problem of falsified medicines has expanded vastly, to both developed and developing countries (FIP, n.d.). Falsified medicine trade is probably linked to organized crime, terrorist groups, corruption, the narcotics trade, the business interests of unscrupulous politicians, and unregulated pharmaceutical companies (Moken, 2003; Carpenter, 2006). China and India are reported as the main countries of origin of falsified medicines, the two largest manufacturers and exporters (Delepierre et al., 2012). Russia, China, Brazil, Mexico, Pakistan, Southeast Asian, and Middle Eastern countries are also considered as chief operators in manufacturing and distributing falsified medicines (Clark, 2015; Shepherd, 2004). Dégardin et al. (2014) reported that areas like the middle-east and Switzerland are assumed to be major transit hubs of falsified medicines.

Trafficking in falsified medicines can be extremely profitable; detection of falsified medicines is difficult, and the penalties are relatively moderate. Eser et al. (2015) illustrated the illegitimate supply chain from the design of fake medicines through to the utilization level by willing and unwilling buyers. Among the reasons for this high prevalence were a weak or absent drug regulatory authority; absence of a legal mandate for licensing of manufacture/import of medicines; lack of regulation by exporters and within free trade zones; proliferation of small pharmaceutical industries; complex transactions involving many intermediaries; high demand for curative and preventive medicines and vaccines that exceed supply; high prices of medicines; and inefficient and insufficient cooperation among stakeholders (WHO, 1999).

In some countries, matters related to insurance coverage can be a factor for the use of falsified medicines. People who are underinsured or uninsured tend to access cheap medicines from unauthorized sources such as Internet and foreign pharmacies. The tendency for falsified medicines proliferation when medicines are expensive is high. Over 90% of Nigerians' income is below USD2 a day and they cannot afford good medicines (HAI Africa, 2008). Moreover, an earlier survey showed a low availability of essential medicines in the health facilities where only 46% of key medicines were found. Another study reviewing the efforts made by the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC) to control the distribution of falsified medicines noted that the inability to close the unmonitored, unlicensed, unregulated, chaotic, open pharmaceutical market that forms the major medicine distribution centre patronized by many medicine outlets, has brought about a wider spread of falsified medicines without control (HAI Africa, 2008). Another reason for the spread of falsified medicines was the lack of punishment by the government of perpetrators.

The prevalence of falsified medicines also increases with the expansion of the Internet, consumer accessibility to the Internet, high information communication technology literacy rates, and lack of cybersecurity in a country. Communication and technology have an important role in health. According to the International Telecommunication Union (ITU, 2017a) Internet worldwide users were 16% in 2005 (world population of 6.5 billion) and increased to 47% in 2016 (world population of 7.3 billion). Generally, the statistics by ITU have shown a significant increased in all regions between 2005 and 2016 (ITU, 2017b). In developed countries, the proportion of households with Internet access at home is twice as high as in developing countries (84.4% vs. 42.9%) (ITU, 2017c). The proportion of individuals aged 16–74 in the EU-28 who order or buy goods or services over the Internet for private use continues

Table 1 Examples of counterfeit medicine and its effects on people

Country	*Medicines and class*	*Disease or health problem; indication*	*Case*	*Link and source*
Myanmar	Artesunate	Malaria	Artesunate given to the patient had only 20% of the active ingredient required to kill the parasites; patient died	Ossola (2015). http://www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html
Pakistan	TB agent	Tuberculosis	100 patients were hospitalized at a Lahore hospital in 2012 by triggering severe adverse reactions after taking poor-quality TB drug	Ossola (2015). http://www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html
India	Antibiotic	Infection post-surgery	In 2013, officials in India discovered that 8000 patients died over a five-year period in a remote Himalayan hospital because an antibiotic used to prevent infection after surgery had no active ingredient	Ossola (2015). http://www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html
Democratic Republic of Congo	Not mentioned	Not mentioned	A thousand people were hospitalized after taking a fake drug in 2014 and 2015. It turned out that the drugs contained an antipsychotic used to treat schizophrenia	Bichell (2017). https://www.npr.org/sections/goatsandsoda/2017/11/29/567229552/bad-drugs-are-a-major-global-problem-who-reports
Netherlands	Oseltamivir (Tamiflu)	Flu	Dutch Healthcare Inspectorate warned consumers in early 2006 not to buy Tamiflu through the Internet, after counterfeit capsules were found in the Netherlands containing lactose and vitamin C, and no active substance	WHO (2006). https://www.gphf.org/images/downloads/library/who_factsheet275.pdf
Nigeria	Not mentioned	Not mentioned	NAFDAC destroyed N80 million counterfeit and expired regulated products in Abuja	NAFDAC (2018a). http://www.nafdac.gov.ng/index.php/component/k2/item/390-nafdac-destroys-n80-million-counterfeit-and-expired-regulated-products
China	Anti-diabetic	Diabetes mellitus	A diabetes drug was pulled after samples showed the medicine, which killed two people in the western region of Xinjiang, was six times as potent as it should have been	Lewis (2009). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774384/
Cambodia	Traditional medicines	Pain relieve	The Cambodian Health Ministry has warned the public to avoid using two traditional Chinese medicine products, Tong Mai Dan and Zhuan Guwan. It is thought that both products are falsified and contain dexamethasone, a chemical product which could affect public health	Sotheary (2018). Warning on fake Chinese medicine. www.khmertimeskh.com
Cambodia	Not mentioned	Not mentioned	Police arrested a Vietnamese businesswoman after seizing five tones of whitening lotion and 125 packets of counterfeit medicines during a raid of her warehouse in Phnom Penh's Toul Kork district	Konkkea (2017). Woman held over fake cosmetics and medicine. http://www.khmertimeskh.com/news/38474/woman-held-over-fake-cosmetics-and-medicine/
Argentina	Iron-based preparation	Anemia	In 2004, fake medicines led to a trail of death in Argentina	WHO (2008). https://www.gphf.org/images/downloads/library/whoimpact2008_counterfeit_drugs_kill.pdf
Panama	Cold medicine (syrup)	Cold	In 2006, more than 100 patients were killed in Panama by medicines manufactured with counterfeit glycerin. The toxic syrup contained diethylene glycol	Bogdanich and Hooker (2007). http://www.nytimes.com/2007/05/06/world/americas/06poison.html

to rise: in 2016, it reached 55%, an increase of 11 percentage points compared with 2012 (Eurostat, 2018). The Internet is the biggest unregulated market in the world: a place where people can easily become the victims of dishonest online pharmacies (Sanofi, 2013). In industrialized and developing countries, the sale of pharmaceutical products online, from supplements to life-style to life-saving medicines, is a major source of falsified medicines that can endanger people's health. There are online pharmacies that are perfectly legal, having been created to simply ease the purchase of medicines, however, a large number of websites operates illegally, offering access to controlled medicines without a prescription, not to mention non-approved and falsified products. Organized crime is behind some of these structures, which function as a network while hiding their true identity and location. Internet sites that pose as legitimate pharmacies and serve as a clearinghouse of unapproved and dangerous falsified medicines those unsuspecting patients can buy, even without a prescription also present a significant threat to patient safety. Since it is relatively easy to create Internet presence for falsified medicines, there are currently thousands of these illegitimate sites (Merck, 2014). According to Legitscript (European Alliance for Access to Safe Medicines, 2015), of the 331,430 websites monitored that sell healthcare products, 94.3% are selling pharmaceutical products illegally. INTERPOL's Operation Pangea X in collaboration with 123 countries targeting the illicit online sale of medicines resulted in 3584 websites taken offline and suspension of more than 3000 online adverts for illicit pharmaceuticals (INTERPOL, 2017). All countries with access to Internet are targeted by unscrupulous traffickers who sell medicines at very attractive prices, whose contents are not guaranteed and which can cause serious damage to the health of those that take them (European Alliance for Access to Safe Medicines, 2015).

Perspectives on Falsified Medicines Use

Many parties are involved with pharmaceuticals and in the pharmaceutical sector. There are benefits and risks in dealing with pharmaceuticals. Public access to affordable and quality medicines is important, but there is a growing concern about the increased incidence of falsified medicines around the world. It affects public trust and confidence in the healthcare system, the medicines, and drug regulatory authorities. Thus, countries need strong and effective medicines policy and regulations throughout the medicines supply chain, i.e., from manufacturing, importation, and registration to utilization. There are countries that have reported progress in decreasing the supply and circulation of falsified medicines. In many parts of the world, barriers still exist. Many LMICs lack regulatory infrastructure, resources, trained personnel, quality assurance, and pharmacovigilance activity (Mohamed Ibrahim et al., 2016). Thus, the quality, safety, and use of medicines are not effectively monitored. The issue of falsified medicines is of concern from difference perspectives.

Policy Perspective

Due to the complexity and importance of the pharmaceutical markets, they require careful stewardship. A medicine policy document reflects the commitment of the government to ensure that efficacious, safe, and quality medicines are available, accessible, affordable, and used rationally (Management Sciences for Health, 2012). According to Hoebert et al. (2013), the number of National Medicine Policies (NMPs) worldwide has increased over the years especially in high income countries which have more NMP implementation plans and have an up-to-date NMP. A non-existence or weak NMP could expose a country to the incidence of falsified medicines and increase the prevalence of them in the country's pharmaceutical market. A clear and effective policy can ensure that all the pharmaceutical-related stakeholders in a country know their roles, rights, and obligations in relation to medicines, and that these are supported by monitoring and effective regulation (WHO, 2004). There are six dimensions that can be used to analyze a policy, i.e., "effectiveness," "unintended effects," and "equity" under the domain "*Effects*," and "cost," "acceptability" and "feasibility" under the domain "*Implementation*" (WHO, 2012). There is a relationship between policy and governance. A quality policy should cover aspects such as conviction, penalties, and requirements. Because of the extent of the falsified medicines problem around the world, it is important to have multilevel policies, i.e., at the national level (country-specific), regional (such as GCC, European Union), and international (such as WHO). Policies related to falsified medicines need to be evaluated against their objectives such as impact, e.g., problem containment and eradication, and cost-saving. It is important for policymakers to monitor the implementation of the relevant polices and then to evaluate them. For example, the European Union initiative on medicine falsifying-related policy development and implementation requires safety characteristics on medicines packages (i.e., for most prescription-only medicine) allowing to detect individual packages and confirm their authenticity.

Merck established a Public Policy statement in 2014 (Merck, 2014) and designed an Anti-Counterfeiting program to keep the legitimate medicine distribution system secure and safe. One aspect of the policy requires customers to purchase Merck medicines and vaccines directly from Merck or a Merck authorized distributor. This action could prevent falsified medicines from entering the pharmaceutical supply chain. In addition, part of Merck's commitment is to cooperate with government agencies, INTERPOL, other pharmaceutical industries, and to educate the public. Merck provides effective advocacy on high-priority anti-counterfeiting policy initiatives. In summary, there should be a zero tolerance policy.

Regulatory Perspective

The manufacture, distribution, and the sale of medicines in a country can be protected from falsified medicines if there is proper and strict regulation related to these aspects. Organized criminal enterprises that work for high profit, approximately 25 times higher

than legitimate medicines, with low risk business (Ness, n.d.). Countries with lax regulations will provide the opportunities for falsified medicines. Absences in nationwide and international-wide legislation and enforcement are mostly discussed and criticized at different international forums. There are countries that rely on a high percentage of imported medicines, and have a weak distribution network and supply chain. Some authorities are not able to accept their weaknesses and to be criticized or are willing to cover up the failure of the pharmacy authority to prevent falsified medicines entering the country. There are countries where medicines, especially prescription and controlled items, can easily be found in open market, street vendors, or sold without a prescription. Counterfeiters know the laws and their weaknesses. They also plan for falsified medicines to enter the legitimate supply chain and reach health institutions and patients. It is important to have a working and effective authority in place to control and regulate the whole pharmaceutical supply chain and protect it from the penetration of falsified medicines into the market. Unfortunately, many LMICs are underfunded and lack human and financial resources to evaluate the quality of medicines and control the problem. A 2014 report published by the Independent Joint Anti-Corruption Monitoring and Evaluation Committee (Ossola, 2015) found, for example, that government officials in Afghanistan and China received bribes to approve untested medicines. The size and effects of falsifying are so significant that they require effective and continuous action from governments, consumers, and businesses. It is critical to have more effective and strong enforcement to fight against falsifying, as well as increased cooperation between the stakeholders. For example, police, customs, drug regulatory authorities, international organizations, and private sector partners from some 100 countries participated in Operation Pangea VI in 2013, which saw the seizure of 9.8 million potentially dangerous medicines worth USD41 million and more than 13,700 illicit websites shut down (INTERPOL, 2014a). Unless laws are harmonized and unless there are no gaps in regulatory and enforcement schemes globally, criminals will exploit markets at their weakest points (INTERPOL, 2014a). Unlike many other African countries, Zimbabwe has strict medicine control laws. People caught selling falsified or unregistered medicines can face sentences of up to 20 years if convicted (Musvanhiri, 2017). Still, strict laws do not seem to be enough to stop the spread of falsified medicines. In China, people who are caught can be fined between RMB100 ($17) and RMB3000 ($507): they can also face the death penalty (Lewis, 2009). Recently the European Commission (2018), revealed that medicine falsification in 22 countries is punishable by imprisonment. The sentences range from one year in Greece, Finland, or Sweden up to 15 years in Austria, Slovenia, and Slovakia. Fines can range from Euro4300 in Lithuania to Euro1million in Spain.

The Council of Europe has long been concerned about the absence of harmonized international legislation, non-deterrent sanctions that were not proportionate to the harm caused to patients, and the involvement of criminal organizations which do not respect geopolitical borders (Mackay and Liang, 2011; Keitel, 2012). International cooperation is crucial. To crack the global networks of counterfeiters, authorities need to cooperate across borders. In mid-2013 several European countries joined forces to scan international shipments for an entire week in order to track down falsified medicines.

Social Perspective

What is the public perception about this matter? What do health professionals say about this problem? What are the reactions of other stakeholders? It is not easy for consumers in the pharmaceutical market to realize whether a pharmaceutical product is safe or not, or to recognize if a product is genuine or falsified. According to Liu and Lundin (2016), there are three crucial problems: first, related to the definition of good versus poor quality medicines; second, poor level of awareness regarding the extent of the problem; and third, low level of knowledge and skill in conducting proper research to identify the problem, investigate the quality of medicines, and to make proper documentation and reporting. Newton et al. (2009) and the Center for Economics and Business Research Ltd (2002) have provided study designs and data analysis procedures in relation to falsified medicines. Further, Newton et al. (2009) also encouraged the use of Medicine Quality Assessment Reporting Guidelines (MEDQUARG).

Public ignorance is a factor contributing to the availability of falsified medicines. Illiteracy is a problem in many parts of the world and it is difficult for some people to differentiate between genuine medicine products and fake medicines, especially when they want cheap and easy access to medicines (Chinwendu, 2008).

Sanofi conducted a study to help understand Asians' perceptions of falsified medicines and how buying habits help fuel the falsified medicine market worldwide (Sanofi Le Hub, 2015). The study was conducted in six countries—China, Indonesia, Malaysia, Philippines, Thailand, and Vietnam—and asked consumers whether they thought taking falsified medicines was a risky business. The results shed new light on the falsified medicine trade in Asia. Of those surveyed, 67% considered falsified medicines to be dangerous, and around 31% considered them potentially dangerous, though this level of recognition rose substantially in Indonesia to 86%. While understanding of the dangers of falsified medicines is generally widespread, of more concern is a lack of knowledge on the subject. Of those surveyed, 67% of Thais and more than half of Indonesians said they did not know how to tell the difference between a fake medicine and the real thing. Around 64% of Asian respondents thought that it is possible to be exposed to falsified medicines online. Online purchasing is particularly widespread in Asia, thus it is very essential to have preventive actions.

A study in Tanzania evaluating public awareness found that a significant number of respondents were able to differentiate between genuine and falsified anti-malarial medicines (Mhando et al. 2016). Respondents who had knowledge on health effects of falsified medicines were nearly three times more likely to distinguish genuine and falsified medicines than their counterparts. A study in Iran of pharmacists' professional attitudes and practices toward falsified medicines illustrated that pharmacists showed low knowledge and a poor practice level about falsified medicines but had high level of knowledge about preventing the spread of counterfeit medicines in the community (Shahverdi et al., 2012). Nagaraj et al. (2015) noted that medical practitioners had more knowledge regarding falsified medicines than medical storekeepers and dental practitioners. A study in Lebanon showed that

falsified medicines were found in 33% of the households visited and demonstrated awareness in both the public and pharmacists of the perceived risks these medicines pose to both individual and public health (Sholy, 2015).

There are several initiatives that could be taken to create and raise awareness and educate the public and healthcare professionals about falsified medicines, ranging from printed materials to providing a 24-hour anti-counterfeiting hotline.

Economic Perspective

Falsifying medicines is an illegal business in which criminal networks thrive. A study conducted by the OECD (2007) reported that falsified products are produced and consumed in almost all countries regardless of economic level. The study also indicated that Asia is the single largest producing region. Falsified medicines businesses take away from governments, genuine private businesses and communities legitimate jobs, profits and tax revenues (ICC, n.d.). Costs are incurred in combating the problem. For poor countries, limited resources have to be used to deal with detection, enforcement, and awareness programs. Falsified medicines take income from consumers by having them pay for products that have little or no medical value (Liang and Mackey, 2012). Genuine products can experience loss of sales potentially from loss of confidence in those products. Figures reported by the International Chamber of Commerce (ICC, n.d.) indicate that by 2022, the negative impacts of general falsifying and piracy are estimated to drain US$4.2 trillion from the global economy and affect 5.4 million legitimate jobs. Transnational organized crime networks involved in falsifying medicines and pharmaceutical products are so focused on making profits that they turn a blind eye to the health risks this presents to unsuspecting consumers (EUROPOL, 2015). According to the OECD report, more than US$250 billion in revenue is lost in falsifying products (OECD, 1998).

Falsified products infringe trademark and intellectual property (IP) rights of the originator company (Ness, n.d.). The goal of the IP is to create funds for future innovation in therapies and technologies. Pharmaceutical products are research and development (R&D) intense: R&D is time consuming and costly. Patents are designed to run for 12–15 years. The most recent analysis by the Tufts Center for the Study of Drug Development of the average cost to develop and gain marketing approval for a new medicine is estimated to be $2.558 billion (Tufts CSDD, 2016).

Based on the cost of the problem (e.g., USD75 billion in globally per year), the need for action is clear (INTERPOL, 2014b). The Council of Europe Convention noted that the administrative costs for investigation and prosecution, and physical and emotional harm to countless victims, are not known. The Council also noted increased long-term economic costs due to an increasing global disease burden (Council of Europe, 2015).

Medicine quality surveys can be expensive, mostly because of the costs of chemical analysis, and this has inhibited such work with the result that we have very little objective information. Given the large expense of clinical trials, the cost of medicines, and the enormous economic burden of life-threatening diseases, this lack of investment is a false economy. More investment in laboratory infrastructure and personnel training is needed. It has been argued that surveys with random selection of outlets are not necessary, too complicated, or too expensive, however, it has also been suggested that they are vital and that the additional expense in comparison to the chemical analysis cost is small (Newton et al., 2009).

In short, falsified medicines can affect a country significantly, especially LMICs, in terms of lost tax revenues, lost sales revenues, wasted money by individuals purchasing useless medicines, costs incurred to fight against falsified medicines including analyzing samples, and unnecessary healthcare costs due to problems caused by poor quality medicines.

Laboratory Analysis and Technology

One important aspect in dealing with falsified medicines is detection technologies and methods. It is unethical to use a wrong procedure or analysis and falsely ill repute a genuine medicine or falsely support non-quality medicine. Thus, authorities and researchers need to be familiar with the different methods of analysis to measure the quality of medicines in the medication supply chain. The main challenges for countries are lack of well-equipped laboratories, analytical know-how, competencies, resources, and managerial ability (Newton et al., 2009). The most important considerations in choosing the appropriate technology for detecting poor quality medicines are the testing site and the purpose for testing. Factors related to the testing site include whether there is a consistent electrical supply, competent staff, and whether the purpose of the testing is screening or confirmation.

According to Kovacs et al. (2014), there are at least 42 unique technologies to detect poor quality medicines. In another report, Newton et al. (2009) highlighted the common chemical analysis techniques for quality of medicines research. It is a challenging task to test for poor quality medicines because of the cost to carry out the test, facilities and skills required. Kovacs et al. (2014) considered 17 technologies as either portable or requiring only a basic laboratory.

Table 2 illustrates few examples of medicines and methods used for detecting poor quality medications.

The methods and technologies used should be able to evaluate if the packaging is fake, the chemical composition correct, the presence of unexpected active ingredients in the product, and if the product is substandard or falsified (Newton et al., 2009). The choice of the methods and technologies used by the drug regulatory authorities should be based on the availability of the instruments, knowledge and skill of the operator/technician, cost, and the advantages and disadvantages of the techniques.

Other Anti-Counterfeiting Technologies

Many anti-counterfeiting technologies are being utilized by pharmaceutical companies to ensure distribution of the authentic product from the manufacturing site to the pharmacy. These technologies must be non-clonable. Among the technologies used by

Table 2 Examples of method used for detecting poor quality medications

Method	*Medicine*	*Reference*
Thin-layer chromatographic-densitometric	Clotrimazole	Nyamweru et al. (2014)
Library of chemical color tests embedded on an inexpensive paper card	Anti-malarial	Weaver and Lieberman (2015)
Colorimetric assay	Both lumefantrine and artemether in Coartem® tablets	Green et al. (2015)
Colorimetric assay	Artemether, dihydroartemisinin, and artesunate tablets	Green et al. (2001)
Chemical and bioassay methods	Miltefosine	Kaur et al. (2015)
Detection reagent and micro-fluidic platform	Anti-malarial	Ho et al. (2015)
MiniLab® semi-quantitative TLC test	Anti-malarial	Visser et al. (2015)
Combination of Thin Layer Chromatography, High Performance Liquid Chromatography and Raman spectroscopy	Artemether/lumefantrine	Yemoa et al. (2017)
Combination of CD3+ tool with TruScan™ Portable Raman spectrometer and GPHF Minilab®	Anti-malarial (artemether-lumefantrine tablets and artesunate-amodiaquine tablets)	Batson et al. (2016)

pharmaceutical manufacturers are holograms, color-shifting inks, and embedded codes, images, and dyes. These anti-counterfeiting features allow pharmacists to identify suspicious medications as possible falsified products (Williams and McKnight, 2014).

Techniques based on interference pattern, encryption, spectroscopy, and chromatographic principles used by pharmaceutical industries to authenticate genuine products have curtailed the problem to a limited extent (Kumar and Baldi, 2016). Bansal et al. (2013) reviewed the different anti-counterfeiting authentication technologies that can be used in different ways, e.g., tamper-evident/tamper-resistant packing; product authentication; and track and trace technology.

Table 3 shows few examples of additional technologies.

Developing reliable detection and diagnostic technologies is crucial for national drug regulatory authorities and international organizations to detect falsified medicines and take action against the illegal enterprises involved. Countries, especially LMICs, need to establish good laboratories for monitoring, checking quality of all pharmaceuticals manufactured locally, and those imported or donated to these countries. It is important to acknowledge that having good technologies is not the only solution to the problem.

Table 3 Examples of anti-counterfeiting authentication technologies

Technology	*Description*	*Reference*
Counterfeiting Incident System (CIS)	Record falsifying pharmaceutical products worldwide; CIS incidents come from a variety of sources, including open media reports, PSI member company submissions, and public-private sector partnerships	PSI (2018c)
mHealth Technology	A company, Sproxil, developed a creative mobile solution, which comprises of text messaging and scratch-off labels. The company works closely with pharmaceutical companies to provide verification services of for their products; providing brand protection and product authentication	Sproxil (2015) and Goldstein (2011)
mPedigree Network	A verify-by-mobile system; printed barcodes and scratch-off stickers, developed in partnership with US tech giant Hewlett-Packard, help consumers check authenticity against a central database	Wall (2016)
Counterfeit Detection Device, Version 3 (CD-3)	The CD-3 tool contains a library of information about authentic medicines and the packaging they come in. It allows the user to compare authentic images of a product with the suspect product, instantaneously showing clear differences between suspect and authentic products that would not have been clear to the naked eye	Autor and Plaisier (2013)
TruScan	A handheld spectrometer being used at airports and border posts to analyze the chemical composition of medicines, helping to spot "bad medicines" in seconds	Sambira (2013)
Integrated mobile telephony-based consumer verification	Countries like Ghana, Nigeria, and Kenya have included it in their safety regulations	Sambira (2013)
Radio Frequency Identification (RFID) device	Track-and-trace system uses information stored and remotely retrieved on transponders to provide automatic identification. An RFID tag is a chip that can be used to provide serial numbers to confirm the identity of a product	Coustasse et al. (2010)
I-Checkit	An INTERPOL pilot project which assisted citizens in determining the authenticity of medicines and other products before making a purchase, by scanning a code on the item to check it against information provided by the manufacturer	INTERPOL (n.d.)
Rapid Alert System (RAS)	A web-based communications network involving focal persons and representatives of countries and areas in the Western Pacific Region, WHO and partner agencies. It alerts member countries and areas and relevant partner organizations, through their focal points and representatives in the network, about cases of counterfeit medicine	WHO-WPRO (2005)

Table 4 Summary of steps or strategies to fight against counterfeit medicines

Steps or strategies	*Aspect*
Educate the public, healthcare providers, and regulatory officers to increase their awareness	Education and training
Increase the knowledge, skills, and competencies to empower healthcare professionals to be effective partners in the fight against falsified medicines	Education and training
Increase training for regulatory officers and lab technicians in chemical analysis and forensic techniques	Education and training
Broadcast advertisements for fake medicine	Media
Involve media, e.g., TV channels and printed media to educate and create awareness	Media
Strengthen the law and regulation in relation to dealing with counterfeit/falsified medicines	Policy, law, and regulation
Apply tougher penalties for individuals involved in this crime	Policy, law, and regulation
Seizure of related assets that belong to the criminal	Policy, law, and regulation
Take action on healthcare providers who prescribe and dispense counterfeit/falsified medicines to their patients	Policy, law, and regulation
Strengthen the medicines registration and vendor licensing process	Policy, law, and regulation
Increase cyber security to protect the public and consumer from getting medicines through the Internet	Policy, law, and regulation
Initiate the use of technology to fight against counterfeit/falsified medicines, i.e., developing protection technologies on product packaging	Technology
Improving detection with the development of analytical methods with reliable techniques	Technology and analytical method
To have expert enforcement officials including police, prosecutors, customs, and judges	Human resource
Improve management of medicines supply chain	Management and practice
Improve government quality control and assurance activities	Management and practice
Having a good governance	Governance
Increase dedication of regional cooperation with other countries, i.e., harmonization regarding counterfeit/falsified medicines to make tracking and tracing more effective	Networking and cooperation

Source: Burci (2013), Clark (2015), Cockburn et al. (2005), Council of Europe (2015, 2011), European Alliance for Access to Safe Medicines (2015), European Commission (2018), FIP (n.d.), Kumar and Baldi (2016), Pincock (2003), TGA (n.d.), US FDA (n.d.), and WHO (2011, 2012).

In summary, Table 4 lists the steps, approaches, and strategies that different stakeholders can carry out solely or in collaboration with partners.

Counterfeit Medicines in Pharmaceutical Supply Chain: Organization's Involvement and Country Case Studies

There are various government, non-governmental, for profit, and non-profit organizations that work against falsified medicines. Below are different local, regional, or international organizations, authorities, and associations. This list is not all-inclusive but enough to provide some idea about the initiatives of various, diverse organizations (Table 5).

No country is immune: falsified medicines can be found in developing and developed countries. Falsified medicines cases are more prevalent in LMICs due to many reasons discussed above. Table 6 presents example of cases.

Table 5 Organizations and their roles against counterfeit medicines

Organization	*Roles*	*Link*
International Chamber of Commerce (ICC)	Urges government action and resources to strengthen intellectual property rights enforcement, seeking significantly higher benchmarks for government performance against counterfeiting and piracy at the national, regional, multi-lateral, and international level	ICC (n.d.). https://iccwbo.org/global-issues-trends/innovation-ip/counterfeiting-piracy/
International Medical Products Anti-Counterfeiting Taskforce (IMPACT)	The launched by WHO in 2006 to respond to the increasing public health crisis of counterfeit drugs	WHO (2011). IMPACT International Medical Products Anti-counterfeiting Taskforce. The Handbook. Facts, Activities, Documents Developed by the Assembly and the Working Groups, 2006–2010. http://apps.who.int/medicinedocs/en/d/Js20967en/
International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)	Represents the research-based pharmaceutical companies and associations across the globe; it collaborates with other organizations around the world and creates a global movement of people to fight against fake medicines and trying to limit the consequences of this criminal traffic	International Federation of Pharmaceutical Manufacturers and Associations. https://www.ifpma.org/

Table 5 Organizations and their roles against counterfeit medicines (*cont.*)

Organization	*Roles*	*Link*
National Agency for Food and Drug Administration and Control (NAFDAC)	The government agency in Nigeria that is fully empowered to regulate and control the importation, exportation, manufacture, advertisement, distribution, sale, and use of drugs to ensure that safe and quality drugs are available to the public	National Agency for Food and Drug Administration and Control. http://www.nafdac.gov.ng/
Medicines & Healthcare products Regulatory Agency (MHRA)	Regulates medicines, medical devices, and blood components for transfusion in the UK. The agency plays a leading role in protecting and improving public health and supports innovation through scientific research and development	Medicines & Healthcare products Regulatory Agency. https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
United States Food and Drug Authority (US FDA)	Responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation	US FDA. What we do. https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/default.htm
Therapeutic Goods Administration (TGA)	Part of the Department of Health it safeguards and enhances the health of the Australian community through effective and timely regulation of therapeutic goods	TGA. Australian Government. Department of Health. Who we are & what we do. https://www.tga.gov.au/who-we-are-what-we-do
World Health Organization (WHO)	A specialized agency of the United Nations that is concerned with international public health. Working through offices in more than 150 countries, WHO staff work side by side with governments and other partners to ensure the highest attainable level of health for all people	Burci (2013). American Society of International Law. https://www.asil.org/insights/volume/17/issue/2/public-health-and-%E2%80%9Ccounterfeit%E2%80%9D-medicines-role-world-health-organization
Organisation for Economic Co-operation and Development (OECD)	Uses its wealth of information on a broad range of topics to help governments foster prosperity and fight poverty through economic growth and financial stability. It helps ensure the environmental implications of economic and social development are taken into account	OECD. What we do and how. http://www.oecd.org/
International Pharmaceutical Federation (FIP)	Concerned with the continuing, even increasing, risk to public health represented by counterfeiting of medicines, particularly in countries where legislation governing the manufacture and distribution of medicines, or the enforcement of legislation, is ineffective	International Pharmaceutical Federation (FIP). FIP Statement of Policy on Counterfeit Medicines. http://www.fip.org/www/uploads/database_file.php?id=164&table_id
Centers for Disease Control and Prevention (CDC)	Works to protect America from health, safety and security threats, both foreign and in the US	Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/about/organization/cio.htm
Management Sciences for Health (MSH)	Supports all levels of a country's regulatory infrastructure, from helping implement accredited drug seller initiatives in the private sector, to developing registration software to streamline access to medicines, to providing technical assistance to countries to draft national pharmaceutical policies; promotes the development of comprehensive pharmacovigilance systems and availability of drug information	Management Sciences for Health. https://www.msh.org/our-work/health-systems/pharmaceutical-management/policy-legislation-and-regulation
Médecins Sans Frontières (MSF)	A private, international, independent, medical humanitarian organization; provides assistance to populations in distress, to victims of natural or man-made disasters and to victims of armed conflict irrespective of race, religion, creed, or political convictions	Médecins Sans Frontières (MSF). MSF Charter. http://www.msf.org/en/about-msf
Pharmaceutical Security Institute (PSI)	Based on the need to face the challenge of counterfeit pharmaceuticals, in 2002, the Security Directors from fourteen major pharmaceutical companies established the Pharmaceutical Security Institute as a not-for-profit corporation based in the Washington, DC metropolitan area. PSI has developed improved systems to identify the extent of the problem and to assist in coordinating international inquiries	Pharmaceutical Security Institute (PSI). The Challenge of Counterfeit Pharmaceuticals. http://www.psi-inc.org/about.cfm
International Criminal Police Organization (INTERPOL)	Established in 1923 as the International Criminal Police Commission (ICPC). It is today heavily involved in the international enforcement of counterfeit medicines controls. Its mission is to facilitate cross-sector international action to identify, investigate, and prosecute the criminals behind falsification	INTERPOL. Pharmaceutical crime. https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-crime

(*Continued*)

Table 5 Organizations and their roles against counterfeit medicines (*cont.*)

Organization	*Roles*	*Link*
Global Pharma Health Fund (GPHF)	A charitable organization initiated and funded exclusively by donations from Merck, Germany aims to improve healthcare and the work currently supporting the fight against counterfeit medicines proliferation using the GPHF-Minilab™	Global Pharma Health Fund. https://www.gphf.org/en/index.htm
International Institute of Research Against counterfeit medicines (IIRACM)	An independent international organization dedicated to fight against counterfeit medicines. This organization provides information, training, and prevention programs	International Institute of Research Against Counterfeit Medicines (IIRACM). http://www.iracm.com/en/
European Alliance for Access to Safe Medicines (EAASM)	An independent, pan-European initiative dedicated to protecting patient safety by ensuring access to safe and legitimate medicines.	European Alliance for Access to Safe Medicines (EAASM). http://www.eaasm.eu/index.php?cID=32&cType=news
The Siracusa International Institute for Criminal Justice and Human Rights	Organizer of the third meeting of experts to strengthen "The Fight against Counterfeit Drugs in Francophone Africa." The project currently involves eight African states: Burkina Faso, Cameroon, Central African Republic, Guinea, Ivory Coast, Mali, Senegal, and Chad and is intended for representatives of the Ministries of the Interior and of Health. The main objective of this project is to help strengthen the fight against counterfeiting while reaching a political consensus for the preparation, adoption, and implementation of a comprehensive, modern, and adequate national legislation	Siracusa International Institute for Criminal Justice and Human Rights. http://www.siracusainstitute.org/portal/2017/11/27/fight-counterfeit-drugs-francophone-africa-third-meeting-experts/
US Pharmacopeia (USP)	Helps build the safety net across the drug industry and healthcare system, establishing standards to ensure medicine is of the highest quality from the time it's manufactured until the moment someone takes it. USP not only provides standards for what goes into a medicine and how it's named and labeled, but also to ensure that once it's in the hands of a healthcare team, it's prepared and handled safely	USP. Healthcare Quality & Safety. http://www.usp.org/healthcare-quality-safety
The Center For Safe Internet Pharmacies (CSIP)	A nonprofit organization founded in 2011 by a diverse group of Internet service providers and technology companies to address the global problem of consumer access to illegitimate pharmaceuticals from illegal online pharmacies and other sources	Center For Safe Internet Pharmacies (CSIP) (2018). Who we are. https://safemedsonline.org/

Table 6 Examples of case studies of counterfeit medicines in the pharmaceutical supply chain

Year	*Country or areas*	*Case*	*Reference and source*
2000	Cambodia	Fake malaria medicines flooded the Cambodian market have killed dozens of people. The fake drugs—marketed as the powerful malaria medicines Mefloquine and Artesunate, but actually of no medicinal value—accounted for the deaths of at least 30 people	Pharmaceutical Security Institute (PSI) (n.d.). http://www.psi-inc.org/reports.pdf
2000	India	A large batch of out-of-date medicines illegally imported from abroad was burned in Uzbek. The medicines were illegally imported and smuggled into the country. They came by the Delhi-Tashkent route. Government tests showed the medicines were produced in India and did not have all the basic ingredients, making the medicines useless	Pharmaceutical Security Institute (PSI) (n.d.). http://www.psi-inc.org/reports.pdf
2003	India	New Delhi police seized 100 kg of spurious versions of nimesulide, ranitidine, and betadine made in Agra, Meerut, and Ghaziabad	Drug control (2013). http://www.drugscontrol.org/spurious_drugs.htm

Table 6 Examples of case studies of counterfeit medicines in the pharmaceutical supply chain (*cont.*)

Year	*Country or areas*	*Case*	*Reference and source*
2004	Hong Kong	Customs officers arrested nine people and confiscated nearly 18,000 bottles of counterfeit Chinese medicine from a fake-medicine syndicate. Customs also seized about 927 bottles of counterfeit ointment and 17,000 bottles of balm bearing two brand names. Local radio reported the estimated value to be $740,000	South China Morning Post (2004). http://www.scmp.com/article/483156/customs-arrest-nine-confiscate-18000-fake-medicine-bottles
2004	UK	In 2004, two lots of counterfeit Cialis (tadalafil) and one batch of Reductil (sibutramine) were withdrawn	Chaplin (2007). http://onlinelibrary.wiley.com/doi/10.1002/psb.106/pdf
2005	Kenya	A survey from 2005 revealed that 30% of medicines in Kenya were counterfeit, some containing nothing more than water and limestone	Kayaoglu (2016). http://www.euronews.com/2016/02/11/the-dangerous-and-illegal-trade-in-counterfeit-medicines
2006	South Korea	Police served a fresh arrest warrant on two foreigners on suspicion of smuggling and selling fake Viagra and other medicines without a license. The police and customs seized about 100,000 pills at Kansai International Airport and other places related to the suspects	The Partnership for SafeMedicines (2006). http://www.safemedicines.org/2006/06/2-foreigners-served-with-new-arrest-warrant-over-sale-of-fake-viagra.html
2009	Uganda	A raid conducted by INTERPOL and the WHO-supported group IMPACT (International Medical Products Anti-Counterfeiting Taskforce), discovered five tons of fake drugs in the central and eastern districts of the country	Sambira (2013). http://www.un.org/africarenewal/magazine/may-2013/counterfeit-drugs-raise-africa%E2%80%99s-temperature
2009	Egypt	Egyptian police authorities carried out a series of raids in strategic locations in collaboration with World Health Organization—IMPACT. A wide range of counterfeit medicines were identified, including lifestyle products and others intended for organ-transplant patients or serious diseases such as cancer, diabetes, heart disease, epilepsy, or schizophrenia	INTERPOL (2009). https://www.interpol.int/News-and-media/News/2009/N20090529
2011	Various (81) countries	2.4 million illicit and counterfeit pills confiscated with an estimated value of USD6.3 million. Almost 13,500 websites were shut down. Some 45,500 packages inspected by regulators and customs authorities, of which almost 8000 were seized	INTERPOL (2011). https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea
2012	Coast of Africa	A major sweep across 16 seaports on the east and west coasts of Africa in July 2012 allowed the World Customs Organization, an intergovernmental organization that advises customs administrations worldwide, to seize more than 82 million doses of illicit medicines estimated to be worth over $40 million. The fake drugs found during the raid included cough syrup, anti-parasitic and anti-malarial drugs, antibiotics and even contraceptives	Sambira (2013). http://www.un.org/africarenewal/magazine/may-2013/counterfeit-drugs-raise-africa%E2%80%99s-temperature
2012	USA	The US FDA found that some batches of counterfeit bevacizumab (Avastin) contained no active pharmaceutical ingredients at all. This drug was found to have traveled through Turkey, Switzerland, Denmark, the UK, and Canada before reaching the USA	Kollmorgen (2015). https://newrepublic.com/article/121589/counterfeit-medicine-global-problem
2013	The Philippines	In March 2013, Philippine authorities arrested five traffickers attempting to traffic 20 pallets of fake slimming pills, pain relief medication, and antibiotics which had been shipped to the Philippines from Singapore	INTERPOL (2014a,b). https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-crime
2013	Russia	Russian authorities reported that they had dismantled a counterfeiting operation which had been ongoing for several years in Rostov. Fake medicines such as Herceptin, Meronem, Cefobit, Mantera, Sulperason were manufactured and distributed by an organized crime group. Russian authorities arrested seven suspects and carried out 23 raids in connection with this case	INTERPOL (2014a,b). https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-crime

(*Continued*)

Table 6 Examples of case studies of counterfeit medicines in the pharmaceutical supply chain (*cont.*)

Year	*Country or areas*	*Case*	*Reference and source*
2013	India	Officials in India discovered that 8000 patients died over a five-year period in a remote Himalayan hospital because an antibiotic used to prevent infection after surgery had no active ingredient	Ossola (2015). http://www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html
2014	Cambodia	Anti-economic crimes department of the Cambodian Interior Ministry, looks through confiscated fake medicines in Phnom Penh, Cambodia, November 28, 2014. About five tons of counterfeit medicines were seized	Ossola (2015). http://www.newsweek.com/2015/09/25/fake-drug-industry-exploding-and-we-cant-do-anything-about-it-373088.html
2015	The Philippines	Hundreds of thousands of dollars' worth of illegal medicines were seized during 2015, with the majority of fake medicines imported from India, Pakistan, and China	Sanofi Le Hub (2015). https://lehub.sanofi.com/en/access-healthcare/counterfeit-medicines-in-asia/
2015	Democratic Republic of Congo	More than 1000 people were admitted to hospital in a remote area of Democratic Republic of Congo (DRC) in 2015 after suffering toxic effects from "falsified" or wrongly labeled drugs	MSF (2017). http://www.msf.org/en/article/democratic-republic-congo-alarming-consequences-poor-quality-medicines
2015	USA	The San Francisco Department of Public Health released an urgent warning concerning deadly fentanyl disguised as the low-level anti-anxiety medication Xanax. Three people died as a result of consuming the fentanyl-laced pills	The Partnership for SafeMedicines (2015). http://www.safemedicines.org/2015/10/nationwide-epidemic-of-counterfeit-pain-pills-containing-fentanyl-claims-lives-in-22-states.html
2016	Indonesia	In 2016 between May 30th and June 7th, the Indonesian Food and Drug Monitoring Agency seized more than a thousand packages of illegal and fake medicines worth $4.2 million. Thousands of counterfeit pills were seized in 64 factories and drug facilities all across Indonesia. A total of 214 websites selling illegal products were identified and closed	Sari (n.d.). http://integrity-asia.com/blog/2017/09/06/counterfeit-medicine-in-indonesia/
2016	Portugal	In the Operation PANGEA, 42% of 57 products analyzed by Infarmed's Laboratory were counterfeit medicines and/or illegal	European Commission (2011). Detention of counterfeit and pirated goods at EU borders in 2010—Frequently Asked Questions. http://europa.eu/rapid/press-release_MEMO-11-506_en.htm?locale=en
2017	Germany	Fake hepatitis C medicines were available on the German market in numerous instances. According to the Federal Institute for Drugs and Medical Devices (BfArM), various drugs for the treatment of chronic hepatitis C in adults were affected	Bayer (2000). https://www.bayer.com/en/news-about-counterfeit-drugs.aspx
2017	Democratic Republic of Congo (South Kivu)	Two versions of falsified cefixime products were identified and reported to the World Health Organization. Both products were presented in standard white plastic containers of 100 tablets. The label of both products displayed spelling mistakes. Assays indicated only 2.5% of cefixime in the first product and nil in the second product	NAFDAC (2018b). http://nafdac.gov.ng/index.php/world-sport/item/391-falsified-cefixime-products-circulating-in-the-democratic-republic-of-congo
2017	Panama	Panama's national customs authority seized 179,642 counterfeit drugs linked to money laundering and organized crime totaling USD808,202, as part of the international operation "Pangea X" conducted in 123 countries	Panama Today (2017). http://www.panamatoday.com/panama/counterfeit-drugs-linked-money-laundering-was-seized-panama-5333
2018	USA	According to the Department of Justice (DOJ) report, three residents from Florida pleaded guilty to counterfeit drug and illicit steroid charges and were sentenced to prison. United States Postal Inspectors discovered that large volumes of steroid and counterfeit drug ingredients were being shipped from China to locations in Southern Alabama and Northwest Florida	The Partnership for Safe Medicines, 2018. http://www.safemedicines.org/2018/02/counterfeit-drug-manufacturing-trio-from-florida-sentenced.html

Note: to be read in conjunction with Table 1.

Final Remarks

Patient safety is the utmost important aspect in healthcare. Falsified or counterfeit medicines are a real problem, especially in developing countries. They will continue to be a problem unless strategic actions are put in place. Even if the speed of policing increases, it will not enough to prevent falsifying and public harm. Multipronged approaches and strategies are required. Further research is needed to identify the best methods and cost-effective, dynamic and long-term anti-falsification approaches strategies. Product assay methods, regulation of the pharmaceutical supply chain, severe punishment for breaches, and public and professional education and awareness programs, are just a few effective tools to prevent this crime against humanity.

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The Impact of Culture and Religion on Medicine Use

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Introduction

The decisions an individual makes are influenced by many confounding factors and this is no less true for the factors that influence an individual to seek and accept medical interventions. Culture may be one such factor which influences the decision making process. Culture has various definitions including "the way people live which consists of a system of ideals, values, beliefs, knowledge and customs transmitted from generation to generation within a social group" (Jekayinfa, 2000). According to this definition culture is, in itself, influenced by various factors such as an individual's religion, spirituality, ethnicity, etc. This is due to the fact these aspects shape the ideals and beliefs of the individual.

Thus, health care does not merely involve the eradication of disease but also encompasses the holistic care of the patient which includes mental and social wellbeing (World Health Organization, 1946). The changing demographic landscape in health care systems worldwide necessitates research into how this diversity impacts on health care attitude, behavior, and knowledge. Spirituality has emerged as an important social concept in the health of patients (Anadarajah and Hight, 2001; Levin et al., 1997; Matthew et al., 1998), however, research indicates that it appears to be largely neglected (Anadarajah and Hight, 2001; Levin et al., 1997; Matthew et al., 1998) in the caring of patients. There is, also, a growing body of literature that emphasizes the importance of physician behaviors that consider the patient as a whole, beyond the person's disease (Cassell, 1991; Magyar-Russell et al., 2008).

Religion and spirituality form an important component of a patient's value system and may be a unique tool in providing motivation and helping a patient cope with life events (Koenig et al., 2001; Magyar-Russell et al., 2008; Pragament et al., 2005). In a review of the relationship between religion and health (Anadarajah and Hight, 2001; Levin et al., 1997; Matthew et al., 1998), a positive relationship between religious commitment and mental and physical health was found in up to 84% of studies that included a measure of religious commitment as part of the study (Anadarajah and Hight, 2001; Larson et al., 1992).

A multitude of variations attest to the fact that patients are, above all, human beings regardless of class, gender, age, or culture (Fainzang, 2005). Delving into cultural idiosyncrasy does not exclude the anthropological aim of highlighting the universality of certain human behaviors (Fainzang, 2005). Anthropology of medication consists in knowing and understanding not only the use of medications but what that use reveals about individuals and society (Fainzang, 2005).

Aside from the possible health benefits involved in the incorporation of religion and spirituality into health care there is also the autonomy of the patient to consider (Easterbrook and Maddern, 2008). The ideal of informed consent, that is, consent given by the patient based on knowing all the facts about the risks and the benefits of a particular treatment regimen as well as possible future repercussions of the treatment to medication or medication regimens, protects the ethical fabric of a health care system. Unlike other transactions, however, patients rely heavily upon the knowledge of the health care provider when making decisions regarding medicine and health. The incorporation of spiritual and emotional considerations may be a useful tool to increase a patient's adherence to medication and bring about holistic care of a patient.

Cultural beliefs play an important role in determining a patient's inclinations toward accepting treatment. Appreciation of cultural and religious practices could be vital in increasing patient compliance and more importantly cementing a relationship based on trust and mutual understanding, between health care professional and patient. This chapter therefore looks at the influence of culture on medicine use, using race, ethnicity, and religion as surrogate measures. The chapter also looks at this from the perspective of both patient and health care provider viewpoints.

Ethnicity and Medicine Use

Palacio et al. (2002) undertook a systematic review of published studies investigating potential associations between race and/or ethnicity and use of HIV-related medications, including antiretroviral medications and medications used for prophylaxis of opportunistic infections. The authors identified 28 reports, of which: (a) 26 studies published in 1991–2001 addressed antiretroviral use, spanning data collection periods from 1984 to 1999; (b) 11 studies published in 1994–2001 addressed prophylaxis for Pneumocystis carinii pneumonia (PCP), reporting on data collected from 1989 to 1998; and (c) three studies published from 1998 to 2001 addressed prophylaxis for other opportunistic infections, reporting on data collected from 1993 to 1998. Among the studies that addressed antiretroviral use, 14 found a negative association between nonwhite race and at least one measure of antiretroviral use, three studies found a positive association, and 16 studies found no association; 7 studies found mixed results across several measures of antiretroviral use. Only 4 of 11 studies found a negative association between race/ethnicity and PCP prophylaxis; the remainder found no association. Two out of three studies found a negative association between race/ethnicity and prophylaxis for other infections. Thus, it is evident from this review that there is a role between race and ethnicity and medicine use that could affect health outcomes.

Polacek et al. (2007) found that patients from minority racial/ethnic and cultural backgrounds that differ from the majority, are disadvantaged when it comes to advocating for their health care and they evaluate their treatment decision making much less favorably than whites. Many reasons have been suggested (Health Policy Brief, 2011; Morris et al., 2010) for different or disparate care and outcomes among racial/ethnic and cultural minorities. These range from personal factors related to socioeconomic position or geographic area (e.g., educational attainment, income, neighborhood) to health system factors (e.g., differential delivery of care, reduced hospital resources). Yet the authors found that few discussions about differences in receipt or quality of health care discuss the role of patient engagement by health care professionals or involvement in health care decision making, and how this involvement (or lack of) may contribute to differences in use of care and access to treatment (or even adherence to treatment).

Morgan et al. (2011) looked into prescription medicine use by people of different ethnic groups in Canada. The authors found variation in prescription medicine use by ethnicity. Patients who were of South Asian descent, or mixed ethnicity, were almost as likely to fill prescriptions for most types of medicines studied as women and men who identified themselves as white. In addition, South Asian men were more likely than white men to fill prescriptions for antibiotics and NSAIDs. Women of Chinese ethnicity were significantly less likely to fill prescriptions for antihypertensives, antibiotics, antidepressants, and respiratory drugs, and Chinese men for antidepressant drugs and statins.

A pilot study assessed the differences in attitudes toward medications between the different population groups in South Africa (Suleman et al., 2008). The study analyzed the attitudes of a sample of patients, collected from the Durban Metropolitan Area within the province of KwaZulu-Natal, South Africa, to determine the existence of variances based on demographic characteristics, medication knowledge, self-care orientation, medication use, and contact with health care workers (Suleman, 2008). The results of this study indicated, in accordance with a similar study conducted in Sweden (Isacson and Bingefors, 2002), that the population fell into two groups: those who considered drugs as beneficial, and those who considered drugs as something necessary but not always in the best interest of their health care (Isacson and Bingefors, 2002; Suleman et al., 2008). In the South African study, perceptions of medication improved with age and respondents who visited a health care worker in the last six months had a more positive attitude toward medicines (Suleman et al., 2008). In terms of race 64% of black people and 57% of colored (mixed-race) people believed medicines to be good while 53% of whites and 52% of Indians believed that medicines are necessary but not necessarily good for you (Suleman et al., 2008).

Ethnicity has been found to influence not just prescription and nonprescription medicines but also complementary and alternative medicine (CAM) use. Villa-Caballero et al. (2010) studied the effect of ethnicity as a predictor of the use of CAM among patients with diabetes in the United States. The authors reported that the prevalence of pharmacological and non-pharmacological CAM among 806 participants with diabetes was 81.9% and 80.3%, respectively. Overall, CAM prevalence was similar for Caucasians (94.2%), African Americans (95.5%), Hispanics (95.6%), and Native Americans (95.2%) and lower in Pacific Islanders/Other (83.9%) and Asians (87.8%). Pharmacologic CAM prevalence was positively associated with education (P = 0.001). Several significant ethnic differences were observed in specific forms of CAM use. Hispanics reported using frequently prickly pear (nopal) to complement their diabetes treatment while Caucasians more commonly used multivitamins. Similarly, a study by Schoenberg et al. (2004) showed that Hispanics had a higher CAM use (40%) than African Americans (20%), Native Americans (15%), and Caucasians (15%). CAM use was associated with ethnic and cultural background in all the groups studied. Other studies report lower prevalence of CAM use among African Americans compared to other ethnic groups (Eisenberg et al., 1998).

Research has also been conducted in terms of self-care assessments and ethnicity. Johnson et al. (2014) looked at differences in diabetes self-care activities by race/ethnicity and insulin use in the United States (US). From the sample observed, only 20% of adults had high levels of diabetes self-care, while 64% had moderate and 16% had low self-care. Racial/ethnic differences were apparent for every self-care activity among non-insulin users but only for glucose monitoring and foot checks among insulin users. Overall, American Indian/Alaska Natives had higher odds of glucose monitoring; Blacks had higher odds of foot checks; and Hispanics had higher odds of not smoking compared with non-Hispanic Whites. Non-insulin-using American Indian/Alaska Natives had higher odds of foot checks, and non-insulin-using Hispanics had higher odds of fruit/vegetable consumption.

Thus, ethnicity, in terms of the findings of these studies, can influence access to care and treatment, use of prevention measures, attitudes and perceptions of medicine use, including CAM, and thus ultimately health outcomes. Health care workers, especially

pharmacists, need to be aware of these differences and tailor counseling and advice, or other specific interventions, based on the different ethnic groups in the populations they serve and variations within those particular groups.

Religion and Medicine Use

Religious beliefs are likely to impact of health care as well. Devotion to religious values shapes how a group or an individual approaches health care and medicine use. The Amish population in the US, for example, have been known to consult their religious book (or Almanac) and choose to use home remedies in the first instance (Hostetler, 1995). Religious beliefs include trust in God for healing purposes, reliance on individuals within their community, a preference for natural remedies, motivation to reduce health care costs and sometimes, limited access to health care facilities. The Amish have their own healers in their community who tend to prescribe home remedies (Amish Burn Study Group, 2014; Trinkle, 2016). The Bishop is an important agent in the community, as s/he acts as an intermediary between the community members and what the Amish consider as the outside world. Therefore, the views of the Bishop in this faith carry much weight and can be a facilitator or barrier to access to care and medicine use. The Amish will only access health care services and facilities if they feel that their traditions, religion, and values are respected (Ember and Ember, 2003). Similarly, Baptist and Methodist congregations have weekly sermons that incorporate health and healing topics. The congregations are encouraged to rely on the power of prayer for curing the ailments (Dessio et al., 2004).

The most pressing issue with regard to establishing an interfaith friendly medical system is the dietary requirements of individual faiths. Seventh Day Adventists promote vegetarian diets, and abstention from alcohol and tobacco (Dessio et al., 2004). Jehovah Witnesses refuse blood transfusions, organ transplants, and vaccines. Medical literature has detailed the use of religiously forbidden products (for example, in the religions of Islam and Hinduism, etc.), such as gelatin capsules and surfactants (Adappa et al., 2003; Gatrad et al., 2005; Sattar et al., 2004a,b).

However, an extensive literature search only indicated one study that directly investigated the influence of patients' faith and concordance with porcine derived medicine (Sattar et al., 2004a). This study conducted in the United Kingdom provides a glimpse of a previously unexplored avenue. In the study of 50 Muslim patients and 18 Muslim general practitioners, it was found that only 26% of patients would take a medicine if they were unsure as to whether or not it was halal (In Islam food and drink which are forbidden are termed haram, while any food and drink that can be taken are termed halal) (Sattar et al., 2004a). A further 58% stated that they would stop taking a medicine if they found out it was haram (Sattar et al., 2004a). Medical necessity was shown to influence circumstances as 36% of patients and 44% of GPs believed it was acceptable to take a haram medicine for a major illness: for minor illnesses, however, only 8% of patients and 36% of GPs believed it was acceptable to take a haram medicine (Sattar et al., 2004b).

Followers of Judaism and Islam strictly forbid pork within the diet and these restrictions are outlined within the religious scriptures (Easterbrook and Maddern, 2008; Mynors et al., 2004; Shalom, 2005). Hinduism and Sikhism exalt vegetarianism and do not advocate the consumption of beef and pork (Easterbrook and Maddern, 2008; Mynors et al., 2004). Some problem excipients found in medications include gelatin (which is usually of animal origin), glycerol/glycerine (however most glycerol and glycerine used are now of vegetable origin), stearic acid and stearates, and lactose (milk-derived sugar) (Mynors et al., 2004). Although these avenues provide a critical view of possible patient reservations only one study provides a direct link between religious dietary requirements and patient compliance (Mynors et al., 2004).

As a follow on to the United Kingdom study, a postgraduate study was conducted in the eThekwini Municipality of KwaZulu-Natal, South Africa between May 2009 and May 2010 (Pillay, 2010). From the study participants, 35.5% of patients indicated that their specific religious, cultural, or personal belief system had specific dietary requirements. The most commonly prohibited items among those who did have specific dietary requirements was alcohol and porcine/pork (53%), and bovine/beef derived products (43%). 41.4% of patients indicated that they would not take a medication if it contained an ingredient which their specific dietary requirements did not allow; 75.1% agreed that they would take it for a serious illness (such as cancer) while 44.3% indicated that they would not take it for a minor illness (such as the flu). Most patients (63.3%) would take a medication which contained products that are not allowed according to their specific dietary requirements for a chronic condition and 36.2% would stop taking a medication if they found out that it contained prohibited products. 94.3% of patients had never been informed by a health care worker that a medication contained ingredients which may be in contravention of their specific dietary requirements. 93.1% of patients believed that physicians should talk to patients about spiritual faith in terms of a patient's health and medication regimens. 60.6% of the sample agreed that manufacturing companies should indicate the presence of ingredients that may not be allowed according to certain individuals dietary preferences and 48.0% indicated that they were more likely to accept treatment that suited their dietary preferences.

Very few patients (4.9%) were aware that medications contain constituents of bovine, porcine, dairy, or alcohol origin. 94.6% of patients could not identify any product, in a table of eight commonly used prescription and nonprescription items, which contained any ingredients that may not be permissible according to their specific dietary requirements. Religion was a significant factor ($P = 0.008$) when patients were required to indicate if it was difficult to take their medication exactly the way the doctor had told them. When questioned if they would take a medication containing an ingredient which their specific dietary requirement did not allow, only 10% of Muslim patients agreed while 100% of Christians and 64.5% of Hindus indicated that they would take it ($P = 0.000$). When asked if they would be willing to take a medication containing an ingredient that their specific dietary requirements did not allow for a serious illness (e.g., cancer) 37.4% of Muslims, 100% of Christians, and 88.4% of Hindus agreed

that they would take the medication. When asked if they would take it for a minor illness (e.g., the flu) 7.2% of Muslims, 100% of Christians, and 57.9% of Hindus agreed that they would take it ($P = 0.000$). In terms of chronic illness and the taking of a medication containing an ingredient which is not permissible, 18% of Muslim patients, 100% of Christian patients, and 72.3% of Hindu patients indicated that they would indeed take the medication ($P = 0.000$). All religious groups agreed that doctors should speak about spirituality with regard to health and treatment regimens (i.e., 90.6% of Muslim patients, 98.6% of Christian patients, and 89.3% of Hindu patients) ($P = 0.004$). 90.6% of Muslim and 91.7% of Hindu patients believed that manufacturers should indicate the presence of potentially problematic ingredients.

Religion, Medicine Use, and Health Professionals

Health professionals have an ethical obligation to receive informed consent from their patients to conduct treatment or perform a medical procedure but how informed are patients regarding the religious, cultural, and spiritual sacrifices entailed in making a specific treatment choice? Understanding cultural and religious practices could contribute to increasing patient compliance and building a relationship between health professional and patient based on trust and mutual understanding. Religious and spiritual factors also need to be taken into account when counseling a patient and therefore it is important for health professionals to understand patients' beliefs and practices. In addition, health professionals need to be aware of their own cultural influences and reflect on these when interacting with patients.

There are a large number of studies that indicate that most patients would like their physicians to include the spiritual and religious considerations during the illness experience (Armbruster et al., 2003; Daaleman and Nease, 1994; Ehman et al., 1999; King and Bushwick, 1994). Many physicians accept that patients' religion and spirituality can positively affect their health, however, most do not initiate enquiry into religious or spiritual background (Armbruster et al., 2003; Brooks and Chibnall, 2001; Chatters, 2000; Chibnall and Brooks, 2001; Daaleman and Frey, 1999; Ellis et al., 1999). Of 724 quantitative studies of religion and health published during the 20th century, 66% of studies found that a statistically significant relationship existed between religion and improved mental health, greater social support, and less substance abuse (Johnston et al., 2007). Religious patients relied on beliefs as coping mechanisms, while nonreligious professionals and patients did not, as they felt that religion had no role to play in managing and coping with illnesses which was due to psychological and physical factors (Johnston et al., 2007).

Religion and culture in these first world nations also became the basis for withholding medical services, with 14% of health professionals, specifically physicians, indicating that their personal religion and beliefs justified withholding information from their patients (Sloan, 2009). One such example is a study, conducted by Davidson et al. (2010) in Nevada, United States of America (USA), which found that religious pharmacists were more likely to refuse to dispense medical abortifacients and emergency contraceptives, while nonreligious pharmacists were more willing to dispense (Davidson et al., 2010). The primary intention of these health professionals was to honor their own beliefs rather than act in the best interest of the patient (Davidson et al., 2010).

A Dutch study surveyed 120 General Practitioners (GPs) regarding the extent to which the GPs respect the religious beliefs of their patients (Kuyck et al., 2000). The study found that only 16% of GPs enquired about the religious affiliation of their patient during registration at their practice, while 25% enquired during routine consultation (Kuyck et al., 2000). Religious beliefs became more important with situations that were considered a "major life event" such as abortion, terminal illness, and euthanasia (Kuyck et al., 2000). A study conducted in the USA, between 1976 and 1986, indicated increased enquiry about patient's religious affiliation in situations relating to terminal illness, with 69% of physicians indicating that they do enquire about religious beliefs. With respect to near death experiences, 68% of physicians enquire about religion, while 52% enquire about religion when dealing with abortion issues (Craigie et al., 1988). The Dutch study found that the propensity of a GP to enquire about religion was also dependent on their own religious upbringing (Kuyck et al., 2000). In this sample, GPs of Protestant upbringing were more likely to discuss religious beliefs with patients (Kuyck et al., 2000). In an evidence-based medicines study, conducted in Canada, it was found that contextual factors such as the religion and ethnicity of the physician did not significantly influence the physician's decision to prescribe a particular treatment (Tracy et al., 2005). However, there was a significant difference ($P = 0.005$) in the influence of religion on a female physician's decision to prescribe a certain treatment versus a male physician (Tracy et al., 2005). The authors suggested that female physicians were more likely to respond to contextual clues, and spend more time with patients, engaging in more communication that could be considered patient centered than their male colleagues.

In addition, a study conducted by Siegel et al. (2002) on a sample of 165 pediatricians and pediatric residents in the United States of America (USA) found that few pediatricians enquired about spirituality and religion despite believing it to play a role in patient healing. The majority of pediatric residents considered themselves to be religious/spiritual, and were more likely to pray with patients and initiate spiritual dialog. This group was also more likely to contact a religious leader or (spiritual/religious professional) on behalf of their patient.

A study of the awareness, attitudes, and knowledge of psychiatrists in addressing issues of faith (particularly dietary restrictions) was conducted in the south-west of England (2008) by Khokar et al. Results indicated that although the majority were aware of the presence of potentially forbidden excipients (different substances) in medications, more than half (53%) indicated that discussion should only take place if the patient indicated concern (Khokar et al., 2008). However, 55% indicated that information relating to the presence of "forbidden contents" may negatively influence a patient's future compliance to medication (Khokar et al., 2008). This is in contrast to Pillay (2010) who also included health professionals in a study on the influence of religion on medicine use in

the eThekwini District in South Africa. Almost all participants (93.7%) considered themselves to be part of a religion, with 43.4% indicating that they had personal beliefs independent of their religious beliefs. More than three quarters (78.9%) did not routinely enquire about a patient's religious affiliation; this number decreased to 65%, when asked about establishing their patient's religious beliefs in a health crisis or life threatening illness. Over three quarters (88.1%) indicated that they do not take a spiritual history from their patients. Almost two-thirds (64.8%) indicated that they were rarely asked to discuss religious and spiritual issues by a patient.

Doctors were more likely to agree that patients' religious belief positively affects their health, and that patients' and family religious beliefs were important to patients' care. They were also more likely than pharmacists to believe that a patient or patient's family would feel that a health care professional was imposing their religious views on them, if a health care professional engaged in religious discussions. Doctors were more inclined to believe that religious involvement reduces patient morbidity, and that health care professionals should acknowledge/support patients' religious beliefs.

Numerous reasons have been cited for physicians not initiating spiritual discussion. These include physician discomfort in relation to psychosocial and emotional interventions, lack of time, lack of training, and the applicability of spiritual and religious concepts within a patient encounter (Armbruster et al., 2003).

Understanding Culture and the Health System

Health care systems face many challenges with the diverse, multicultural populations of the world. The relationship between medicine use, religion, and culture is complex, has been under discussion for many years and requires investigation employing medical ethnographies. The early works by William Osler in early 20th century medicine viewed religion and medicine in opposition where medicine was scientific, objective, and neutral while religion was irrational and subjective. Science required religion to conform to the values of medicine (Bishop, 2009; Bishop and Trancik, 2013; Stahl, 2013; Trancik, 2013). The secular and scientific viewed medicine as the judge of religion demanding that religion prove it is an effective and efficient biopsychosocial therapy (Bishop, 2011). This view has evolved to the extent that today religion and medicine are seen as binary, and to the extent that religion may be perceived as an alternative form of medicine (Cohen, 2007) and some religious rituals are allowed in hospitals (Taylor, 2012). This indicates some tolerance of religion in the medical arena, however, this must still occur in a defined regulated space (Cohen, 2007).

Arthur Kleinman (1978) described medical systems as both social and cultural systems with meanings and behaviors attached to social relationships and institutional settings and believed that separating the cultural system from the social aspects of health care is not possible. Kleinman developed a model that viewed medical systems as cultural systems to better understand how culture mediates between the external and internal parameters of the medical system. He further stated that culture determines the content, effects, and changes of a medical system. Illness is viewed as a cultural idiom that links beliefs about the cause of the disease, symptoms experienced, patterns of illness behavior, treatment decisions, therapeutic practices, and the evaluation of the therapeutic outcome. A system of relationships exists between these components, governed by the same set of social rules, thus health, illness, and health care must be understood in relation to each other and cannot be dealt with in isolation as this may lead to a distorted understanding of how each function within a health care system and may lead to errors in cross-cultural comparisons. Both semantic network analysis (Good, 1977) and symbolic analyses support this (Ahern, 1975; Gould-Martin, 1975; Harwood, 1971; Ingham, 1970; Obeyesekere, 1976; Turner, 1967). Chinese culture employs cross-cultural medical models (Kleinman, 1975).

The concepts of gender, race, and ethnicity are important in multicultural health care systems. There exists a fair amount of overlap of and distinctions between race and ethnicity and how they relate to health. For example, race was initially associated with the biologic genetic makeup of a person but more recently has been closely associated with the social experiences of belonging to a particular social subgroup, while ethnicity has been associated with social background, shared traditions/cultures, or language and religion that are specific and passed through generations providing a sense of identity and belonging to a specific group. Ethnic inequalities in health and health care exist in some settings as a result of racism and socioeconomic position impacting on the racial/ethnic minority groups (Bhopal, 2007). A report on sex, illness, illness behavior, and the use of health services (Mechanic, 1978) showed that women reported illness more than men and this was related to how women responded to their illness and life situation. This difference was reduced when objective measures were used (more tangible symptom of the illness) implying women reported more subjective symptoms than men, specifically symptoms indicative of physical disease or psychosocial stress.

Culture is often the underlying cause of the burden of diseases borne by communities of color and despite years of research and efforts to reduce the degree of poorer health outcomes for communities of color the gap is widening (Institute of Medicine, 2001). This is due to the fact that the concept of "culture" is rarely defined or adequately measured.

There exists a lack of clarity of the impact of culture on health outcomes as a result of the poor understanding of this concept and the proxy of race is used for culture. When this single proxy variable was used in a multilinear regression, its contribution accounted for an insignificant proportion of variance and was left out of the analysis (Gregg and Saha, 2006) leaving a gap which was filled by socioeconomic status (Zambrana and Carter-Pokras, 2010). Such compounding of race and culture misinforms population science (Kagawa-Singer, 2006).

Scientifically, culture is a complex, dynamic, integrated conceptual framework that is unrelated to how it is operationalized in health behavior theories. If the concept of culture were more appropriately operationalized, results from studies with diverse populations would yield more scientifically valid findings relevant to that specific community. Steps to achieve this include (i) when culture is a factor of behavior then researchers must provide their definition of culture and identify the measures used

to operationalize it; (ii) develop models that capture the holistic influence of culture on health beliefs and behaviors; (iii) establish the cross-cultural equivalence and validity of measures; (iv) address the limitations of acculturation; (v) develop guidelines for the use of culture in population science to resolve confusion with racial/ethnic groups; and (vi) use more inductive and mixed method studies to identify unrecognized domains of cultural influence on health outcomes in diverse cultural communities (Kagawa-Singer, 2012). Thus, more community appropriate results from studies could assist with developing more effective strategies to reduce poorer health outcomes for communities of diverse cultures. Until that time, health care workers need to understand that these contextual factors experienced by patients and by themselves, will influence access to care, adherence to treatment, and health outcomes for patients. However, health care workers need to be careful to not assume that all people belonging to a religion or race group or ethnic group are homogenous. Each patient needs to be engaged on an individual basis and stereotyping should be avoided.

Conclusion

Culture is an important consideration in medicine use. It is a worldview that is embraced by individuals and communities and passed down to generations. Culture affects health care perceptions and attitudes as well as behavior, based on the values and beliefs of an individual. Culture also tends to evolve over time. Studies have indicated that treatment interventions are more effective when they are culturally accepted and recognized. Health care professionals need to recognize the influence of culture (and its many surrogate indicators), when dealing with patients, not just in terms of understanding their medical condition, but also to encourage adherence to medication treatment plans. In this increasing global world, and with the increased movement of populations across countries (as migrants), cultural sensitivity would need to be incorporated into training programs for health care professionals internationally, and strengthening of communication and systems between health providers and spiritual leaders is critical. Finally, more research is required around the impact of culture on health outcomes, and on interventions that can help to promote cultural sensitivity and therefore medication adherence in communities.

Key Lessons

Health professionals need to be aware of the influence of culture on patient's medication use and self-care activities and counsel or create interventions tailored to these ethnic groups.

Health professionals should engage in discussions with patients regarding the ingredients contained in medicines and its impact on patient's observance of religious rules to prevent disruption of treatment in the event of the patient finding out. This will build trust in patients. If alternatives exist, these should be offered.

Patients continue to express the need for transparency in labeling of medicines, which should be introduced by regulators as much as the food industry has introduced transparency in labeling for specific dietary requirements.

Health professionals should include a short religious enquiry as part of their initial consultation to establish any religious limitations regarding dietary requirements.

Health professionals should familiarize themselves with religious organizations in their area so they can consult them for advice and refer patients who require information.

Glossary

Culture The sum of attitudes, customs, and beliefs that distinguishes one group of people from another.
Halal Food and drink that is permissible in Islam of or being meat from animals slaughtered in the manner prescribed by Islamic Law.
Haram Food and drink that is prohibited as it is from meat from animals not slaughtered in the manner prescribed by Islamic law.

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Disease Mongering: Corporate Greed and the Creation of Disease

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Introduction

Pharmaceutical companies operate within a capitalist environment, and therefore, like all other for-profit organizations, are oriented to maximizing revenue and increasing the value of their shares. In simple terms, there are two ways of increasing revenue, raise prices or sell more products. While these are not mutually exclusive strategies, it is not always possible to combine them. Even in the unregulated US market where prices are higher than anywhere else in the world (Langreth et al., 2015), there is a pushback as witnessed by the controversy about the price of the EpiPen used for the treatment of serious allergic reactions that forced Mylan to halve the price (Skinner, 2017). Some US states are starting to take action to try and counter unconscionable price increases (Greene and Padula, 2017).

There are a number of ways that companies can achieve greater sales of their products. They can develop drugs that treat diseases where there were no previous therapies, they can market newer more effective treatments, or they can compete in an existing drug class. However, despite the tens of billions of dollars that companies spend each year on research and development (R&D) (PhRMA, 2016), only about 10% of new drugs are major therapeutic advances compared to existing medicines (Prescrire Editorial Staff, 2017). So-called "me too" drugs that represent the bulk of the output of R&D are less likely to generate the level of sales that companies aim for.

The other way to sell more drugs is to either find new diseases to treat, expand the definition of existing diseases, or set a new benchmark for when treatment should begin. Sometimes this may be entirely appropriate, as with HIV where the early approach to treatment using antiretroviral therapy was to wait until the CD4 level dropped below 500 cells/mm^3, to the current recommendation to start treatment once the diagnosis is made. Whereas this change was made in the interest of achieving a better health outcome, in most cases these changes are made for commercial reasons, that is, to increase revenue. In these circumstances, this approach is usually referred to as "disease mongering."

The term disease mongering appears to have been coined back in the early 1990s by the medical journalist Lynn Payer. Payer's thesis, as summarized in a review of her book by Ray Moynihan, was that "the boundaries of disease are fluid, and that there are too many vested interests trying to push those boundaries as wide as possible." Doctors, drug companies, test makers, medical writers, hospitals, courts, and insurance companies were all: "Trying to convince essentially well people that they are sick, or slightly sick people that they are very ill—is big business" (Moynihan, 2002a, 2002b). Payer's message was only picked up by a relatively small number of people. The notion of disease mongering achieved much wider publicity following the publication of an article by Moynihan in the 2006 April fool's issue of the *BMJ* about a made up disease called "motivational deficiency disorde" and the introduction of indolebant, a supposedly newly discovered treatment for this condition (Moynihan, 2006).

The release of the article coincided with a 3-day conference on the subject in Newcastle, Australia attended by about 150 national and international delegates and the papers presented at this conference were subsequently published in a special edition of *PLoS Medicine* (Public Library of Science, 2006). In their introduction to this special issue, Moynihan and Henry defined disease

mongering as "the selling of sickness that widens the boundaries of illness and grows the markets for those who sell and deliver treatments"; whether that is medicalizing aspects of ordinary life, turning mild problems into serious illnesses, or framing risk factors such as high cholesterol as diseases (Moynihan and Henry, 2006). While they acknowledged that for any "mongered" condition certain individuals with severe forms might benefit from industry-raised awareness, and some people might welcome their symptoms being branded a disease since it "legitimizes" what they experience, their overall conclusion was that disease mongering is dominated by marketers who are primarily interested in profit.

Disease mongering fundamentally corrupts the meaning of modern medicine by elevating commercial goals over the objective of serving the public interest in both health and economic terms. Disease mongering "carries the dangers of unnecessary labeling, poor treatment decisions, iatrogenic illness, and economic waste, as well as the opportunity costs that result when resources are diverted away from treating or preventing more serious disease. At a deeper level it may help to feed unhealthy obsessions with health, obscure or mystify sociological or political explanations for health problems, and focus undue attention on pharmacological, individualized, or privatized solutions. More tangibly and immediately, the costs of new drugs targeted at essentially healthy people are threatening the viability of publicly funded universal health insurance systems" (Moynihan et al., 2002).

The remainder of this article will first delve into the general techniques that companies use to expand or create definitions of disease and then it will use case examples of disease mongering to show how these techniques have been used in the past. Finally, the article will conclude by putting disease mongering into the context of how society deals with the boundary between health and illness.

Approaches to Disease Mongering

The message from the pharmaceutical industry collectively and from companies individually is that they are not disease mongering, rather they engage in appropriate marketing. At one conference, Harvey Bale, at the time the director general of the International Federation of Pharmaceutical Manufacturers and Associations, conceded that there were examples of unethical marketing but maintained that most promotion was ethical. The Association of the British Pharmaceutical Industry produced a pamphlet for journalists where it claimed that companies do not define diseases. Individual companies, such as GlaxoSmithKline, have denied that they engaged in disease mongering to sell more of its drug for restless leg syndrome (Moynihan et al., 2008). But a report from Reuters Business Insight makes the motivation behind the campaigns clear. The strategy is to "change the way that people [and doctors] think about common ailments and to make natural processes into medical conditions"; to see problems that were previously regarded as trivial or part of the human condition, such as baldness, short eyelashes, or skin wrinkles, as issues that are worthy of medical attention, and that in fact need medical attention (Moynihan and Cassels, 2005). Moreover, the message in disease mongering campaigns always follows the same pattern—pushing out the boundaries of diseases as far as possible, while at the same time restricting the treatment for these conditions to medications alone.

Disease mongering campaigns are directed both at consumers and at health care professionals who have the ability to prescribe, primarily doctors. While the methods described further are common in disease mongering campaigns, they are also widely used in promotion, in general.

Disease Mongering to Doctors

Obviously, expanding the definition of what requires pharmacological treatment is key to the success of disease mongering. Traditional methods of influencing doctors, such as journal advertisements and visits of sales representatives, while still important, are giving way to methods that use the direct control of knowledge and the means of transmitting that knowledge. This section focuses on three of those methods—key opinion leaders, ghost management of clinical research, and the use of clinical practice guidelines and continuing medical education.

Use of Key Opinion Leaders

In trying to get their message out to doctors, companies are cognizant of the reality that if they communicate directly with doctors, their message risks being perceived as having a commercial bias. As a result, the concept of using "key opinion leaders" (KOLs) as an "independent" source of information has significantly expanded. In the United States, a 2007 survey found that 16% of physicians, or about 141,000 received payments for serving as a speaker or being part of a speakers' bureau (Campbell et al., 2007). More recently, in just 5 months of 2013, companies made what appear to be speaker payments of US$400 or greater to 55,000 US doctors (Sismondo, 2015).

One way of judging the importance that pharmaceutical companies place on KOLs is the fact that roughly one-third of the marketing budget for pharmaceutical companies is spent on them (Millard, 2008; Elliott, 2010). This amounts to an average of about US$38 million on each product as it moves from clinical testing to launch (Cutting Edge Information, 2005). Companies are willing to spend this amount of money because of the return that they get. According to an internal Merck document, doctors who attended a lecture by a KOL on Vioxx (rofecoxib) wrote an additional US$623.55 worth of prescriptions for the drug over a 12-month period compared with doctors who did not attend. "After factoring in the extra cost of hiring a doctor to speak, Merck calculated that the 'return on investment' of the doctor-led discussion group was 3.66 times the investment, versus 1.96 times for a

meeting with a sales representative" (Hensley and Martinez, 2005). Whereas in 1998, in the United States, the number of talks by sales representatives and KOLs were about equal at just over 60,000 each annually; by 2004 there were almost twice as many talks by KOLs compared to sales representatives (Hensley and Martinez, 2005)—a reflection of the economic benefits of using KOLs instead of sales representatives. Anton Ehrhardt, the senior medical director for the Global Medical Affairs division of Millennium Pharmaceuticals, was quite open about the value of KOLs. "The 'dirty little secret' in this field . . . is that people working in pharma view the KOLs as sales agents" (Millard, 2008). According to Kimberly Elliott, a former drug company sales representative, her company "would routinely measure the return on our investment, by tracking prescriptions before and after their [KOLs'] presentations . . . If that speaker didn't make the impact the company was looking for, then you wouldn't invite them back" (Moynihan, 2008b).

Finally, KOLs are often used as guest editors for journal supplements where a series of articles favorable to a new drug are published. Previous work has shown that, in general, the quality of articles in paid journal supplements is inferior to that in the parent journal (Rochon et al., 1994).

Manipulating Clinical Research

Clinical trials form the basis for medical practice. Regulators such as the Food and Drug Administration (FDA) use them to decide whether or not to approve a new drug. Doctors may not read the original research, but that research is incorporated into continuing medical education (CME) talks, clinical guidelines, and review articles. Pharmaceutical companies fund the vast majority of clinical trials (Moses et al., 2005) but these trials also present an economic and ethical dilemma to drug companies. Trials using rigorous methodology, the appropriate population groups, and that are properly analyzed and published in a manner that accurately and completely presents their conclusions are the ideal. At the same time, companies can use trials with positive results in order to drive sales. Negative trials can have significant adverse effects on sales. Within 1 year of the publication of the Women's Health Initiative trial that found that the estrogen/progestin combination caused an increased risk of cardiovascular disease and breast cancer in postmenopausal women, prescriptions for Prempro, the most widely sold estrogen/progestin combination, had declined by 66% in the United States (Hersh et al., 2004).

There is, therefore, a strong temptation to deviate from the ideal for economic reasons. The result is trials that are often biased in some manner. The contention is not that every industry-funded trial is biased but the accumulating evidence provides strong grounds to believe that this type of behavior is common. The results of clinical research are comprehensively manipulated through the practice of ghost management that encompasses ghostwriting and guest authorship. Ghostwriting refers to the practice of an article being written by a person who is not listed as an author, usually an employee of a medical writing firm working for the product's manufacturer. Guest authorship refers to named authors, usually academic clinicians, who have not written the article or been directly involved in the study it describes, and who often have no access to study data. Sismondo describes a broader, integrated process of "ghost-management" consisting of the publication of clinical trial results to provide a positive body of evidence concerning the effects of a specific drug (Sismondo, 2007).

Ghost management takes place in the context of all clinical research, but is perhaps most pernicious when it comes to Phase IV or "seeding trials," trials that are conducted once the product is on the market. These are trials without a scientific design to test a specific research hypothesis whose main goal is to encourage physicians to use new drugs on a widespread basis. A fifth of drug trials published in the six highest impact general medical journals in 2011, including the *New England Journal of Medicine*, *Lancet*, and *PLoS Medicine*, had features that were suggestive of being designed for marketing purposes (Barbour et al., 2016).

When individual principal investigators have financial ties to the manufacturer of a study drug, then regardless of who funded the trial, a financial tie is significantly associated with a positive outcome in randomized controlled trials (Ahn et al., 2017). When a pharmaceutical company sponsors a drug study, both the results and conclusions of the study are more favorable to the product under examination than when sponsorship is undertaken by any other source (Lundh et al., 2017).

Controlling Clinical Practice Guidelines and Continuing Medical Education

With the exponential increase in medical information, doctors are finding it harder to sort out the wheat from the chaff and decide how to manage their patients. Many doctors are increasingly turning to clinical practice guidelines (CPG) to help them in preventing illness and diagnosing and treating it once it occurs (O'Malley et al., 2007). CPGs are print and/or electronic documents that, when rigorously done, involve "defining the primary clinical question the guidelines will address, surveying stakeholders (physicians, patients, policy makers) to identify priority areas, conducting an extensive systematic review of the scientific literature on the chosen topic . . . rating and synthesizing the evidence, convening a panel of experts to discuss the evidence and make clinical recommendations, submitting the recommendations for review to independent experts, and finally, publishing the guidelines and creating knowledge translation tools to push the information out to clinicians" (Collier, 2011).

Clinicians rely on CPGs for guidance when making treatment decisions for patients. Although CPGs should be based on a critical analysis of the best available scientific evidence, authors' recommendations in some guidelines have been based on lower levels of evidence or expert opinion (Tricoci et al., 2009). Therefore, recommendations may be vulnerable to biases (Bindslev et al., 2013), which are of particular concern since financial ties are common among guideline authors, committee members, and drug companies that manufacture medications recommended in guidelines (Abramson and Starfield, 2005; Norris et al., 2011). Just as financial conflicts of interest can influence the reporting of clinical trials, the same is true for CPGs. Cosgrove et al. evaluated the American Psychiatric Association's Practice Guideline for the Treatment of Patients with Major Depressive Disorder to determine the existence of financial and intellectual conflicts of interest and examine their possible effects. Financial ties to industry were disclosed by all

members of the guideline development committee. Fewer than half of the studies cited in support of the recommendations met criteria for high quality and 17.2% did not measure clinically relevant results. One-fifth of the references were not congruent with the recommendations (Cosgrove et al., 2013).

CME is complementary to clinical practice guidelines; it is also subject to commercial bias. Data from the United States suggest that, in 2014, support from the pharmaceutical industry accounted for approximately 25% of total income reported by CME providers (Accreditation Council for Continuing Medical Education (ACCME), 2014). Although industry representatives maintain that their funding of CME is motivated by the desire to provide up-to-date information to doctors, researchers independent from the pharmaceutical industry suggest that this financial support is used to advance sponsors' marketing interests (Relman, 2001; Rodwin, 2010; Steinbrook, 2010). Funding for CME is generally considered by researchers to be part of the marketing budget, dedicated to producing sales, and they include it when reporting promotional expenses (Gagnon and Lexchin, 2008; Kornfield et al., 2013). Fugh-Berman and Hogenmiller argue that even when CME activities have not received pharmaceutical industry funding, speakers who are funded by industry can still be used (Fugh-Berman and Hogenmiller, 2016).

In early 2004, mdBriefCase, a commercial CME provider that was approved for CME credit by the Canadian College of Family Physicians, distributed material regarding a case of a man who was supposedly suffering from andropause, a decrease in his level of testosterone. At that point there had not been any long-term randomized controlled trials showing the benefits of androgen replacement in men who met the description of the patient in this case. (There still have not been any convincing studies (Huo et al., 2016).) The doctor in charge of reviewing the case before it was distributed was on the advisory board for Solvay Pharma, the company that funded production of this material. The doctor's conflict of interest was not disclosed in the material. One of the questionnaires mentioned in the case, the Androgen Deficiency in Aging Males, was developed in part by Solvay. This potential commercial bias was also not disclosed. Finally, the therapy given to the patient in this case fits the description of the product that Solvay was currently promoting. Moynihan documents how one Australian provider of medical education allowed companies to have input into the selection of some seminar speakers despite the fact that these seminars were advertised to general practitioners with the claim that "all content is independent of industry influence" (Moynihan, 2008a).

Disease Mongering to Consumers

Company executives portray promotion to consumers as a way to empower them and enable them to act as partners with their doctors in deciding the best course of treatment. While there may be examples of this, for the most part what we are witnessing are campaigns that skew the understanding of the causes of illness and distort the knowledge of treatments, playing up the benefits, and minimizing the harms (Moynihan and Cassels, 2005). Three main methods that companies use that will be covered in this section are funding patient groups, direct-to-consumer advertising (DTCA), and the use of mass media.

Funding Patient Groups

Just as doctors are suspicious of messages coming from sales representatives, patients are likely to be skeptical about what drug companies say about the products that they produce. To get around this problem, companies are increasingly funding patient groups. Funding of groups is widespread, at least in the United States, as demonstrated by the results of recent surveys published in the *New England Journal of Medicine* (McCoy et al., 2017) and *JAMA Internal Medicine* (Rose et al., 2017). The former looked into the financing of 104 patient-advocacy organizations (PAOs) and found that 83% (86) reported receiving financial support from industry. Of the 59 that published the amount of donations, 23 (39%) reported receiving at least US$1 million annually from industry donations and in 11 of these 59 cases the donations made up at least 10% of their annual income. In the latter survey, a total of 165 of 245 PAOs (67.3%) reported receiving industry funding, with 19 of 160 PAOs (11.9%) receiving more than half of their funding from industry.

Information from other countries is not as detailed but funding of breast cancer groups in Canada is widespread (Batt, 2017). In Australia, in 2008, Pfizer spent A$135,000 to set up the Australian Lung Foundation in conjunction with the launch of its antismoking medication Champix (varenicline) a year earlier, and in 2009, GlaxoSmithKline spent A$1.3 million sponsoring 14 groups (Dunlevy, 2010). Nine out of 15 British patient organizations reported receiving corporate sponsorship that constituted a median of 11% of their revenue (Ball et al., 2006). Finally, in Finland, 71% (39) of 55 organizations said that they had received some form of financial support from pharmaceutical companies (Hemminki et al., 2010).

Although it is not possible to attribute a cause and effect relationship to the receipt of industry funding and the positions that patient organizations take, there are a number of documented cases where the latter have publicly supported industry. The president and CEO and the vice president of research and professional education of the Canadian Diabetes Association (now Diabetes Canada), which acknowledged receipt of unrestricted education grants funding from 11 companies, including Sanofi, the maker of insulin glargine (Lantus), wrote a letter to the *CMAJ* protesting the decision by the Canadian Coordinating Office for Health Technology Assessment, the national health technology assessment body, to recommend that provincial governments not fund Lantus (Howlett and Lillie, 2006). The British Multiple Sclerosis Trust wrote to the Daily Telegraph to criticize the negative funding decision of the National Institute for Health and Care Excellence regarding nabiximols and fampridine, two drugs the Trust characterized as "life-changing." Although the Trust did receive money from the companies marketing these products it did not disclose that fact in its letter (Arie and Mahony, 2014). In a more systematic review, Health Action International, a consumer-oriented non-governmental organization based in Amsterdam, examined the association between patient and consumer organizations' financial sponsorship from the pharmaceutical industry and their positions on the European Commission's proposal to allow

a limited form of DTCA. An association was observed between receiving sponsorship and support for an expanded role of the pharmaceutical industry as an information provider about its medicines to consumers (Perehudoff and Alves, 2011).

Direct to Consumer Advertising

Only the United States and New Zealand allow full DTCA, that is, mentioning the name of a drug along with its indication in a single advertisement. However, other countries such as Australia, Canada, and The Netherlands allow disease awareness ads where a condition is mentioned and then readers or viewers are advised to consult their doctor about a treatment for the condition. In addition, Canada also allows the mention of the name of a product without stating its indication although that indication can be implied. The pharmaceutical industry's viewpoint about DTCA is encapsulated in a statement from the Association of the British Pharmaceutical Industry (ABPI): "The public want more information about their medicines from a wide range of sources, a survey has shown. And the Association of the British Pharmaceutical Industry (ABPI) said today that the results indicated that information provided by the industry would be welcomed by patients" (abpi, 2003). In other words, patients want more information about the medicines that they are taking or are potentially going to take and pharmaceutical companies are in a position to provide that information and are willing to do so. In the United States, drug companies are currently spending about US$5.8 billion annually on DTCA (statistica, 2017).

Studies on the three main forms of DTCA—broadcast advertising, print advertising, and websites—have all found that the quality of information that they contain is seriously flawed. A review of DTCA ads airing on television between 2008 and 2010 concluded that of the 84 most emphasized claims, 55% of them were potentially misleading (Faerber and Kreling, 2013). An earlier analysis of television ads found that while 82% made some factual claims and 86% made rational arguments for product use, only a quarter described the causes of the condition, risk factors, or prevalence. More than half of the ads portrayed the product as a medical breakthrough (Frosch et al., 2007). Ads in magazines generally did not fare any better. In 67 unique drug ads that appeared in 1998 and 1999, two-thirds used emotional appeals and almost 90% described the benefits of the medication with vague, qualitative terms while only 13% used hard data. None of the ads mentioned cost (Woloshin et al., 2001). Ads for bleeding disorders in a patient-directed magazine devoted twice the amount of text to benefits as compared to risks/adverse effects, and the information about the latter was more difficult to read. Experts in the area found that only slightly more than one-third of the ads presented the claims fairly and accurately (Abel et al., 2008). DTCA websites were noted to offer benefits on the homepage 82% of the time, whereas risk information was two clicks away in 75% of the cases. While most websites had a direct link to benefit information in the main navigational button set on the homepage, only 8% of websites provided the same tool for risk information (Huh and Cude, 2004). Drug company-funded mental health websites were significantly more biased toward biogenetic causes of illness and medication than were sites that were financially independent of the industry (Read and Cain, 2013).

The accumulated evidence strongly suggests that DTCA indirectly changes prescribing behavior through its effect on motivating patients to request particular products from their doctors and that there are more negative than positive consequences from the effects of the medications that patients get. Kravitz et al. carried out a randomized controlled trial of the influence of patient requests for paroxetine using standardized patients who described symptoms of depression or of a less severe temporary condition, "adjustment disorder" that is due to life problems and does not require antidepressant treatment (Kravitz et al., 2005). If patients requested an advertised brand-name drug, they were equally likely to receive an antidepressant prescription whether they had symptoms of depression or "adjustment disorder."

US magazines, cable, and satellite television reach Canadian audiences with prescription drug advertising that is illegal under Canadian law. Researchers looked at three drugs that were being promoted on US media and compared prescribing rates in English-speaking Canada versus Québec, which is mainly francophone, and thus is less affected by US media. They found an effect on prescribing rates for one product, tegaserod, a drug that was later withdrawn from the market for safety reasons (Law and Soumerai, 2008). Among US men residing in the 75 designated market areas, regional exposure to televised direct-to-consumer advertising was associated with greater testosterone testing and receipt of new prescriptions for testosterone products without recent testing for androgen deficiency (Layton et al., 2017). Finally, DTCA may promote over-diagnosis of high cholesterol and over-treatment for populations where risks of statin use may outweigh potential benefits (Niederdeppe et al., 2013).

Use of Mass Media

The introduction of new medicines or the findings of medical research are almost invariably accompanied by press releases either directly from pharmaceutical companies or via public relations companies, advertising companies, or media and communication companies acting on their behalf. The objective is to generate public interest in the announcements by creating news value, obtaining editorial attention, and, in general, generating free publicity (van Nuland and Damen, 2010). The website of one Dutch communication company is quite clear about what the value of engagement is for the company marketing the product: "And there are more groups than just the prescriber that determine your market! We all want to work in a patient-oriented fashion, but there are more stakeholders. We know who they are, but where is the win/win? How do you get eyes on you and your product/service? Walking the tightropes intersecting rules, laws, ethics and still managing to get the market moving" (van Nuland and Damen, 2010).

The press releases that are generated are not neutral documents. One study looked at 235 from 10 pharmaceutical companies that were based on the results of original research. Twenty-one percent were not explicit about the source of original data, and almost one-third did not quantify study results. Moreover, almost half of the releases quoted a study author who was typically the lead

researcher, but although the authors usually commented on the benefits of the research only 10% described the limitations (Kuriya et al., 2008). The companies issuing the press releases are also relying on the fact that, at least in The Netherlands, print media and news websites often publish verbatim copies of press releases (van Nuland and Damen, 2010).

One particularly insidious form of disguised press release are video news releases (VNR) that are designed to look like independently produced news but are actually prepackaged promotions containing film footage typically created by public relations firms working for the corporation (Lenzer, 2006). According to a 2002 survey by a leading VNR producer, 88% of US television stations used VNRs from medical, pharmaceutical, and biotech corporations (Price, 2005). VNRs are regarded as particularly valuable as they can deliver a targeted message to the public in the disguise of real news and news reports are a major source of health information for people (Kaiser Family Foundation, 2005). In January 2006, a television station in Rochester, Minnesota, ran a 90 second story on an inhaled form of insulin that was taken entirely from a VNR prepared by Pfizer, the company marketing the product (Lenzer, 2006). VNRs have run in Australia for an estrogen patch for menopausal women (Media Watch, 2005) and a flu medication made by GSK (Moynihan and Sweet, 2000).

Although experts are often quoted in press releases or featured in news stories, their conflicts of interest are typically omitted. Moynihan and colleagues (Moynihan et al., 2000) reported that 50% of news stories about research on three medications cited at least one expert or study with a relevant financial conflict of interest, of which only 40% were reported. Another analysis of 104 comments in news stories about medical research found that there was a financial conflict of interest in 33 cases of which only one-third were actually mentioned in the news story. When there was a financial conflict, 93% of the comments were favorable to the research. In addition, 23 comments were provided by representatives of advocacy organizations. In six instances, the organization had received sponsorship from a commercial entity but none of those conflicts were reported (Wang et al., 2017). Similarly, of 306 news articles about medication research, 130 did not report that the research had received company funding (Hochman et al., 2008).

Examples of Disease Mongering Campaigns

This section uses documented examples of disease mongering campaigns in a number of areas to show concretely how the various tactics that were described are implemented in practice. This is not meant to be a comprehensive review of all of the industry efforts but rather a representative sample.

Erectile Dysfunction

There is no doubt that rofecoxib (Viagra) is effective in treating ED secondary to organic causes, but had Viagra been confined to use in these cases it would probably have been just a modest commercial success for Pfizer. In order to grow the market, Pfizer had to make Viagra the treatment of choice for a much wider population of men. The perceived prevalence of ED needed to be expanded. The impression had to be created that ED was of significant concern to many, perhaps even most men. The criterion of success for treating ED had to be redefined, and finally, Viagra had to be seen as an important treatment option for men with any degree of ED, including rare or transitory failures to achieve or maintain erections.

This process was started by widely and misleadingly promoting the results of the Massachusetts Male Aging Study (MMAS) (Feldman et al., 1994) to argue that 52% of the entire male population in the United States between the ages of 40 and 70 suffered from ED (Pfizer, 2004) despite using a possibly unrepresentative sample of men in the survey (Lexchin, 2006). Moreover, the MMAS results were at variance with those from a number of other studies. Out of 13 studies on the prevalence of ED that were published prior to June 1998, the MMAS results were the highest (Burls et al., 1998).

The Massachusetts study was also used to support the position that ED has a major psychological impact on men (Feldman et al., 1994) even though it may have been an outlier. In a Dutch study only one-third of all men and 20% of men over the age of 70 with significant ED had major concerns (Blanker et al., 2001). Furthermore, in these sexually active Dutch men, 17–28% had no normal erections, indicating that full erectile function is not essential for sexual functioning.

To make Viagra into a lifestyle drug, Pfizer needed to convince men that it was the first choice of therapy for any degree of ED whatever the genesis of the problem. Here is a sample of the Questions and Answers that used to appear on the "Common Questions" portion of the Viagra website:

> "Question: I don't have erectile dysfunction (ED) because the problem doesn't happen often. Does this mean that VIAGRA isn't for me?
> Answer: Even if it happens once in a while, it's still ED. Most men with ED have it just some of the time. VIAGRA has helped about 16 million men around the world with their ED. And VIAGRA helps treat ED whether it happens often or only once in a while" (Pfizer, 2004). Pfizer reinforced its message with direct-to-consumer magazine ads like one featuring a virile looking man around 40 saying "A lot of guys have occasional erection problems. I chose not to accept mine and asked about Viagra."

The initial television ads for Viagra used an aging Bob Dole (born 1923), a 1996 Republican presidential candidate. Pfizer refocused its advertising campaign to match the lifestyle message on its website and replaced Dole as a spokesman with then 39 year-old Rafael Palmeiro, a former Texas Ranger baseball player (St. John, 2003). Between 1999 and 2001 Pfizer spent over $303 million on direct-to-consumer advertising to get its message about Viagra to men (Findlay, 2000; IMS Health, 2001; Yuan and

Duckwitz, 2002). Besides the large promotion budget, Pfizer has also paid a number of doctors to act as "consultants" delivering public lectures and appearing in the mass media to expound on ED and Viagra (Deer, 1998).

Pfizer denied that it was targeting younger men or that it was positioning Viagra as a life-style drug. Mariann Caprino, a spokeswoman for the company, was quoted in the *New York Times*: "Have we gone out and given our advertising agency instructions to speak to this young population? No, we haven't" (St. John, 2003). But the message from the pictures on the website, in magazine ads, and from people like Rafael Palmiero was that everyone, whatever their age, at one time or another, can use a little enhancement, and any deviation from perfect erectile function meant a diagnosis of ED and treatment with Viagra.

Out of 70 websites dealing with ED, the 31 that were drug company funded were significantly more biased toward biological factors in general, and toward medication in particular, compared with the 39 websites that were not industry funded (Read and Mati, 2013).

Social Anxiety

Social phobia or social anxiety disorder is characterized by a significant level of fear in one or more social situations, causing considerable distress and impaired ability to function in at least some parts of daily life. A literature survey conducted in the early 2000s estimated that the lifetime prevalence was between 0.5% and 2.6% of the population, although one US study put it at 13.3% (Martin, 2003). In the late 1990s, SmithKline Beecham (SKB, now GlaxoSmithKline) received approval to market its antidepressant paroxetine (Paxil) for the treatment of social phobia. That prevalence figure quickly escalated to an estimated 10 million in the US, making it the third most common mental disorder after depression and alcoholism, although the US National Institute of Mental Health continued to put the figure at about 3.7% of the population (Vedantam, 2001).

The approval for the use of paroxetine to treat social phobia coincided with a campaign orchestrated by the public relations firm, Cohn & Wolfe on behalf of SKB. The company created a slogan "Imagine Being Allergic to People" and put up posters with pictures of a dejected looking man vacantly playing with a teacup with messages such as "You blush, sweat, shake – even find it hard to breathe . . . That's what social anxiety disorder feels like" (Koerner, 2002). The campaign used television shows such as "Ally McBeal" and magazines such as *Rolling Stone* to get the message across and, according to the *Washington Post*, media accounts of social anxiety rose from 50 stories in 1997 and 1998 to more than 1 billion references in 1999. About 96% of those media references had the message that "Paxil is the first and only FDA-approved medication for the treatment of social anxiety disorder" (Vedantam, 2001). A month after 9/11, SKB attempted to play on peoples' fears to further increase the sales of paroxetine. The company used an advertisement of a woman walking on a crowded street, her face strained, in a crowd otherwise blurred. The caption on the ad read "Millions suffer from chronic anxiety. Millions could be helped" (Mintzes, 2002).

The medical director of SKB denied that the company had a fiscal motive behind its campaign and said that "the reason we do all this is to enhance the lives of our patients. To be in it for financial reasons only would be short-sighted" (Rose, 1999). Paxil's product manager offered a different perspective. "Every marketer's dream is to find an unidentified or unknown market and develop it. That's what we were able to do with social anxiety disorder" (Goetzl, 2000).

The day that paroxetine was approved for treatment of social phobia, a patient group called Freedom From Fear released a telephone survey that claimed that people with the problem spent nearly 40 hours per week worrying. The survey mentioned neither SKB nor paroxetine, but the media contact listed was an account executive at Cohn & Wolfe (Koerner, 2002). In the United States, there was a coalition of nonprofit groups, the Anxiety Disorders Association of America (ADAA), partially funded by SKB, and in July 1999 as part of its effort, the ADAA held a press conference to publicize the findings of a study that purported to quantify the high economic cost of anxiety disorders. The study in question was underwritten by a group of drug manufacturers (Cottle, 1999). Jerilyn Ross, the founder of the ADAA denied that her organization had ever promoted any drug and maintained that her organization had even got into "fights" with SKB because the company wanted the ADAA to do things it was uncomfortable with (Vedantam, 2001). However, a 1996 ADAA brochure on social phobia that was supported by an educational grant from SKB, advocated the use of medication for the disorder and did not mention the high rate of relapse associated with drug therapy (Cottle, 1999).

Key opinion leaders who have served as paid consultants or scientific investigators for companies marketing treatments for social phobia discount any notion of conflict of interest (Vedantam, 2001). One of the people featured in a video on social phobia that was distributed by Cohn & Wolfe was Dr. Jack Gorman who would later give talks on SKB's behalf about paroxetine. Another prominent physician advocating for paroxetine was Dr. Michael Liebowitz, a consultant to many pharmaceutical companies. Dr. Leibowitz was on the advisory panel that updated and expanded the definition of social phobia that appeared in the Diagnostic and Statistical Manual III-R, the widely used manual of psychiatric diagnoses (Cottle, 1999). Along with Dr. Gorman, he was also the author of an article that maintained that social phobia was significantly underdiagnosed (Liebowitz et al., 1985).

Overactive Bladder

Overactive bladder (OAB) is the symptom complex of urinary urgency, frequency, and urge incontinence. Until 1996, it was more commonly known as incontinence or more formally as "detrusor instability." The renaming was done by two urologists, Dr. Alan Wein from the United States and Dr. Paul Abrams from the United Kingdom, with marketing in mind, although they maintained that Pharmacia was opposed to the name that they chose (Abrams and Wein, 2012). As Dr. Wein said, "detrusor instability sounded like it referred to a psychiatric condition, whereas the phrase overactive bladder was immediately recognizable" (Fiore et al., 2016).

These two doctors organized their first conference on OAB in London in 1997, sponsored by Pharmacia (now part of Pfizer), which started to market tolterodine (Detrol) for its treatment in 1998. A year later, there was a new definition of OAB written by the International Continence Society that expanded the number of people who met the criteria for OAB. The International Continence Society does not list its funding sources on its website (https://www.ics.org) but it does note that it offers Pfizer International Fellowships.

Drs. Wein and Abrams were two of the KOLs that Pharmacia set out to cultivate. A slideshow presented by Neil Wolf, group vice president at Pharmacia, is titled "Positioning DETROL (creating a disease)" (Wolf, 2002). One of the slides titled "Creating OAB KOLs" listed activities, including "advisory board, consultant meetings, significant Phase IV activity (postmarketing trials) leading to ICS definition of OAB changed rapidly and dramatically." Although Pharmacia may have been initially unhappy with the name change, this slide seems to indicate that it later enthusiastically supported that change. The expansion in the recognition of OAB was furthered in December 1997 with the publication of a 114-page supplement of the journal *Urology* that was paid for by an unrestricted educational grant from Pharmacia and guest edited by Drs. Wein and Abrams.

In the slideshow, one slide was titled "Broaden and Own the Understanding of the Market" while another one was titled "Converting a Niche Product into a Mass Market Opportunity." The contents of a third slide listed one of the critical success factors of the campaign as "Establish[ing] OAB as a serious medical condition with profound negative impact on people's quality of life." The latter was achieved in Canada when a new drug for OAB was launched with the manufacturer (Astellas) describing OAB as "a chronic, debilitating condition that can have a profound, negative impact on a patient's quality of life. Many patients with OAB are plagued by depression, experience a disruption in sleep, limit their social activity and experience a loss of control and decreased self-esteem" (Cassels, 2013). Neil Wolf denied creating a disease. His point of view was that "We created awareness of a condition so that people who suffered from the condition could recognize themselves and talk with their doctors" (Fiore et al., 2016). In The Netherlands, Astellas contributed to creating awareness through a website that offered a self-test with four questions. It was recommended that even in the case of mild complaints consumers print the results and take them to their general practitioner (van Nuland and Damen, 2010).

Industry-funded consultants continue to play a major role in the way that OAB is investigated. The majority of nonrandomized controlled trials, epidemiological studies, and randomized controlled trials are industry funded and the majority of authors in these types of studies report conflicts of interest (Tikkinen and Auvinen, 2012). KOLs have also played a major role in expanding the number of people who could potentially be treated for OAB. The initial 2001 survey, with Abrams and Wein as two of the six authors and funded by Pharmacia, that identified 17% of people of 40 years of age and over as having OAB based this figure on a positive answer to any of the three symptoms: frequency, urgency, or urge incontinence. There was no question about whether these symptoms interfered with people's lives or whether they were distressed by them (Milsom et al., 2001). A subsequent survey published in 2009, also funded by Pfizer, and published as a journal supplement with three of the six authors declaring being consultants for Pfizer and one a Pfizer employee upped the number of Americans with OAB to 42 million or 18.6% of the adult population 40 years or over (Onukwugha et al., 2009). The most recent survey, again funded by Pfizer with three authors having a financial relationship with the company and the other two employed by the company, concluded that in 2008 one in nine people in the world had OAB with direct annual costs approximating 2 trillion (Irwin et al., 2011). By contrast, a study in Finland done without the involvement of a pharmaceutical company found numbers approaching these levels only among people 60 years and older (Tikkinen et al., 2007).

The guidelines on the diagnosis and treatment of OAB issued by the American Urological Association (AUA) in 2012 and updated in 2014 were produced by a panel of 11 with 8 of those listing financial ties to companies that marketed treatments for OAB (Gormley et al., 2014). After the initial guidelines were released, the AUA put out a pocket guide for primary care doctors summarizing the recommendations, paid for by Astellas, that by that time was marketing two of the most widely prescribed drugs for OAB (Fiore et al., 2016).

Osteoporosis and Osteopenia

The definition of osteoporosis came out of a World Health Organization-sponsored Working Group that met in 1992. The group defined "normal" bone mineral density as that of a 30-year-old woman and somewhat arbitrarily proposed that osteoporosis should be diagnosed when bone mineral density dropped 2.5 standard deviations below normal and that when it was 1.0–2.5 standard deviations lower then the diagnosis of osteopenia should be applied (WHO Study Group, 1994; Alonso-Coello et al., 2008). However, the report made it clear that "The argument for treating or screening all women is poor" and "[t]he cost of preventive measures may possibly outstrip the savings made by preventing fractures" (WHO Study Group, 1994). Specifically, the group created the osteopenia category for public health researchers for epidemiological purposes and, according to two of the people who attended the meeting, they never intended that people would come to think of osteopenia as a disease in itself to be treated (Alonso-Coello et al., 2008; Spiegel, 2009). This message was repeated in a meta-analysis that looked at the ability of measurements of bone density in women to predict later fractures (Marshall et al., 1996).

However, this is not the message that Merck took away from the WHO report. In 1995, the company had just received approval to market alendronate (Fosamax) for the treatment of osteoporosis. Merck faced a challenge in selling its drug because the condition needed to be diagnosed in the first place. To overcome that barrier, Merck bought the exclusive rights to bone-testing technology from one company, gave a loan to another company to help develop a different machine for testing bone mineral density, and created a leasing program so that doctors could finance the purchase of a machine (Kellcher, 2005; Spiegel, 2009). According to a

former lobbyist for Merck, "Merck would tell you virtually every woman post-menopausal should go on Fosamax." Merck was looking at screening and potentially treating all 40 million postmenopausal women in the United States (Kellcher, 2005; Spiegel, 2009).

When Merck started its campaign in 1995, there were 750 bone-measuring devices in the United States and by 1999 there were between 8,000 and 10,000 (Kellcher, 2005; Spiegel, 2009). Merck also helped push the Bone Mass Measurement Act through the US Congress that allowed Medicare coverage for bone scans. As a result of the substantial increase in the number of machines and Medicare coverage, the number of claims for screening went from 77,000 in 1994 to over 1.5 million in 1999 (Spiegel, 2009). However, by the early 2000s, it was clear that a fracture prevention strategy based on bone mineral density was looking at the problem from the wrong perspective. Most of the fracture burden comes from uncommon events among people who do not have osteoporosis, rather than from common events in those with the diagnosis (Järvinen et al., 2015). This is especially true in women aged 50–59, where a bone mineral density score compatible with osteoporosis will miss 80% of the women in this age group who will actually have a fracture and the cost of preventing one fracture is US$156,400 (Sanders et al., 2006). Overall, 104–270 women would need to be treated for 3 years to prevent a single hip fracture (Alonso-Coello et al., 2008; Järvinen et al., 2015).

These were not the figures that Merck and the groups that it sponsored were putting out. Merck targeted ads and brochures directly at younger women, telling them that "menopause is the single most important cause of osteoporosis" (Kellcher, 2005). The US-based National Osteoporosis Foundation, which received money from drug companies, estimated that 10 million Americans had osteoporosis and that the disease was "a threat for an estimated 44 million Americans or 55 percent of people 50 years of age and older" (Kellcher, 2005). Osteoporosis Australia, which also received funding from companies making osteoporosis treatments, in the early 2000s "issued a press release recently urging people to take a one minute test for their risk of osteoporosis. According to the foundation, 'we call this disease a silent thief: if you're not vigilant, it can sneak up on you and snatch your quality of life and your long-term health.' An accompanying 10 point checklist suggests that merely being a menopausal woman was enough to justify a trip to the doctor to be tested for this disease" (Moynihan et al., 2002).

The consensus conference that came up with the definition of osteoporosis and osteopenia was funded by two drug companies—Sandoz Pharmaceuticals (now part of Novartis) and SmithKline Beecham (now GlaxoSmithKline)—and one foundation—Rorer Foundation—set up by a pharmaceutical company. Recognizing that doctors are much more favorable to company-sponsored consensus conferences as a source of information compared to journal advertising and sales representatives (Pitt and Nel, 2007), companies selling drugs for osteoporosis have also heavily backed these types of meetings. The conference that produced the consensus statement from the Scientific Advisory Board of the Osteoporosis Society of Canada on the prevention and management of osteoporosis was sponsored by nine pharmaceutical companies and the recommendations were published in a supplement to the *CMAJ* that was paid for by three companies (Green et al., 1997). All of the studies up to the end of 2007 looking at the treatment of people with osteoporosis were funded by pharmaceutical companies. These trials were subsequently reanalyzed to look for subgroups of women with osteopenia who would benefit from treatment. In three of four cases, drug company employees were part of the team conducting the reanalysis. In the other case, the reanalysis was conducted by a group that included investigators with financial ties to industry (Alonso-Coello et al., 2008).

Conclusion

Disease mongering represents a fundamental threat to how society draws the boundary between health and illness and how it responds to what to do in the face of illness. Disease mongering promotes a view of people not as healthy autonomous beings but as vulnerable individuals always at risk from a threat just around the corner. And the way to deal with that threat, if it even exists, is only through the consumption of pharmaceuticals. As Iona Heath eloquently puts it: "The rhetoric surrounding disease mongering suggests that it will promote health, but the effect is in fact the opposite. Much disease mongering relies on the pathologizing of normal biological or social variation and on the portrayal of the presence of risk factors for disease as a disease state in itself . . . Disease mongering exploits the deepest atavistic fears of suffering and death" (Heath, 2006).

What are the consequences of widening the boundaries of what is considered a treatable medical problem? One of them is how general practitioners balance the risk/benefit ratio of pharmacotherapy. No drug is without side effects, but side effects are more acceptable as the illness being treated becomes more serious. What degree of side effects are acceptable in treating someone who feels she is too shy? Compared to the other selective serotonin reuptake inhibitors, paroxetine causes significantly more sexual dysfunction (Montejo-González et al., 1997). As the number of people being treated for shyness rises, so will be the number with sexual problems. Other, even more serious consequences from disease mongering are not far behind, including iatrogenic illnesses, the waste of resources on drug therapy when other forms of treatment, or no treatment at all beyond reassurance are much more appropriate. "At a deeper level it may help to feed unhealthy obsessions with health, obscure or mystify sociological or political explanations for health problems, and focus undue attention on pharmacological, individualized, or privatized solutions" (Moynihan et al., 2002).

Many of the conditions that disease mongering focuses on have a direct or indirect social origin or are shaped by natural forces that are out of our control. Much of ED comes from type 2 diabetes that is a result of the way that corporations produce and market food. Concern about ED is also based on a societal definition of what it means to be a man. Social phobia seeks to homogenize how people relate to one another and does not recognize the wide spectrum of how individuals react in a social situation. In many cases,

what is defined as overactive bladder is simply the product of the natural ageing process. Osteoporosis and osteopenia are also largely secondary to other forces that promote obesity, smoking, and a sedentary lifestyle.

None of this should imply that we should ignore people who are genuinely suffering from one of these conditions and who might benefit from drug therapy, but in the vast majority of cases pharmacotherapy is not necessary. The first, and perhaps biggest, step in countering disease mongering is to adopt the recommendation put forward by Moynihan and colleagues and reject the definition of disease put forward by the corporations and their allies in the medical profession and patient movement (Moynihan et al., 2002). We need to forge a new way of looking at these problems based on independent unbiased sources of information and find ways of disseminating these points of view as widely as possible. The medical profession and patient groups also need to reject the offer of resources and perks, however tempting they may be in the face of the absence of alternatives and reestablish themselves as reliable and trusted sources of information about how to deal with problems that distress people. We need to reject the corporate construction of illness in favor of social construction (Moynihan et al., 2002). None of this will be easy but the alternative is to succumb to corporate greed.

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Factors Influencing Pharmaceutical Policy Implementation

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Introduction

The concept of a National Medicines Policy (previously referred to as a National Drug Policy) is most commonly associated with the guidance provided by the World Health Organization (WHO) in two documents, issued in 1988 (World Health Organization, 1988) and in revised form in 2001 (World Health Organization, 2001). The first of these emphasized the role of political will in ensuring that such a document did not languish on policymakers' shelves but was actually implemented: "A vital requirement is that governments should exert the political will necessary to formulate and implement a drug policy. Lack of political will, even more than lack of resources, has been a decisive factor in the failure of some countries to ensure adequate provision of drugs and vaccines" (World Health Organization, 1988). However, political will is itself not sufficient to ensure implementation, or to explain why implementation has not delivered the desired results.

The Lancet Commission on Essential Medicines Policies reported that by 2015 a total of 95 countries had developed a National Medicines Policy (NMP) (Wirtz et al., 2017). This number now included the full range of low-income, middle-income and high-income countries. The proportion that were classified as low-income had declined from the peak in the early 2000s, as such countries improved their economic status. Even though more than half the countries in the world, however, had, at least at some point, developed an NMP, the Commission identified the need for even more attention to comprehensive essential medicines, or pharmaceutical policies, to ensure equitable access to affordable, quality essential medicines, and their quality use, as well as to the development of the medicines for presently unmet needs.

Despite a large literature, the limitations of the evidence base for the success or failure of NMP implementation cannot be ignored. For example, a review of the literature on the impact of NMPs on improving medicines use in developing countries identified a dearth of well-conducted studies with rigorous designs (Ratanawijitrasin et al., 2001).

Content, Process, Context, and Actors

A key consideration in identifying the factors influencing pharmaceutical policy implementation is that the process is profoundly political in nature, and is far from merely technocratic. The seminal publication in this regard, which has inspired an entire category of policy analysis, is that by Walt and Gilson in 1994 (Walt and Gilson, 1994). The Walt and Gilson model recognizes that it is not merely the content of a policy that determines how it is developed and implemented but also the context in which it occurs, the processes involved, and the actors involved in each of those processes. It is in the intersection of these elements that the true lessons can be drawn, for example understanding how the processes are influenced by the context at a particular point in time, and how those processes shape the ability of actors to engage with the policy development and implementation process. Critically, there is no simple dividing line between policy development and implementation. The two are inextricably linked. To ask what the factors are that influence pharmaceutical policy implementation is therefore to ask, at the same time, what the factors are that influenced its development.

A Stagist Viewpoint

The classical "stagist" approach to policy development encompasses the following steps (or stages):

- agenda setting;
- policy formulation; and
- policy implementation.

This neat, theoretical description of the process is temptingly simple, and can result in the expectation that implementation automatically follows "ticking the boxes".

The WHO guidance outlined the following steps in the development process (World Health Organization, 2001):

- Step 1: Organize the policy process
- Step 2: Identify the main problems
- Step 3: Make a detailed situation analysis
- Step 4: Set goals and objectives for a national drug policy
- Step 5: Draft the text of the policy
- Step 6: Circulate and revise the draft policy
- Step 7: Secure formal endorsement of the policy
- Step 8: Launch the national drug policy.

This does not imply, however, that a simple "cookbook" approach was advocated. The guidance contained many warnings of the need to consider the very different positions that could be taken by different stakeholders ("actors" in the Walt and Gilson sense): "The draft document should be widely circulated for comments, first within the ministry of health, then in other government ministries and departments, and finally to relevant institutions and organizations outside the government, including the private and academic sectors . . . Once this wide consultation is complete, the draft document should be revised in the light of the comments received, and finalized (p14)"

Specifically, the WHO offered detailed guidance on the need to manage opposition to the policy proactively, listing the following strategies (World Health Organization, 2001):

- "At an early stage, prepare the relevant legislative structure to enable the development and implementation of the national drug policy.
- Seize a window of political opportunity, such as a specific political change or developments in neighboring countries, to advance policy development or implementation.
- Start implementing the policy in relatively easy subject areas, in order to ensure initial high visibility and success, and support for the policy at the critical early stage.
- Adopt a flexible approach; be prepared to postpone an activity if more time is needed to prepare for it, to explain it and to build consensus for it.
- Have national experts and respected political figures publicly express support for the policy and vouch for its technical soundness. It is important that the public feels confident about the policy.
- Mobilize key groups in society to support the policy. Consumer organizations, trade unions, religious organizations and the media, for example, can be important in building such support.
- Anticipate shifts in opponents' positions, and identify strategies to involve them and to win their support. For example, the pharmaceutical industry may oppose drug pricing policies and the introduction of an essential drugs list, but will usually support strategies to strengthen drug regulation and improve drug quality assurance.
- Create constituencies that support the policy both inside and outside the government. This is crucial to the policy's long-term success and sustainability. (Box 1, pg 16)"

A more detailed, stepwise approach can be considered, as follows:

- Establish an implementation working group
- Prepare a draft NMP implementation plan
- Prepare a draft priority action plan
- Workshop the drafts with stakeholders, possibly by means of a multisector seminar
- Publish the NMP implementation plan and the priority action plan.

Nonetheless, failure to complete each and every step, in order, does not explain the shortcomings in NMP implementation that are responsible for the gaps in medicines access that still prevail.

The 2001 WHO guidance outlined the key content components of an NMP, as follows (World Health Organization, 2001):

- Selection of essential drugs
- Affordability
- Drug financing
- Supply systems

- Regulation and quality assurance
- Rational use
- Research
- Human resources
- Monitoring and evaluation

That structure has been followed by many NMPs across a range of countries and levels of development. They are not, however, the only components that are necessary. The 2017 Lancet Commission report focused on five areas of concern: "paying for a basket of essential medicines, making essential medicines affordable, assuring the quality and safety of medicines, promoting quality use of medicines, and developing missing essential medicines" (Wirtz et al., 2017). Some, but not all of these concerns, can be seen in the components proposed in 2001. As the challenges of ensuring equitable access to increasingly expensive medicines now affect every country, at every level of economic development, the need for new policy approaches is evident. Although by no means comprehensive, data from the World Health Survey point to persistent gaps in access to medicines (Wagner et al., 2011).

The Window of Opportunity

The concept of taking advantage of a moment of political opportunity—a "window"—is most commonly associated with the work of Reich (Reich, 1995). Based on an analysis of the pharmaceutical policy processes in Sri Lanka, Bangladesh, and the Philippines, Reich argued that "health sector reform is feasible at certain definable, and perhaps predictable, political moments, especially in the early periods of new regimes". This concept of manageable political timing was also mentioned by WHO—the 2001 guideline stated that "Very often an acute emergency or an important political change created a window of opportunity to start the policy formulation process" (World Health Organization, 2001). A subsequent description of the NMP development process in a WHO policy perspective underlined the concept, giving the example of South Africa's 1996 National Drug Policy: "Part of its success was due to the political "window of opportunity" immediately after the end of apartheid in 1994" (World Health Organization, 2003). That "window" may not always be represented by a change of regime; however, it can be created by an event, a crisis that affects or highlights access to medicines for an individual, a group of patients, or the population at large.

A particular example is provided by the responses to sudden changes in economic conditions, as represented by the financial crisis in Greece in 2008. Faced by severe fiscal contraction, the Greek government was forced to implement a range of cost-containment measures, which resulted in a dramatic reduction in public drug expenditure (Vandoros and Stargardt, 2013). Included in the package was the re-introduction of a positive list (in essence, an essential medicines list), as well as reductions in the margins charged by community pharmacies and wholesalers. Such changes would always have faced opposition from those with vested interests. In the face of the financial crisis and the austerity measures agreed with the International Monetary Fund, European Union and the European Central Bank, their implementation was possible, despite resistance. Greece was not alone in facing an economic crisis. A crisis can also be caused by the imposition of political sanctions. The impact of responses to such crises, however, may result in cost-savings but also deleterious effects on access to needed medicines. A review of 89 policies implemented in 11 countries that had faced either economic crises or sanctions showed that there was little evidence of improved access to medicines as a result of the implementation of such policies (Kheirandish et al., 2015). Italy has also been through a series of pharmaceutical policy reforms over more than a decade, which have responded to the need to implement cost-savings, while protecting access (Fattore and Jommi, 1998; Ghislandi et al., 2005).

The emergence of a new, highly effective but expensive group of medicines can pose a new crisis. While the global response to HIV has seen new financial resources and the emergence of measures to ensure faster access to cost-effective generics, the same cannot (yet) be said about the new direct acting agents for hepatitis C virus infection (Assefa et al., 2017).

On a more positive note, the substantial changes to China's health policy have created the demand for pharmaceutical policy reform, at least at the national level. Provincial and county-level implementation has lagged somewhat, again emphasizing the complexity of the implementation task even in highly structured and hierarchical systems (Tian et al., 2012; Xiao et al., 2013). Similar challenges are posed in all countries that are attempting to advance universal health coverage, especially where this implies the development of a new National Health Insurance system. Ghana provides an object lesson in this regard, where both positive and negative implications for medicines access and quality of use have been identified by key informants (Ashigbie et al., 2016). Across five sub-Saharan African countries, key data to allow for the monitoring of access to medicines as these countries implement health insurance reforms has been noted to be lacking (Carapinha et al., 2011). A systematic review identified a lack of published evidence on the ability of health insurance systems in low- and middle-income (LMIC) countries to use active pharmaceutical management strategies, such as selection, purchasing, and utilization management strategies (Faden et al., 2011).

Policy Coherence

Perhaps more compelling than crisis-engendered policy-making and implementation, the ideal of policy coherence can explain whether particular pharmaceutical policies are developed and effectively implemented.

A country which follows a careful, yet sustained, incremental approach to advancing equitable access to healthcare services can make substantial progress. Brazil's NMP was first issued in 1998, reviewed after 20 years of concerted effort and showed sustained improvements in access to medicines but also a vulnerability in the face of inadequate financing of the Unified Healthcare System (SUS) (De Vasconcelos et al., 2017). Access to affordable essential medicines still lags behind the standards enshrined in the Brazilian constitution (Bertoldi et al., 2012). In particular, Brazil has been noted for its use of public sector production to meet the need for specific, strategically important essential medicines (Figueiredo et al., 2017).

Among high-income countries, Australia has a coherent NMP, which has tackled the thorny problem of balancing health and industrial policy objectives (Morgan et al., 2008). Australia has seemingly managed to achieve relatively low prices for generic medicines, yet still enabled access to "breakthrough" patented medicines at globally competitive prices. Simultaneously, it has offered incentives for local innovation and capacity development. Sustaining that policy coherence in the face of ever-growing demands for newer, more expensive medicines will remain a challenge, even for the best-resourced health systems. Many low- and middle-income countries' NMPs contain a commitment to improving access through reducing prices yet at the same time aim to foster the development of a national pharmaceutical manufacturing capacity. Those objectives can be in conflict, and can be difficult to achieve when affordability is a key consideration.

Interconnected Systems

Although the WHO guidance on developing and implementing NMPs lists discrete areas of attention, such as the need to promote generic medicine use as a cost-saving measure, a key lesson from decades of implementation is that many of the elements are interconnected, and rely on the existence of a comprehensive system. For example, it has been shown that a key determinant of the success of pro-generic policies has been the existence of a functioning medicines regulatory authority (Kaplan et al., 2012).

Other areas of interconnectedness relate to the operation of the intellectual property system, and its ability to effectively assess the patentability of new inventions, but also to implement the flexibilities in the global system that are available (Wirtz et al., 2017).

Transparency

Over the years, both the World Bank and WHO have placed great emphasis on the need for good governance in the entire pharmaceutical system, for which country ownership is critical (Kohler et al., 2014). Although some assessments have identified progress in reducing vulnerability to corruption (Dalia et al., 2015), there are persistent challenges in some settings, particularly with regard to medicines regulatory practice (Vawda and Gray, 2017).

Opportunities for Engagement

Inherent in the Walt and Gilson emphasis on the role of "actors", and also in the WHO guidance about repeatedly engaging in the publication of draft policy documents and draft implementation plans, as well as multisector workshops, is the concept of creating opportunities for engagement.

Many policymakers rely on Brinkerhoff and Crosby's model as guidance (Brinkerhoff and Crosby, 2002). The model describes the following implementation tasks:

- Creating legitimacy
- Building constituencies
- Accumulating resources
- Modifying organizational structures
- Mobilizing resources and actions
- Monitoring impact.

The first two steps can be achieved through events that raise awareness by identifying champions and by creating new forums for discussion. This can be done though policy dialog workshops, public–private forums or the creation of task forces. Some of the techniques that can be employed are stakeholder analyses and political mapping.

A 20-year retrospective view of the South African NDP implementation process has pointed to the narrowing of the opportunities for engagement over time (Gray et al., 2017). While some of the formal opportunities for engagement (such as parliamentary hearings and the opportunities to comment on draft legislation) had been maintained, other consultative bodies (such as the National Health Consultative Forum) had lapsed. Much of the detailed debate was now occurring in the National Health Council technical committees, which were accessible only to senior bureaucrats and political office-bearers. An earlier analysis of the same policy process had emphasized the need for "learning by doing", a process which can only occur when the opportunities for engagement are deliberately sustained (Gray et al., 2002). Similarly, interviews with key stakeholders in Australia highlighted the need to ensure that "on stakeholder groups imperatives do not stifle those of other groups" (Lipworth et al., 2014). One possible reason for the differences in implementation of policies on dispensing practitioners seen

between Japan and Korea was attributed to the engagement of progressive civic groups in the latter country (Jeong, 2009). Despite this, the Korean reforms were the cause of unprecedented physician strikes, and perhaps unintended consequences in terms of access and cost (Kim et al., 2004).

It has been argued that pharmacists have a particular responsibility and opportunity to engage in the development and implementation of effective pharmaceutical policies (Morrow, 2015a; Morrow, 2015b).

A Focus on Data and Accountability

Globally there is an increasing focus on improved accountability, at both national and international levels. Civil society is increasingly holding governments to account for the outcomes of public policy. This is entirely consistent with the focus on monitoring and evaluation which has always been part of the WHO NMP concept but which has often been neglected during implementation. A greater focus on the development of rigorous policy analysis and impact assessments has been specifically advocated for in relation to pharmaceutical policies (Almarsdóttir and Traulsen, 2006).

Conclusion

Although the WHO documents that have guided the development and implementation of NMPs in many countries are now dated (World Health Organization, 2001), the penetration of this concept across countries of widely differing economic status and health systems design has been considerable (Wirtz et al., 2017).

The factors that could potentially affect the implementation of pharmaceutical policies are as varied as the national contexts and legislative and legal systems that pertain across the globe. There are some key concepts; however, that can guide policymakers and implementers. Both Walt and Gilson (1994) and Brinkerhoff and Crosby (2002) have drawn attention to the key roles of "actors"/"stakeholders" and the need for active and sustained engagement during both policy development and implementation.

No simplistic checklist of steps to be completed can suffice to guarantee success, but there are principles that can inform such steps. The window of opportunity that can enable an issue to become an issue, for a policy intervention to become feasible when previously it was not, can vary considerably. Crisis-engendered policymaking is possible, but pharmaceutical policy must always be coherent with broader health, economic and industrial development policies, and must seek to take into account the interconnectedness of many systems that determine access to and quality use of affordable, quality-assured essential medicines. Finally, there is a need for a greater focus than ever before on the data that are essential to enable accountability and a learning system that is able to take remedial action where necessary.

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Funding Mechanisms for Community Pharmacy Service Provision

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Introduction

The focus of this chapter is on the comparison of a range of funding mechanisms for community pharmacy in high-income countries around the globe. It is reasonable to ask the question "why bother doing this type of comparative analysis?" and "what does it add for the policy-driven pharmacy sector and the academic literature?." Of course, these are two rather significant questions and ones that are not easily answered in a single sentence. Suffice to say, to survive, community pharmacy needs to drive a global "reprofessionalization" agenda based on extended clinical roles and professional leadership (Roberts et al., 2003; Ruston, 2001; Scahill et al., 2010). This has been talked about for some time, but to continue on in a sustainable manner, the community pharmacy sector needs to think carefully about how and what value it adds and in which ways this is going to be funded, depending on the type of market within which these pharmacies sit. Clearly this is easier said than done, but the sector as a whole will benefit from an analysis (summative enquiry) of this nature.

Being both a retail business and a health-care provider in most international markets (Scahill, 2010), the community pharmacy sector generally relies on a combination of funding from external third-party agencies (government or insurance fund) alongside

public free market spending by the patient/consumer, to make business viable in the long term. To this end, John Chave, in a commentary in the *Pharmaceutical Journal* comparing UK and European community pharmacy, highlights the importance of collectively demonstrating "value" in order to receive funding streams for community pharmacy; publicly funded or through private markets (Chave, 2014).

> *"Pharmacy stands or falls (in the UK and everywhere), on its ability to show it meets a public need worth paying for. There are plenty who argue that technological change, from Amazon-style distribution to mobile apps, challenges retail business and intellectual services. Pharmacy is both of those."*

This demonstration of public need must be ratified by the community at large and health funders and planners. Founded on this notion then, the chapter compares and contrasts the funding policies and associated politics for pharmacy services among selected high-income countries. What we don't often think about, nor even talk about, as pharmacy academics, practitioners, or thought-leaders within pharmacy professional bodies is where pharmaceutical policy sits within the wider political arena and from where funding arises and via what mechanisms and streams; and how these might vary around the world. Also, are there particular pharmaceutical systems we can learn from, for example? There is the need for greater consideration of the requirement for change in business models to deliver cognitive services in pharmacy that both government and the private paying public will be comfortable to remunerate. This chapter attempts to address this by drawing together individual countries "whole of health system" with facts and figures pertaining to the "pharmaceutical system" from a variety of high-income nations around the globe.

The focus of this Chapter is on the subsector of community pharmacy; the reason being 80% of the pharmacy workforce ends up in this sector and it is where most of pharmacy activity occurs (Hawthorne and Anderson, 2009). It is also an area where in some countries, public monies are invested into a service environment that also involves the conduct of retail-based business activities and so funding models are most important and may vary considerably country to country. However, before we can begin to compare funding mechanisms for community pharmacy services it is important to define what is meant by a "pharmaceutical system" and within this "community pharmacy services". A pharmaceutical system has been defined as: "all structures, people, resources, and their interactions within the broader health system that aim to ensure equitable and timely access to safe, effective, quality pharmaceutical products and related services that promote their appropriate and cost-effective use to improve health outcomes" (Hafner et al., 2017). This definition has been adopted for this analysis.

What this highlights is that when thinking about the funding of pharmaceutical services, it is difficult to unpack and disentangle in a systematic way (across countries) the various components when comparing pharmacy service provision within different high-income countries. For example, in large parts of Europe, dispensing remuneration is linked to the pricing of pharmaceuticals per se; whereas in New Zealand, it is not the case. As such, the pricing mechanism of pharmaceuticals cannot always be completely separated (or at least omitted) from the analysis of funding for community pharmacy services, which may include the provision of enhanced pharmaceutical care (also denoted cognitive pharmacy services) or even the counseling associated with a basic medication dispensing service. Community pharmacy services must be considered "as a whole" sitting within the overall pharmaceutical system, which is embedded within a country's overall health system. It is upon this framework that the cross-country analysis is undertaken. As such, this summation may include elements of pharmaceutical pricing, dispensing/counseling fees, regulatory facets, and payments for pharmaceutical care within some of the country portfolios (Fig. 1).

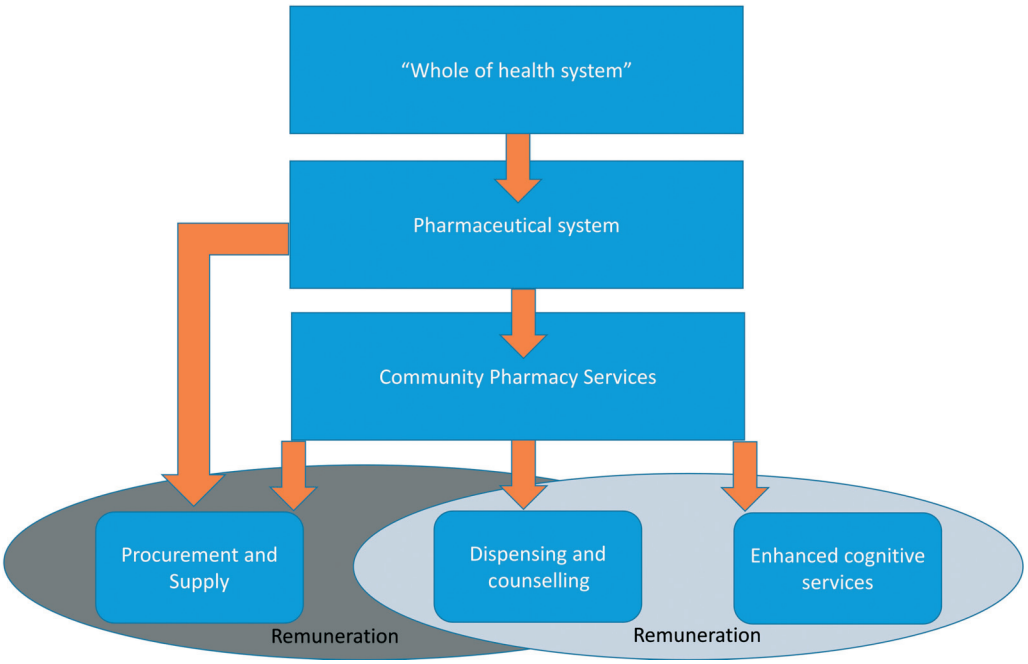

Figure 1 Community pharmacy services embedded within pharmaceutical and whole of systems funding.

What is apparent from the analysis is that the world is a diverse place, health systems are complex and different, and pharmacy has not escaped this. In fact, as individual countries' health systems become more and more alike due to migration and a degree of "sameness" in global health pressures (Crisp, 2017), pharmaceutical systems within the overall health systems appear to represent the diversity in these systems. Just as service provision is diverse, so are the funding models that drive business activity and clinical behavior in the dichotomy that is community (retail) pharmacy (Jacobs et al., 2011; Mossialos et al., 2015).

Looking to the literature for appropriate context, a systematic review has been , which identifies remunerated pharmacist clinical care programs worldwide (Houle et al., 2014). The review found remuneration for pharmacists' clinical care services to be highly variable, with very few programs reporting clinical outcomes. Sixty new remunerated programs (over and above their previous review) were included in their update from Canada, the United States, Europe, Australia, and New Zealand. These ranged in complexity from emergency contraceptive pill (ECP) counseling to full minor ailments programs, and comprehensive medication management reviews.

Their findings suggest that in North America, the average fee provided for a medication review is $68.86 (all figures are given in Canadian dollars), with $23.37 offered for a follow-up visit and $15.16 for prescription adaptations. Time-dependent fees were reimbursed at $93.60 per hour on average. Few programs evaluated uptake and outcomes of these services but, when available, indicated slow uptake but improved chronic disease markers and cost savings. They concluded that programs and pharmacists are encouraged to examine the time required to perform these activities and the outcomes achieved to ensure that fees are adequate to sustain these patient care activities. This sets the scene for the need to understand international funding systems. The analysis suggests that information is not as publicly available and transparent across all countries, as one might expect. The aim is to build on this work by searching the academic literature for the 2014–17 period.

This chapter represents a synthesis of global pharmacy funding policies based on publicly available "grey" policy literature and academic literature across a range of high-income countries. For an extensive analysis of pharmaceutical policy in developing countries, the reader is referred to a book edited by Prof Zaheer Babar titled "Pharmaceutical Policy in Countries with Developing Healthcare Systems" (Babar, 2017).

International "whole of health" Systems

The study of global health systems is fascinating in its own right, and there is a need to understand the wider system as pharmaceutical subsystems are embedded within overall health systems (**Fig. 1**). As Babar and Scahill highlight, pharmacist activity needs to be embedded in a strong, appropriately funded and well-developed pharmaceutical system (Babar and Scahill, 2009); otherwise, there is no point in embarking on clinical advancement in pharmacy. The pharmaceutical system needs to be supported by an overall health system, which is efficient and effective and transparent in its decision-making processes, especially with regard to access and affordability of high cost medicines (HCM) (Babar, 2018). This also must apply to the funding of community pharmacy activities, and it is wholly surprising how little information is publicly available on this topic. Personal communication with pharmaceutical policy leaders in some countries has been required to obtain even the most basic information.

When considering health system structure and function, New Zealand research provides a sound platform for understanding the different types of health-care funding models that influence policy making and the funding and delivery of services in a health system (Gauld, 2009). Gauld covers mechanisms of tax funding, social insurance, and private funding, as well as providing historical insights into health funding models in New Zealand, Great Britain, and the United States. This chapter uses Gauld's work as a platform to understanding the health systems of the countries for which community pharmacy funding is being analyzed while continuing to focus on pharmaceutical policy of countries not reviewed by Gauld (i.e., Sweden, Belgium, Spain, Germany, the Netherlands, and so forth). The aim is to explore differences and similarities between country structures, overall health systems, pharmaceutical systems, community pharmacy funding, and any relevant policy discourse within the community pharmacy sector of selected high-income countries.

Despite being high income, these countries have been selected to represent a diverse range of funding models. This type of comparative health policy analysis is informative as there is the perception by governments that shared challenges in health policy development and implementation exist, and useful insights can be gained by comparing and contrasting policies, and experience in enacting them. The indication is that there are significant global trends in how health policies are formulated and the result is that national health systems are becoming increasingly "alike" in high-income countries (Blank and Burau, 2018).

The glut of health reforms that have occurred in high-income countries since the 1990s has led to a degree of convergence of health systems where there appears to be a universal paradigm for health care financing, organization, and management that is irrespective of whether services are public or private and regardless of whether political ideologies are centrally driven or decentralized. An example supporting this thinking is how the social organization of medical work is increasingly similar across global health systems, leading to health systems sharing more common elements. Other ways in which health systems appear to be converging is through internationally recognized uses of a large number of complex medications (some essential, others high-cost), hospital quality standards being utilized across countries, and health care as a business while working within the parameters of being a publicly funded service.

Health policy is very much a political matter and is therefore dependent upon the political arena, which impacts on subsystems such as the pharmaceutical system (Birkland, 2016). This certainly applies to the funding of community pharmacy services as a subsector of pharmaceutical policy, particularly with respect to the discourse globally around remuneration for

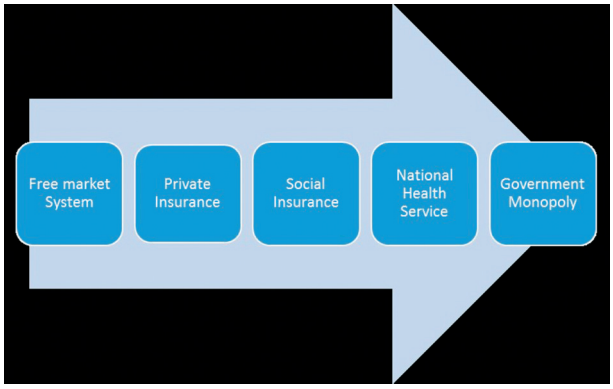

Figure 2 Funding continuum from free market to Government monopoly.

enhanced services. The political arena includes not only the formal political institutions such as legislatures, executives and courts but also regulatory agencies, semi-public bodies, and specialized committees and commissions (Blank and Burau, 2018). In addition to these formal practices, there are informal practices and structures that have evolved within the particular formal institutional frameworks, the institutional cultures. Although it is argued that no two political systems are the same, many share similar characteristics or typologies.

Having said this, and despite facing similar health-care challenges, there are distinct differences among the health systems reviewed in this chapter. This is recognized by the organization for Economic Cooperation and Development (OECD), which have developed a typology for the different types of health-care system using service provision and funding as the determinants (Mossialos et al., 2016; Thomson et al., 2012). The different types of health systems can sit anywhere on a continuum from a completely "free market" driven health system, with little or no government involvement through to the scenario of a Government monopoly involving fully tax supported provision of funded health services for all, i.e., little or no private sector (Fig. 2). However, in reality, the two extremes do not exist (at least in the context of high-income countries) with government involvement in health services varying along a continuum.

In high-income countries, three major models sit within the continuum outlined in Fig. 2. They all impact on the development and implementation of pharmaceutical policy and include privately funded health insurance (consumer sovereignty model), social insurance (Bismarck model), and National Health Service (Beveridge model). What we are considering here is the degree of access to care with financial risk protection (Kutzin, 2001). Total "free market" in the completely neoliberal sense and full Government monopoly in the communist sense sit at either end of the spectrum. Funding streams for health systems as a whole, and for pharmaceutical systems in particular, are determined by the classic funding models found within each of these types of system. Blank and Burau (2013) have suggested that the United Kingdom and New Zealand are located at the end closest to the National Health Service (Beveridge) model, whereas Australia and the United States, for example, are located more toward the private insurance (consumer sovereignty) model (Blank and Burau, 2018). This suggests that there is no set pattern of health system structure based on British Commonwealth status, with New Zealand and Australia having quite different health systems. Based on this, the analysis is not structured to compare pharmacy service funding in Commonwealth vs non-Commonwealth countries. What is of interest is whether there is broad alignment of funding mechanisms for community pharmacy services in countries that operate under Free market, Sovereignty, Beveridge, Bismarck, and Government monopoly funding models.

A sound overview of the different types of system is available (Lameire et al., 1999). Each of these systems is outlined in general terms in this section and then within the pharmaceutical analysis the reader will be reminded of the model under which the health system of that country falls.

Free Market

Purely free market health systems are generally found in developing nations where health services are largely funded "out of pocket" by the consumer and competition drives pricing and service provision. In a paper to the New Zealand Treasury in 2013, Professor Nick Mays (London School of Hygiene and Tropical Medicine) suggests that supplier competition for individual health-care services in neoliberal markets is not good (for chronic care management), causing fragmentation of care and lack of integration (Mays, 2013).

Sovereignty Model

Also known as "private insurance," this mechanism includes predominantly private funding through medicare/aid + managed care. In the United States, this predominantly involves private health care, and Australia appears to be heading more toward this direction than the Bismarck Model. This type of model is often denoted as "Private" (Kutzin, 2001; Lameire et al., 1999).

Beveridge Model

It includes nations such as the United Kingdom, New Zealand, Italy, Spain, Sweden, Denmark, Norway, Finland, and Canada. Funding occurs through national taxation, and infrastructure is provided through a National Health Service. This type of model is often denoted as "Public" (Kutzin, 2001; Lameire et al., 1999).

Bismarck Model

It includes France, Germany, Switzerland, Belgium, Holland, and Japan. This system is premium-funded through mandatory insurance and draws on a combination of private/public providers. This type of model is often denoted as "Mixed" (Kutzin, 2001; Lameire et al., 1999).

Government Monopoly

This form of funding sits with the communist/socialist model, whereby the only form of health care in place is a government funded structure without any private-sector health service delivery and no "insurance-based" model. All funding comes from one source, the government, and there is the suggestion that reforms in the Beveridge-type systems aim to increase choice and reduce waiting times. Bismarck models on the other hand have been directed toward cost control by restricting choice of provider (Or et al., 2010).

This chapter sets out to explore funding mechanisms associated with community pharmacy services and so the focus is on the primary health care sector as it relates to the pharmaceutical subsystem. This is important to bear in mind because in many countries (and particularly developing countries) hospital care (and medicines/pharmaceutical services) is provided free; however, community pharmacies are deemed to be in the "private sector" in many countries, and people are expected to pay "out of pocket" for their medicines. This analysis draws out those countries.

Funding the Value Proposition: Community Pharmacy in Context

This section provides context for the value proposition of community pharmacy and the rationale for funding enhanced services. The readiness for change by pharmacists embracing funded cognitive services is outlined in the country monographs as appropriate. There are commonalities and differences between government health policies in developed countries; many call for pharmacy to "reprofessionalize" through role extension into enhanced cognitive services. There are commonalities in the response of the pharmacy sector in different countries to these policies. This chapter highlights the commonalities and some of the differences in policy and response across countries with very different macro health funding policies and pharmaceutical systems. Interestingly, though, many of the professional issues seem to be the same. Funding is a lever and readiness for change and the acceptance of service implementation seems to have been something that has challenged the international community pharmacy sector in a profound way, for a long time.

Sustained funding is only going to come with the complete reprofessionalization of community pharmacy. This needs to be a collective and ongoing global agenda extending a relatively long history (Birenbaum, 1982; Edmunds and Calnan, 2001; Gilbert, 1998). The need to reprofessionalize suggests that community pharmacy has the roots of a profession but that its professionalism has been eroded in some way. There has been a growing sense of urgency both from within and external to the profession that community pharmacy needs to change (Edmunds and Calnan, 2001; Scahill et al., 2010). Professional pharmacy bodies are calling for this reprofessionalization and their expectations seem to align with health policy makers who have historically been shy address community pharmacy remuneration (Edmunds and Calnan, 2001; Scahill, 2008; Scahill et al., 2010).

An occupation such as pharmacy becomes a profession when it is granted autonomy, is recognized by society as possessing a technical knowledge base, has lengthy and superior education, and adopts a code of ethics with a commitment to common good (Birenbaum, 1982; Edmunds and Calnan, 2001; Holloway et al., 1986). Professional autonomy exists in the medical sphere when an occupation has economic, political, and clinical autonomy. There has been a view that pharmacy's professional development has been hindered, largely because of the control of the medical profession over clinical autonomy and therefore economic autonomy (Edmunds and Calnan, 2001). This functional role based on trait theory seems to suggest that community pharmacists have a number of the characteristics of professions including monopoly over practice, compounding, dispensing and advice, possess specialized knowledge, and have a service orientation toward health-related service provision. However, more modern professionalization theory suggests that time, place, identity, and market place also feed into the notion of professionalization. Community pharmacy has been guided by commercial interests, and pharmacists lack control over "medicines," which are the social object of the profession (Traulsen and Bissel, 2004).

A historical lens suggests that community pharmacy has had access to and control over a unique body of specialist knowledge around procurement, storage, and compounding of medicines and other remedies (Gilbert, 1998). Until the 20th century, community pharmacy sourced raw product, formulated dosage forms, and dispensed potions; the formulas for which were often controlled by pharmacy. Industrialization involving large-scale manufacturing of medicinal products resulted in pharmacy losing the source and compounding aspects of its role with the pharmaceutical industry making community pharmacy's role in the manufacture and production of medicines largely redundant (Bissell and Morgall Traulsen, 2005; Edmunds and Calnan, 2001;

Gilbert, 1998). With this comes the loss of deeply rooted functions, endangering the identity of the profession which must change to survive (Birenbaum, 1982). The simple act of dispensing medications on the order of a medical prescriber, and the associated financial transaction, has meant that the pharmacists have found themselves overtrained for what they do and underutilized for what they know (Gilbert, 1998). In some regards, a loss of function, social power, and status have resulted in a loss of identity for pharmacy (Adamcik et al., 1986; Bissell and Morgall Traulsen, 2005; Edmunds and Calnan, 2001).

Part of the response to this has been the drive for reprofessionalization, where there has been a gradual shift in focus away from the technical role of pure procurement, supply, and distribution of medications, toward disease and patient-oriented approaches to pharmaceutical decision making, and the adoption of more clinical roles (Adamcik et al., 1986; Bissell and Morgall Traulsen, 2005; Gilbert, 1998). It is the role expansion through these enhanced or cognitive clinical services that has received most attention in the literature. The need to reposition the pharmacy profession as medicines management experts through delivering cognitive services (Benrimoj and Roberts, 2005; Hopp et al., 2005, 2006; M. B. Roberts and Keith, 2002) has been one of the main drivers for the "reprofessionalization" of pharmacy (Bissell and Morgall Traulsen, 2005). This has been supported by professional pharmacy bodies and health policy makers (Edmunds and Calnan, 2001). The bottom line is that this requires significant funding to achieve.

Seven Directions of Future Focus that Influence Funding for Community Pharmacy

Critical review of the academic pharmacy practice literature and pharmacy-related health policy documents has resulted in the synthesis of seven themes, which were deemed to influence development and funding within the community pharmacy sector. These themes included (Scahill et al., 2010):

- A greater emphasis on integration and collaboration.
- A focus on the provision of quality primary health care.
- A focus on patient-oriented services vs selling a product.
- Looking after your patient...looking after your population.
- The provision of enhanced pharmaceutical services.
- Developing new models of pharmacy practice.
- A defined agenda and processes for change.

In summary, internationally, there is a diverse range of developed and underdeveloped community sectors. It is clear, however, that both policy makers and pharmacy professional leaders see the move to the provision of enhanced services as imperative. Internationally, significant barriers to this have been identified at the level of the individual pharmacist, suggesting a lack of readiness by community pharmacy to engage and deliver. The barriers and facilitators to change are considered in the context of the country profiles in this chapter. Pharmacy needs to become more autonomous and express its evidence-centered value proposition to gain the confidence of key stakeholders who will be funding services in the long term. Positioning for appropriate funding is key.

Funding of Medicines, Distribution and Enhanced Services: Country Monographs

This section outlines the individual country monographs and divides them (as far as possible) into Sovereignty, Beveridge, Bismarck, and "Other" health system models. Within a whole pharmaceutical system, components that require funding can be thought about (Fig. 3).

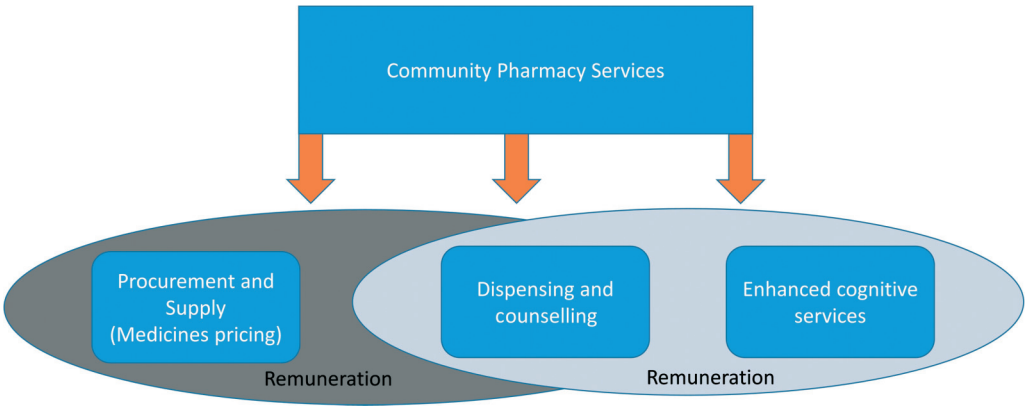

Figure 3 Remuneration schema for community pharmacy services; core and enhanced services.

Table 1 Country by funding models

Sovereignty like	*Beveridge*	*Bismarck*
USA	UK	France
Australia	Canada	Germany
South Africa	Spain	Belgium
	Sweden	Netherlands
	Denmark	
	New Zealand	

Central to pharmacy is the procurement and cost of the medicines that are being dispensed and cost, availability, access, and affordability can be considered. The fee for providing a dispensing and counselling service by the pharmacist is a second component to think about. Finally, funding for extra clinical services such as long-term conditions (LTC) programs and medication reviews which have been called for by policy makers are the most recent funding considerations for the sector (at least for this chapter). Funding of these activities is likely to vary considerably around the globe and this chapter aims to explore these similarities and differences in a structured way, and to report on the international situation (from selected countries) within a coherent framework that outlines historical development.

This section of the chapter is structured to group countries into the type of health system they have adopted, i.e., Sovereignty, Bismarck and Beveridge systems, rather than whether countries are British-Commonwealth or non-Commonwealth countries or European/non-European. The groupings are made up as follows (**Table 1**):

The overview provides comparison by funding model as opposed to geographical location of nations. This demonstrates how similar many of the Commonwealth nations are (except Australia/South Africa). In addition to this *funding model-based approach*, there have been regional analyses undertaken, e.g., of European nations, which demonstrates how different the pharmaceutical systems are despite being within the EU.

Beveridge Funding Model

United Kingdom (UK)

Policy Reform Relating to Funded Service Provision

The United Kingdom is dealt with as one country but of course there are pharmaceutical subsystems with differing activities in England, Scotland, Wales, and Northern Ireland. For the purposes of this chapter, they are considered "as one.' From an historical viewpoint, the United Kingdom has been a leader in pharmaceutical policy reform, especially regarding the community pharmacy context (Dept of Health (UK), 2000, 2003, 2008; Galbraith, 2007). The UK Department of Health has been prolific in its commissioning of consultation reports (Galbraith, 2007) and health policy relating to community pharmacy (Dept of Health (UK), 2000, 2003, 2008). There has been commitment to develop community pharmacy services and the early White Paper on Community Pharmacy (Dept of Health (UK), 2008) (citation or at least date) drew on what Galbraith described as the "attributes of a good pharmaceutical service." The UK Government was one of the first (of the Commonwealth countries at least) to attempt to define what constitutes an "effective" community pharmacy. At the time Commissioner Galbraith noted the potential contribution of community pharmacy and outlined a list of distinguishing features of a world class pharmacy; characteristics that pharmacies where meant to aspire to in order to achieve sustainable funding streams (**Panel 1**).

From a contractual viewpoint, Galbraith suggested there needed to be adequate incentives to drive changes in best practice at that time. The greatest shift in practice was the requirement to provide enhanced "cognitive" services in addition to the traditional supply and distribution roles community pharmacy has held and the focus of this chapter is on what the funding for this activity looks like some years following these policy drivers (**Panel 2**).

New models of practice were expected to enhance the patient experience, support well-being, and promote the safe use of medicines. Community pharmacy was expected to develop integrated "pharmaceutical care management" services with greater clinical focus, integration with other providers, and a quality focus. In the mid-2000s, the UK Government appeared to be happy enough to pay for these value-added clinical services. The positive climate, however, seems to have changed when in May 2017 an announcement meant that thousands of small community pharmacies were facing closure. The High Court upheld cuts equating to GBP320 million in NHS Government funding to the pharmacy sector (Robinson, 2017). Although cohorts of pharmacists in the United Kingdom were positive about implementing enhanced services, uptake and action was much slower than stakeholder expectation (Celino et al., 2004; Elvey et al., 2006). Some of the cited barriers included: lack of time (Bush et al., 2006; Ewen et al., 2006; Hall and Smith, 2006; Staton et al., 2006; Warchal et al., 2006); inadequate remuneration (Bush et al., 2006; Celino et al., 2004; Hall and Smith, 2006; Staton et al., 2006); patient expectations and knowledge (Ewen et al., 2006; Hall and Smith, 2006); lack of GP understanding (Celino et al., 2004); professional boundaries and turf protection (Adamcik et al., 1986; Gilbert, 1998; Nathan and Sutters, 1993); increased documentation and accreditation processes (Celino et al., 2004; Elvey et al., 2006); and lack of a common medical record (Warchal et al., 2006). Human factors such as pharmacist confidence (Elvey et al., 2006; Hall and Smith, 2006); an unwillingness to leave the comfort zone of the dispensary (Bush et al., 2006); a

Panel 1 Galbraith's (2007) view of future service provision by UK Pharmacy

Attributes of a good pharmaceutical service – what it might offer patients and consumers

- Accurate
- Knowledgeable
- Providing value for money
- Professional
- Supporting patients
- Convenient service
- Personal
- Informative
- Integrated
- Accessible
- Evaluation
- Full service

Potential contribution of pharmacy to various levels of patient care including promoting better health, prevention and early detection, long-term conditions/chronic care management, case management.

Distinguishing features of a 'world-class' pharmacy

- Primary source of health information and advice
- Helping people to stay healthy and to improve health where needed
- Routinely promoting self-care and being associated with key public health initiatives
- Providing new services to help people with acute conditions and long term conditions
- Skilled, knowledgeable, competent and considerate staff
- Part of a strong local network of health improvement services and local leaders for health in the community
- A wider information retailer of medicines but also broader health, wellbeing and social matters i.e. sustainable development

Panel 2 Contracted services for community pharmacy (UK)

Essential Services

- Dispensing and repeat dispensing
- Health promotion
- Healthy lifestyle advice
- Signposting to other services
- Support for health care
- Disposal of medicines

Accredited Advanced Services

- Medicines Use Review

Local Enhanced Services – commissioned by PCTs

- Smoking cessation
- Supervised methadone administration
- Patient group directions (ECP, NRT)
- Minor ailments

uniprofessional culture (Walker, 2000); and pharmacy's inexperience of the commissioning process (Bush et al., 2006) have been cited as barriers by stakeholders in the United Kingdom. It has not been made explicit that these factors have played a part in the reduction in funding over time for community pharmacy in the United Kingdom, or whether it is simply economic factors post the global financial crisis (GFC). This discourse is very important and what we do know is that pharmacists will be paid less this year by the UK Government than in the previous year, and it will be interesting to see whether this trend continues.

Current Service Funding Changes in the United Kingdom

Unlike the Australian Government which is significantly increasing funding to the community pharmacy sector. On October 20, 2016, the Government announced that funding for NHS contractors providing services under the community pharmacy contractual framework was to be:

- GBP2.687 billion in 2016
- GBP2.592 billion in 2017/2018

This represented a 4% reduction in funding in 2016/2017 and a further 3.4% reduction in 2017. As part of the package the Department of Health (DH) made changes to the way in which funding was distributed, introducing quality payments and a Pharmacy Access Scheme (PhAS) for isolated pharmacies (n = 1341). Pharmacy establishment payments will be phased out, and a range of dispensing fees have been amalgamated into a single activity fee. The Government has also recently announced a pharmacy urgent repeat medicines supply pilot along with plans to refer NHS#111 callers with minor ailments to pharmacies. It is unclear what the funding package for this will look like. There is also a Pharmacy Integration Fund available, which is expected to support closer working between pharmacy and other parts of the NHS (Jones and Baker, 2016).

Canada

In 2002, the Commission on the Future of Health Care in Canada, headed by former Saskatchewan Premier Roy Romanow, released a report on the nation's health-care system (Romanow, 2002). The Commission's findings and recommendations have taken a central place in the debate on the value and future of Canada's public health-care system. A key element identified in the Commission's report was the need to transform Canada's health-care system to focus squarely on primary health-care strategies. In October 2001, the Canadian Pharmacists' Association (CPA) produced a submission for the Romanow Commission on the Future of Health in Canada. The CPA submission outlined the challenges facing the Canadian community pharmacy sector and included a section on the development of new models of pharmacy practice. There was the recognition by the CPA of the need for the pharmacy profession to continue to evolve. The need for change within the profession, as well as within the wider health-care system in Canada, was highlighted (Canadian Pharmacists Association, 2001). The main recommendations regarding "re-professionalization" were:

- The profession of pharmacy must work with health-care administrators and other health-care providers to effectively define and structure new consultative practice models focusing on more direct patient care.
- The federal Government must recognize the value of pharmacists' services and remove fiscal barriers to access.
- The need for multidisciplinary educational programs to ensure that pharmacists have up-to-date knowledge and to foster collaboration and respect among the profession.

With respect to community pharmacy, the Romanow Commission highlighted that:

> There is a growing emphasis on medication management programs. This is likely to have a direct impact on the role of pharmacists and make it possible for them to play an increasingly important role as members of the healthcare team. (Romanow, 2002, p. 107)

In 2008, the CPA launched the Blueprint for pharmacy: Designing the Future Together (Canadian Pharmacists Association, 2008). The aim of the Blueprint was for pharmacists to provide optimal drug therapy outcomes for the peoples of Canada, through patient-centred care. A shift was required from dispensing and technical duties to a focus on services that would improve patient outcomes (Rosenthal et al., 2010). One study suggested that over 60% of Canadian pharmacists participating in a national survey (Jorgeson et al., 2011) felt it was time to begin taking on new responsibilities, and over 70% of pharmacists surveyed wanted to be performing expanded clinical duties within 5 years. The authors concluded that:

> . . . pharmacists responded positively to the proposed vision for the future of pharmacy and are eager to move away from the traditional dispensing role to an extended clinical role. (Jorgeson et al., 2011, p. 125)

Pharmacists surveyed in the United Kingdom also held similar views, however, these have not translated into action and implementation has been slower than stakeholder expectation. Some of the lack of responsiveness and progress has been attributed to the way pharmacists think and act (Bush et al., 2006; Hall and Smith, 2006; Walker, 2000). Rosenthal and colleagues imply that in Canada, pharmacists themselves might be the ultimate barrier to successful implementation due to their own psyche and culture (Rosenthal et al., 2010). Rosenthal and colleagues call for a cultural research agenda in much the same way as previous New Zealand commentary has (Rosenthal et al., 2010; Scahill et al., 2009a).

Alongside the work of Rosenthal, the engagement of pharmacists in patient-oriented health care in Canada has been largely driven by the efforts of Professor Ross Tsuyuki and his team at the University of Alberta (Tsuyuki and Schindel, 2004). The focus in Canada has been on the application of classic change management strategies in an attempt to provide a framework to engage the entire profession in a wholesale change management program (Kotter, 1995). The direction of change is on pharmacist practice as opposed to organizational level change. The eight steps of Kotter's change framework have been applied to the pharmacy context and a descriptive narrative of each step outlined as it relates to community pharmacy. It is expected that this systematic application of Kotter's work around change will provide an informed and robust platform for community pharmacy moving forward (Kotter, 1995; Tsuyuki and Schindel, 2004). Funding is required to achieve this!

Medicines Pricing and Core Dispensing Services in Canada

Medicines pricing in Canada has been well covered by Joel Lexchin in Professor Zaheer Babar's book in 2015 titled "Pharmaceutical Prices in the 21st Century" where he highlights that there is divided responsibility between Federal and Provincial Governments (Lexchin, 2015). Unlike other Commonwealth countries such as Australia and New Zealand, Canada does not have a set dispensing fee that is legislated by Central Government policy. As such the dispensing fee charged to the patient

varies significantly not just between, but within provinces. While private insurance pays for over one-third of all drug costs, the industry has very little influence in either setting prices or containing costs. Overall Canada has among the highest drug costs across developed countries, but a lack of drug insurance means that up to 35% of low income people without insurance do not fill their prescriptions (Lexchin, 2015). This funding issue is different from that required to enact clinical services but it adds to the wider discourse around medicines-related funding.

Funding Extended Clinical Services in Canadian Community Pharmacy

In February 2016, the Canadian Pharmacists Association published a review of Pharmacy services in Canada and Health and Economic Evidence (Canadian Pharmacists Association, 2016). The Canadian system is complex, as funding models for extended services vary considerably across provincial jurisdictions. Payment for pharmacy services—both expanded scope and core services—can happen through public payer compensation, insurer coverage, or out-of-pocket payment. There is significant variation across jurisdictions on public payer compensation—some pay for many services while others pay for none. This raises interesting questions about equality of medicines access across the various constituencies in Canada. In terms of renew/extended prescriptions for continuity of care and changes to dosage/formulation in Alberta, public remuneration is highest (CAD20/assessment; renewals, adaptations and discontinuations) and lowest in Saskatchewan (CAD6 to renew or alter dosage/missing information). For making therapeutic substitutions again public remuneration is highest in Alberta (CAD20/assessment) and lowest in Newfoundland and Labrador (CAD11.96-12) for provincial drug plan beneficiaries. For initiating prescription drug therapy, Pharmacists in Alberta receive CAD25/assessment from public funding. In many other provinces such as Manitoba, Saskatchewan, New Brunswick and Nova Scotia, the authority to initiate prescription drug therapy does not come with attached funding; however, this activity is able to be undertaken within a collaborative practice agreement with prescribers. Public funding for prescribing for minor ailments and smoking cessation also varies considerably across the Canadian provinces. For example, Saskatchewan provides CAD18 and Quebec provides CAD16 funding per minor ailment assessment, while funding is not provided in Manitoba, Prince Edward Island, or Newfoundland and Labrador for this service. All provinces provide public remuneration for influenza vaccination (except Quebec, where this service is not authorized except for demonstration purposes). Alberta provides the highest public payment (CAD20), and Manitoba provides the lowest (CAD7). Clearly there exists significant variation in public funding models for pharmacist services across Canada not only in terms of availability/access for patients but also in terms of reimbursement for pharmacist time. Some believe that this lack of compensation is an impediment to realizing the full potential of the expanded scope possible for pharmacists in Canada. As with the other jurisdictions, however, there is very limited evidence of cost–benefit of pharmacist activities for the overall health system (Canadian Pharmacists Association, 2016). This is an area that needs to be addressed globally so that pharmacists are ensured ongoing and sustained reimbursement (**Table 2**).

Research by the CPA highlights the following payer priorities for Community Pharmacy Services in Canada (**Panel 3**):

Funding pharmacy initiatives for future savings in the overall health-care system appears to be a policy discourse in Canada. The Conference Board of Canada suggests that Pharmacists are an integral part of the health care delivered to many Canadians and that they could play an even greater role in ensuring the sustainability of the healthcare system if the state can further capitalize on pharmacists' role as medication experts and expand the services they provide. The highlights of the Conference Board's report—*The value of expanded pharmacy services in Canada*—includes:

- Expanding three community pharmacy services (smoking cessation, advanced medication review and management for cardiovascular disease, and pneumococcal vaccination) could lead to cumulative savings between CAD2.5 billion and CAD25.7 billion over the next 20 years.
- Scaling up advanced medication review and management for cardiovascular disease could generate cost savings between CAD1.9 billion to CAD19.3 billion.
- Population health benefits of expanding these services include avoiding cases of chronic disease and premature deaths.

Obviously one of the significant impediments to funding is lack of evidence for cost-effectiveness and health outcomes. Commentary around the evidence for pharmacy service provision in Canada is outlined in **Table 3**.

Table 2 Publicly funded pharmacy services by province

	B.C.	*Alta.*	*Sask.*	*Man.*	*Ont.*	*Que.*	*N.B.*	*N.S.*	*P.E.I*	*N.L*
Medication review/assessment—basic/standard	X	X	X		X		X	X	X	X
Medication review/assessment—specific for diabetes		X			X				X	X
Medication review/assessment—advanced/comprehensive		X			X			X		
Minor ailments assessment/prescribing		X	X			X		X		
Smoking cessation		X	X		X	X				
Immunization	X	X	X	X	X		X	X	X	X
Prescription adaptations, renewals, trial prescriptions, refusal to fill prescriptions, pharmacists opinion, etc.	X	X	X		X	X		X	X	X

Source: *Canadian Pharmacists Association (2016)*

Panel 3 Canadian Public payer priorities

- Achieving health system savings by reducing the costs associated with unnecessary doctor and emergency room visits
- Leveraging the core skill set of pharmacists with a focus on safety, adherence, compliance, and appropriate use
- Improving health outcomes
- Serving the high-needs/high-cost population
- Exploring approaches to better leverage the skill set of pharmacists, and services of community pharmacies, in primary care

Table 3 Health and economic impact of pharmacy services

Service	*Comments*
Tobacco cessation	There is good evidence for the use of community pharmacy for cessation interventions for smoking and chewing tobacco. A significant likelihood of quitting was established but very few studies were controlled. Most programs in the literature included remuneration. Candidate for scale-up consideration and modeling based on WHO focus on implementation of cessation interventions.
Influenza vaccinations	Activity increased dramatically over past few years in Canada but research is only starting to publish evaluation results. Lack impact assessment with research to date having focused on pharmacist and patient readiness. Appears to be data to support an increased uptake of vaccination but no cost-effectiveness data is available in the Canadian context.
Other vaccinations	There is some research showing the effectiveness and feasibility of administering other vaccines with some low-quality evidence, such as pneumococcal (pneumonia) and herpes zoster (shingles) vaccinations. The report suggests that there is potential to model the future impact of expanding pharmacist privileges (in those provinces where this service is not currently authorized) and providing remuneration (to increase implementation and uptake) and/or increasing access in those provinces where the authority exists for pneumococcal or herpes zoster vaccination in Canada.
Cardiovascular disease and related conditions—hypertension/dyslipidemia	Several studies report the significant improvement in blood pressure in patients managed by pharmacists in the community setting compared with usual care. Given the strength of the evidence for health benefits and some evidence of lower costs for community pharmacist intervention for the management of hypertension, it would be feasible and justifiable to model the scale-up of this therapeutic service. Several studies have been published to explore the impact of community pharmacist intervention for the control of dyslipidemia with variable but mostly positive results. Improvements in health outcomes have been realized in models where pharmacists collaborate with other health professionals to co-manage care of individuals with certain conditions.
Coronary heart disease and heart failure	Much of the evidence on community pharmacists in cardiovascular care is strongest for managing cardiovascular risk factors—specifically in managing hypertension and cholesterol. Impact of this downstream on events could be assessed. Although there is some evidence of pharmacist impact on heart failure in terms of reducing health system utilization, there is not enough evidence of scale-up interventions for the purpose of reducing cases of CHD or heart failure at this time.
Diabetes	Few studies are available in community pharmacy which assess impact on HBA1c and there are contradicting studies on the difference between pharmacy intervention and control. More evidence is required but the fact pharmacists have an impact on hypertension and hyperlipidemia plays into this. Hypertension and dyslipidemia interventions in community pharmacy should be considered priority service areas for high-risk populations, including patients with type 2 diabetes.
Asthma and COPD	Further research on the role and impact of community pharmacists and pharmacy on asthma and COPD management is required to make any conclusions on intervention effectiveness or cost-effectiveness. The evidence of effectiveness to date is not strong enough to warrant evaluation of potential scale-up at this time.
Mental Health	The amount of evidence for community pharmacy in Mental Health is too low in Canada. Some work has been undertaken in Australia.
Parkinson's Disease	Due to the paucity of evidence and the slow increase in the number of new studies over the past several years, community pharmacist services to address drug-related problems in Parkinson's disease may not be considered a good candidate for scale-up at this time.
Medication Review	A recent review of systematic reviews suggests promise in medication management interventions by pharmacists including medication reviews, and care services including care plan development and follow-up. Furthermore, there is evidence finding technology-assisted pharmacist interventions effective in reducing medication errors.
Minor ailments assessment and prescribing	Future research requires the examination of cost implications and other contextual barriers and facilitators to scale up. In the context of managing and prevention of diseases and risks, prescribing authority would be an important component of a community-pharmacist intervention for scale-up for any one or more ailments or conditions for which there is supportive evidence.

Source: Synthesized from the Canadian Pharmacists Association (2016)

New Zealand

As with the Canadian reforms, historically the focus on health policy and funding reform in New Zealand has been on primary care, mainly surrounding general practice. In the early days (the 1990s and early 2000s), the place of community pharmacy in the reforming health-care system was not explicitly stated compared with the United Kingdom, Australia, and Canada. New Zealand health policy makers expect primary care provider organizations to contribute to improving access, equity, quality, and service delivery through improving levels of integration and multidisciplinary team work. This started with the New Zealand Primary Health Care Strategy (NZPHCS) of the former Labour Government in the late 1980s and was carried forward by the National Government in their primary care initiative paper titled Better, Sooner, More Convenient Primary Health Care (BSMC) (Ministry of Health, 2001a, 2001b, 2006; Ryall, 2007). The 2017 Labour Government continues to focus on the improvement in youth health, mental health, particularly with respect to access to primary health care (Labour Government, 2017). There is no particular direction at this point in their policy with regard to pharmaceutical management and/or community pharmacy.

The NZPHCS expects community pharmacy to undertake counseling, and deliver education, and be integrated into service provision as part of the primary care team. This is in addition to the traditional source, dispense and distribution roles it has held over time. However, the NZPHCS was not explicit in how community pharmacy would contribute to health outcomes. One of the major thrusts of the National Government's BSMC strategy was the development of Integrated Family Health Care Centres (IFHC). These centres are expected to support the devolution of services from secondary to primary care including: specialist assessments, minor surgery, walk-in access, chronic care management, increased nursing and allied health services, as well as selected social services. Aside from outlining pharmacists as one of nine professional groups that could be co-located to an IFHC setting, and the implicit connections of "different islands of health care," there is nothing which specifically relates to future service provision by community pharmacy within BSMC.

By virtue of accessibility and skill set, community pharmacy is arguably in a strong position to triage and refer to general practice or deliver appropriate first contact primary care. Community pharmacy is an integral part of the primary healthcare system in New Zealand but has been an under achiever in terms of meeting the expectations of primary healthcare policy (Scahill et al., 2010). Pharmacists complete a 4-year degree and a 1-year preregistration internship training program in New Zealand. While pharmacists are highly trained, in many instances community pharmacists spend their time counting tablets in a dispensary. One study suggests that the interventions pharmacists make are predominantly bureaucratic, legal or stock related, with less than 20% being professional in nature (Bryant, 2006).

Working documents (under the broad umbrella of health policy) were developed for community pharmacy in the early-mid 2000s, but they were largely operational in nature. The District Health Board New Zealand (DHBNZ) National Framework for Pharmacist Services (District Health Boards New Zealand, 2006) was launched in 2006. The DHBNZ framework was squarely directed at individuals not organizations and provides service specifications rather than organizational level activities or outputs (4) (**Panel 4**).

Level A services involved providing education to patients when they collected their prescriptions. Level B services required focus on assisting patients to be more concordant with their medication regimens. The aim of Level B was to identify medicine-related problems and to formulate solutions and communicate these back to the general practice teams. Provision of Level C and D services required a much higher level of clinical training and more interaction with the prescriber. Issues with the medication regimen are addressed in addition to aspects of patient concordance. Patients who receive a level D review have chronic conditions, are on 10 or more medications, and have significant medication-related problems. Payment for the provision of these services was made through contractual discussions at the level of the Programme Manager—Pharmacy within District Health Boards. It was never clear where the funding was coming from to achieve this.

After wide consultation in 2007, the Medicines New Zealand (MedNZ) strategy was released (Ministry of Health, 2007). Prior to this, New Zealand health policy had not been explicit in signalling the role of community pharmacy within a wider health-care team

Panel 4 DHBNZ National Framework for Pharmacist Services (2006)

Existing Pharmacy Services

- Base dispensing services
- Methadone services for opioid dependence
- Monitored therapy medicine services (clozapine services)
- Aseptic pharmacy services – syringe driver services

New Pharmacist Services

Level A – Services: Information services

- Health education
- Medicines and clinical information support

Level B – D Services: Medicines Review Services

- Level B – Medicines Use Review and Adherence support
- Level C – Medicines Therapy Assessment
- Level D – Comprehensive Medicines Management

(Ministry of Health, 2001a, 2001b, 2006). The MedNZ document outlines opportunities where the optimal use of medicines in New Zealand could be improved. The framework was based on the tenets of: safety, efficacy, access, and optimal use of medicines in New Zealand. It was founded on sector involvement, system capability, efficient structures, and excellent systems, with knowledge transfer. The framework was underpinned by the principles of equity, effectiveness, trust, confidence, and affordability.

At this point, community pharmacy did not appear in the discourse around primary care collaboration, and there was little or no talk about funding for enhanced cognitive services (Scahill, 2011). The MedNZ document was implicit in its role of community pharmacy, rather than explicit and there was no signaling about funding for enhanced services. Subsequent to the launch of the MedNZ strategy document, some engagement with the community pharmacy sector occurred.

Barriers and Issues to Moving Forward with MedNZ

In August 2009, the Hon. Peter Dunne (Associate Minister of Health) hosted a health sector workshop on "realizing the potential of the pharmacy workforce to achieve optimal use of medicines" as a biannual review of the MedNZ strategy (Dunne, 2010). A summary of the issues and the response to these outlined by the Pharmaceutical Society of New Zealand included:

- The lack of connected primary care sector information technology.
- The lack of a consistent and appropriate funding model for pharmacist services.
- Deficiencies in the current medicines legislation.
- The sector doesn't maximize the potential of the GP-pharmacist professional working relationship so improved patient outcomes have yet to be maximized.
- The bureaucracy surrounding current prescribing and dispensing and service payments and its impact on pharmacists is not well understood.
- A lack of understanding of pharmacy activities by DHBs, lack of appreciation of the value of advanced pharmacist services and their benefits to patients and GPs, and the poorly defined role of pharmacists in the primary health-care team and within PHOs. (Pharmaceutical Society of New Zealand, 2010).

Significant value was expected for the New Zealand health-care sector through integration of community pharmacy mainly through the delivery of value-added enhanced pharmaceutical services yet the funding did not follow (Scahill, 2011; Scahill et al., 2010). The expectation is that general practice will have patients who are better informed about their medications and more likely to be concordant. It is then more likely that health targets set by health funders and planners will be achieved (Ministry of Health, 2006, 2007). Community pharmacy, however, should not be solely responsible for integration of their professional activities with general practice and some accountability lies with health funders and planners. Primary Health Organizations (PHOs) are meso-level community-based support organizations for the primary care sector in New Zealand. They sit within 21 geographically based District Health Boards (DHBs) that have health funding, planning, and service delivery responsibilities. PHOs are expected to support integration of health-care providers such as community pharmacy into the primary care sector. PHOs were expected to demonstrate that all of their providers and practitioners (doctors, nurses, pharmacists, other allied professionals) are in the position to influence PHO decision making, rather than one professional group such as GPs being dominant (Ministry of Health, 2001a). Although a minority of PHOs have taken a lead in developing relationships with community pharmacy and there are small pockets of activity around New Zealand, integration of community pharmacy representation into PHO governance structures has been slow. Involvement of community pharmacy in integrated primary care initiatives has also been tardy (Scahill, 2011; Scahill et al., 2010). The underlying problem is that PHOs had no budget or fiscal (or any other) accountability to incentivise community pharmacists to integrate their clinical services.

District Health Boards (DHBs) have significant responsibility for the development of integrated community pharmacy services. In much the same way as the PHOs, the DHBs have been relatively slow to engage with community pharmacy (Scahill et al., 2010). MedNZ calls for increased involvement of community pharmacy to ensure the optimal use of medicines, and DHBs were expected by the former National Government to fully support this strategy. In some DHBs, this occurred at the time through the formation of district wide advisory groups with project leaders being assigned to community pharmacy development portfolios. Involvement of community pharmacy in integrated care projects has flowed from this approach. This also requires full engagement by community pharmacy which has been equally tardy (Scahill et al., 2010).

The Community Pharmacy Services Agreement (July 2012)

The Community Pharmacy Services Agreement (CPSA) was introduced on the July 1, 2012, and represented the greatest shift in community pharmacy funding mechanisms in New Zealand since colonization in the 1840s (Technical Advisory Service (TAS), 2012). The CPSA reflects the Government's drive for a shift to a patient-centered pharmacy delivery model, which encourages integration between health professionals—doctors, nurses, and pharmacists. The CPSA is a contract between individual District Health Boards (DHB) and each individual pharmacy throughout New Zealand. The contract covers the provision of pharmacy services. Part C of the contract provides the Summary of Services to be Provided. Services that are funded are outlined in **Panel 5**.

Core pharmacy services

The New Zealand Government funds core pharmacy services to enable eligible patients where appropriate to access pharmaceuticals and advice services that are responsive to the health needs and priorities of these patients and the communities they live in. It is

Panel 5 Description of the services

Core Pharmacy services
Long Term Condition pharmacy services
Specific pharmacy services

- Class B Controlled Drug Services
- Aseptic Pharmacy Services
- Sterile Manufacturing Services
- Special Foods Services
- Pharmacy Clozapine Services
- Age-related residential care (ARRC) Pharmacy Services; and/or
- Community Pharmacy Anti-coagulation Management Services
- Extemporaneously Compounded Preparations Services;
- Named Patient Pharmaceutical Assessment (NPPA) Services A; and
- Named Patient Pharmaceutical Assessment (NPPA) Services B.
- Community residential care (CRC) Pharmacy Services
- Any other pharmacy services, if applicable

intended that these services will enhance the effectiveness of medicines usage by patients in the community. Core pharmacy services are expected to be part of an integrated community-based service that provides patients with the best quality and most cost-effective services, within the available funding. This is expected to occur through applying current pharmacy knowledge and skills to ensure a high standard of professional competence. Both patient and staff safety are paramount. Within this service, there is a requirement to dispense pharmaceuticals and provide advice and counseling while maintaining appropriate patient medical records. The dispensing process must include:

- Ensuring completeness of prescription information.
- Verification of appropriateness of prescribed pharmaceutical, suitability, dosage, possible interactions.
- Checking medication history for consistency of treatment, possible interactions, and evidence of noncompliance or misuse.

Pharmacists are contracted to provide essential professional advice and counseling and to take reasonable steps to ensure that patients have sufficient knowledge to enable optimal therapy. This process includes:

- Directions for the safe and effective use of the pharmaceutical;
- The expected outcomes of therapy;
- What to do if side effects occur;
- Storage requirements of the pharmaceutical; and
- Disposal of unused pharmaceuticals (needle exchange scheme for some pharmacies).

Long-term condition (LTC) pharmacy services

This service is provided to patients, with a diagnosed long-term condition, who have poor medicine adherence and who are assessed as having the capacity and willingness to receive additional support from a designated pharmacy. Patients must meet the LTC Access Criteria. Community Pharmacy is expected to be a key member of the multidisciplinary team linking with doctors and nurses in general practice but even wider than that. The CPSA contract calls for regular, proactive contact between the pharmacist and the LTC patient. The essential LTC services provided to each patient must include:

- Core pharmacy services outlined previously
- Medicines reconciliation services—collect and compare information from prescribers to make the most accurate list of medicines being taken
- Synchronization services—coordinating the quantities so prescription periods align
- Reminder services—about when the next supply of pharmaceuticals is to be collected
- Regular screening of compliance with and adherence to medicines regimes
- Regular engagement with multidisciplinary care team to provide information about progress in improving management of medications.

All of the LTC pharmacy services provided to each patient must be supported by appropriate documentation, which is available for inspection and audit.

Specific pharmacy services

There are many funded specific services and a brief summary is provided in Table 4.

Table 4 Service fee and handling multiplier

Service	*Service fee (NZD)*	*Handling multiplier*
Core Pharmacy Services	2.50	1.00
LTC Pharmacy Services	30/month and 43.32/month High Needs Adherence Management	1.00
Extemporaneously Compounded Preparations Services	0.00	7.95
Age-related residential care (ARRC) Pharmacy Services	0.00	5.30
Class B Controlled Drug Services (Methadone)	0.00	6.89
Aseptic Pharmacy Services	0.00	26.50
Sterile Manufacturing Services	0.00	26.50
Special Food Services	0.00	5.30
Pharmacy Clozapine Services	0.00	10.60
Named Patient Pharmaceutical Assessment (NPPA) Services A	0.00	5.30
Named Patient Pharmaceutical Assessment (NPPA) Services B	0.00	7.95
Community residential care (CRC) Pharmacy Services	0.00	5.30

Financial remuneration

The annual contracted remuneration package for each individual pharmacy is dependent on the mix of activities undertaken in terms of core, LTC, and specific services. This is a significant change from the previous contract whereby the bulk of medicines-related funding came from claims on dispensed items/scripts. The aim of this contract (the CPSA) is to spend less of the national budget on the dispensing and distribution of medicines and more (proportionately) on value-added clinical services that are expected to improve patient health outcomes. The provisions in the Consolidated Agreement (in July 2017) were the same for all DHBs, in the interests of maintaining one common agreement that governs funding arrangements with each community pharmacy services provider in New Zealand. This reduces complexity and ensures a degree of equity across the country.

The formula for reimbursement is complicated by the fact that the new funding system was implemented in stages. The figures provided in this section are from Stage 3 (July 1, 2013, to June 2014). There are a complicated set of equations, which underpin the funding calculations for Core Pharmacy Services, LTC Pharmacy Services, and Specific Pharmacy Services. In addition to handling and service fees, there was a transition payment made to pharmacies during the initial stages of the transition from the dispensing-based contract to the CPSA contract. This amount varied by pharmacy dependent on historic activities. Over this period, there was a transition pool of funds with a monthly transition payment, based on market share of initial items calculated from historical dispensing figures. Funders also acknowledged the need for quality management and a quality incentive payment is under development.

It is apparent from this analysis that pharmacy income in New Zealand has transitioned from one of dispensing fee payment and retailing to the inclusion of a remuneration structure that includes specific defined clinical activities, attached to a remuneration schedule. Individual pharmacy owners will understand the impact of this new business model on their own pharmacy business. To make the change in model sustainable and ensure that the sector was not disrupted too much financially, a transition payment was provided. This transition payment period has now ceased, and remuneration comes from core pharmacy/LTC and specific services alongside a quality incentive payment.

European Member States

In 2015, FIP collected data on remuneration models for community (and hospital) pharmacy across numerous countries. There was found to be large variations and a focus on product over cognitive (enhanced clinical) services (International Pharmaceutical Federation (FIP), 2015). The European countries under study in this chapter include the Netherlands, Germany, France, Spain, and the Scandinavian countries of Denmark and Sweden. Pharmacists remuneration for distribution (dispensing) in most European countries consists of the combination of a fixed fee per item and a certain percentage of the acquisition cost or the delivery price of the medicine (Dylst et al., 2012).

At the 3rd International Pharmaceutical Pricing and Reimbursement Policies Conference in Vienna, Austria, October 12–13, 2015; Vogler and colleagues presented the results of a survey comparing remuneration policies for wholesale and community pharmacies for 30 European countries (all 28 EU member states, Norway and Switzerland). They found that in 28 of the 30 countries surveyed, pharmacy remuneration was regulated or agreed upon between the pharmacy sector and funders for reimbursable medicines. In 16 of the 28 countries remuneration depended exclusively on the price of the dispensed medicine and was usually a regressive scheme. A performance-based fee for service remuneration was in place in Croatia, Ireland, the Netherlands, Slovenia, and the United Kingdom. Pharmacy remuneration that involves a remuneration framework that is both price-based and performance-based existed in only seven countries Belgium, Denmark, Finland, France, Germany, Norway, and Switzerland.

Spain

Spain is the fifth largest pharmaceutical market in the EU after the United Kingdom, Italy, Germany, and France in terms of market value at ex-factory prices. ISPOR—the Professional Society for Health Economics and Outcomes Research—Road Map for Spain (International Society of Pharmaceutical Outcomes Research (ISPOR), 2017a) highlights that there are three reimbursement categories for medicines in that country:

- 100% reimbursement for hospital pharmaceuticals.
- 90% reimbursement for pharmaceuticals for the management of chronic illness.
- 60% reimbursement for the majority of prescription only pharmaceuticals.

Medicines Availability

To gain entry to the Spanish market, medicines must obtain marketing authorization from the Spanish Medicinal Products and Medical Devices Agency (*Agencia Española de Medicamentos y Productos Sanitarios*) (AEMPS) or the European Medicines Agency (EMA). The product must be registered with the medicines registry within the AEMPS. The pharmaceutical company must have offered it to the national health authorities for inclusion in the reimbursed medicines public health system before marketing begins. Medicines can only be sold by pharmaceutical companies holding the appropriate marketing authorization and their local representatives, or by licensed wholesalers (Paz-Ares and Cocina, 2017). The distribution (technically "dispensing") of prescription medicines to patients is reserved by law to:

- Authorized retail pharmacies open to the public

Pharmacies in hospitals, health centers, and primary health-care facilities of the National Health Service and medicine deposits (first aid kits) (Paz-Ares and Cocina, 2017).

The drug distribution system is organized mainly through wholesalers, who distribute 85% of medicines. The main purchasing bodies are cooperatives of retail pharmacists accounting for 75% of supply and the other 25% is purchased by hospitals. Pharmacists need to complete a 5-year degree, not only to dispense medicines but also to own a pharmacy. There is a compulsory requirement to belong to the College of Pharmacists (Garcia-Armesto et al., 2010). In terms of site regulation, Spanish pharmacies are all independents, and chains are banned at this point. All pharmacies must be owned by pharmacists. Retail pharmacies must be in possession of an authorization granted by the appropriate authority in the autonomous region where the pharmacy is located (Paz-Ares and Cocina, 2017). This is issued according to a quota system based on geographic location and population. Both France and Spain are two of the countries in Europe with the strictest levels of regulation. It is more or less impossible to open new pharmacies and pharmacies have the right to sell nonprescription medicines.

It is very important to understand the drug pricing, procurement, and distribution system as funding of pharmacy services seem (in many countries) to be inextricably linked to this.

In 2014, the Spanish Government considered deregulating chain pharmacies, and this deregulation could likely have a direct effect on funding of pharmacy and the services provided. The notion of full deregulation and the relative instability of funding of the system as a whole would leave pharmacies in much of Europe exposed. In many countries in Europe (Spain included) when prices of medicines fall, then so does pharmacy remuneration.

Pharmaceutical services are defined as part of the Governments' common benefits package (European Observatory on Health Systems and Policies, 2017d). This package covers the products—medicines and/or other health products. This package also covers the actions ("the service") that ensures patients receive the right medicine(s), at the correct dose and duration for the lowest cost possible to individual patients, and the community they live within. Unlike other medical services in Spain that are provided free of charge, pharmaceutical services are co-financed by users. In this way, the base price of the pharmaceutical and wholesaler discounts become very important; this is what funding hinges on. Medicines dispensed in hospitals, however, don't attract a co-payment. For prescriptions funded by the Government pensioners and their beneficiaries are exempt from co-payments. Nonpensioners and their beneficiaries pay 40% of the retail price. The remaining 60% is billed to the regional health system in the area where the person lives. There are specific groups that are subsidized such as those with AIDS and chronic disease who are subjected to a 10% co-payment; capped at a fee/script. The average reimbursement price (back to the pharmacist) in 2016 was EUR10.99 for a script item.

There have been suggestions of the need to change the reimbursement system to accommodate cognitive (enhanced clinical) service delivery as well as dispensing, into the community pharmacy model in Spain. Community pharmacists considered remuneration as the most important facilitator for practice change while funders thought education and training was most important and remuneration did not feature (Gastelurrutia et al., 2009). At the time of writing, there was no publicly available information in policy documents on payment for cognitive (enhanced clinical) services to pharmacists in Spain.

Denmark

The Danish Ministry of Health is responsible for development of the overall framework for the pharmaceutical system. The Ministry is involved with the approval of pharmaceuticals and pharmacy sector and for making legislation concerning the reimbursement system as a whole and as it relates to pharmaceutical services. The Danish Medicines Agency decides the reimbursement status for each pharmaceutical product after a pharmaceutical company files an application for funding. Safety and efficacy considerations are

Table 5 Different types of primary care pharmacies in Denmark

Type	*Description*
Pharmacy	Must retail all types of pharmaceuticals and also have a suitable and adequate stock in relation to the demand at the place in question. And if the pharmacy is asked to do so, it is obliged to procure a medicine that is not in stock. A pharmacist must always be on duty at the pharmacy.
Supplementary pharmacy unit	Is a pharmacy owned by a pharmacist who also owns another pharmacy. The only difference between a pharmacy and a supplementary unit is the ownership and some technicalities concerning the equalization system among the pharmacies. There should be one or more pharmacists employed of which at least one must be on duty.
Branch pharmacy	Is attached to a pharmacy and is operated at the pharmacy's expense. The branch pharmacy has its own independent premises and professionally qualified staff. For each three pharmacies and/or pharmacy branches there should be at least one pharmacist employed. Branch pharmacies may retail the same products as the pharmacy and may also dispense prescription medicine.
Pharmacy outlet	Is also a unit attached to a pharmacy and operated at the cost of the pharmacy in independent premises. The pharmacy outlet has professionally qualified staff, but there is no requirement for having pharmacists employed. The pharmacy outlet may retail OTC drugs and other products that are also carried by pharmacies, but it may not dispense prescription medicine. However, it may hand out prescription medicine dispensed at the pharmacy (including branch pharmacies) to which the outlet is attached.
OTC outlet	Is in premises not belonging to the pharmacy—typically in another store. The outlet receives products from a specific pharmacy and is operated by a store manager, with whom the proprietor pharmacist has a contracted agreement. The store manager typically has no training within the pharmacy sector. OTC outlets are subject to the same rules as outlets of medicine in the nonpharmacy sector. This means that they may carry only a limited assortment. OTC outlets may also provide customers with prescription medicine and other pharmacy restricted medicine that has been dispensed at the pharmacy (including branch pharmacies) to which the outlet is attached.

Source: The Association of Danish Pharmacies

made and pharmacoeconomic criteria are applied if the company submits a voluntary economic dossier—this is not compulsory. Annual reimbursement policy is set as part of this process (Skrijelj and Strandberg-Larsen, 2017). In the primary care sector, medicines are distributed from the pharmaceutical industry to private pharmacies, retail shops, and web-based pharmacies by pharmaceutical wholesalers. Prices are set by the wholesalers fortnightly, with the reimbursement price being calculated based on the least expensive generic product. The amount of reimbursement a patient receives depends on their accumulated pharmaceutical expenses during a 12-month period (January to December) which ranges between 0% and 100% dependent on categories of expenditure threshold.

The pharmacy sector in Denmark is divided into different "Units" as outlined in **Table 5**.

As of February 20, 2017, the 214 proprietor pharmacists have ownership of 235 pharmacies (21 of the proprietor pharmacists own two pharmacies) and 190 branch pharmacies. The new flexible establishment regulation has resulted in 112 new branch pharmacies since July 1, 2015. Furthermore, there are 52 pharmacy outlets and approximately 550 OTC outlets and 250 delivery facilities. Delivery facilities do not stock medicine, but they receive addressed dispatches from one or several pharmacies and pass them on to the individual customer (Danish Association of Pharmacies, 2017).

All community pharmacies in Denmark are expected to provide advice about medicine use, dose dispensing, generic substitution, and the administration of individual reimbursement registers. Many pharmacies offer Body Mass Index assessment, blood sugar, blood pressure, and cholesterol measurements, smoking cessation counseling, and inhaler technique counselling. Extending services in clinical pharmacy is a priority for all Danish pharmacy organizations. Professional bodies use the competence of the pharmacist/pharmacy to take co-responsibility for the pharmaceutical treatment of the patient and for patient safety (European Observatory on Health Systems and Policies, 2017a).

In terms of payment for enhanced cognitive services, there is not a great deal of publicly available information but it would appear that there is an expectation that this occurs in Denmark.

Sweden

Sweden has a population of over 9 million, and national health coverage for all residents is provided by county councils (World Health Organization (WHO), 2017). As such, the Swedish system is highly decentralized, and there are levels including national government, county councils, and municipalities, which are responsible for health-care funding and delivery. Health services are mainly funded by taxes and patients pay a limited amount of the actual costs for medical service visits and treatment. In 2017, patients paid a maximum co-payment of SEK 2200 (EUR 232) per year, which is payable for out-patient pharmaceuticals included in the benefits scheme. The costs of the pharmaceuticals in the benefits scheme are largely paid for by a government grant (World Health Organization (WHO), 2017). Pricing and reimbursement of new pharmaceuticals in the out-patient setting in Sweden is decided by the Board of Pharmaceutical Benefits based on clinical evidence and health economic dossiers following the principles of Value Based Pricing.

Up until June 2009, Sweden's state-owned Apoteket Abs pharmacies had a monopoly in the market place (Wisell et al., 2016). The market was reregulated in 2009 by a centre-right government, and half of the 900 state-owned pharmacies were sold to private owners. Five large pharmacy chains now exist and there has been a 30% increase in the number of pharmacies from around 929 to over 1355 in Sweden (World Health Organization (WHO), 2017). Despite being a fully liberalized pharmacy sector (and therefore

market), the funding is still mostly public with additional co-payments from patients (Wisell et al., 2016). For pharmaceuticals to be reimbursed, they are included in the Pharmaceutical Benefits Scheme, which means they have been approved by the Dental and Pharmaceutical Benefits Board. This board sets the pharmacy purchase price and the pharmacy margin—a fixed national pharmacy retail price (Faulkner et al., 2017).

In terms of enhanced services, pharmaceutical care was introduced into the then state-owned pharmacies in 2002 and was provided by specially trained pharmacists (Montgomery et al., 2010). The service consisted of a scheduled initial counseling session of 30 min and shorter follow-up evaluation sessions that can be both planned and scheduled or "drop in." Patients are identified by a pharmacy team or they can self-identify their own needs and enrol. Despite searching, the author could not find any publicly available information on the funding directive for these services.

E-commerce has seen rapid growth in community pharmacy in Sweden with increase in the distribution of pharmaceuticals and related products by 70% in 2016, but from a relatively low base. By 2020, it is expected that up to 15% of all combined pharmacy revenue could come from e-commerce distribution channels in Sweden (World Health Organization (WHO), 2017).

As a finishing point, a special government commission of inquiry will review financing, reimbursement, and pricing of medicines in Sweden and the report for this review is due in December 2018. At that time, there will be a better understanding of funding levels for services in community pharmacy looking into the future.

Bismarck Funding Models

The countries analyzed in this section that fit into the Bismarck health systems model include the Netherlands, France, Germany, and Belgium.

Netherlands

The Netherlands Pharmaceutical Country profile was published by the Ministry of Health, Welfare and Sports in collaboration with the WHO (World Health Organisation and Ministry of Health Welfare and Sport, 2011). This report covers a broad remit in outlining pharmaceutical policy, medicines trade and production, financing, procurement and distribution, selection and rational use, and household level data/access. In 2009, the Netherlands spent 9.6% of its total government funded health budget on pharmaceuticals equating to EUR 5153 million or EUR 311.77 per individual. No one group receives medicines free of charge in the Netherlands. Most medicines are reimbursed through social health insurance or a private health insurance fund but, if not, then the patient pays the full or partial cost (if partly subsidized). There are no co-payments or fee requirements imposed for medicines at the point of delivery in the public system. There are pricing regulations for the private sector in the Netherlands. Retail medicine prices are publicly accessible and a maximum price is published in the government Gazette. Pharmacists receive discounts from wholesalers and these are reduced by a statutory clawback of 6.82% (max of EUR6.80/script in 2009). In addition, certain health insurers have preference lists of medications and often these include generic medicines which the pharmacist must supply. In terms of payment for enhanced services such as Pharmaceutical Care, a Special Report was undertaken by FIP in 2012 (Federation Internationale Pharmacists (FIP), 2012). There is significant discourse in this report related to remuneration fees and medicine pricing but also facts and figures relating to funding of the system.

Everyone who lives or works in the Netherlands is required to take out basic health insurance. This is a fixed sum payment for all over the age of 18, regardless of associated health risk. There is also an income-related contribution, which the employer deducts from wages and pays to the government. The statutory insured drug package was EUR220 per person in 2012. People can also take out additional policies for cover if they wish. Some individuals with chronic conditions receive a partial refund. In terms of drug reimbursement, the government decides which medicines are allowed to enter the market and which are included in the GVS (Drug Reimbursement System). A baseline limit is set twice per year based on average prices of a medicine in Belgium, Germany, France, and the United Kingdom. The GVS has been around since 1991. Prior to 2012, a dispensing fee was claimed by pharmacies, and a claw back was able to be claimed on the cost of the pharmaceutical from the wholesaler. Of course, remuneration for pharmacy services then depends on medicines pricing, and the cost of pharmaceuticals in Western Europe has steadily declined over the past 15 years. It is fair to assume that average pharmacy reimbursement has declined in the Netherlands. Revenues from dispensing fees were set centrally and remained virtually unchanged between 2006 and 2012. From January 1, 2012, there has been a treatment-related pricing in the pharmacy sector to reimburse the services provided by the pharmacy. There is no longer "central setting," but these are freely negotiable with the insurers (and have shown a decline of 4% for the average pharmacy). It would appear that ongoing sustainable funding for clinical services is a challenge for pharmacists in the Netherlands.

France

Pharmacy-based remuneration that is both medicines price-based and performance-based is found in France. This is also the case for Belgium, Denmark, Finland, Germany, Norway, and Switzerland. Outpatient pharmaceutical care is paid according to the official tariffs defined by the Economic Committee for Health Products (CEPs). Prices and payments are set for whole units and not broken packages. From 2000 to 2015, Pharmacists in France were remunerated via a fixed-sum component (EUR 0.53 per item) and a digressive sliding-scale margin. From 2015, there has been a move toward a fee-based system where in 2016 pharmacists were paid a

fixed sum of EUR 1, in exchange for a reduction in price-based margins. Since 2013, pharmacists have been paid EUR40/patient for consultations for asthmatic patients and patients on anticoagulant medications. A "pay for performance" scheme centered on the use of generic medicines was also instigated in 2013. There is a bonus available for pharmacists of up to EUR3000/year dependent on the proportion of generics dispensed, as well as the change from baseline. The mark-up in absolute terms paid for generic medicines is the same as for originator medicines, but the manufacturer rebates allowed for generics is much higher (50%) than that for branded medicines (2.5%) (European Observatory on Health Systems and Policies, 2017b). Again this discourse is centered on medicines distribution and pricing not clinical service provision.

The general conditions of the pharmaceutical reimbursement system in France are established by law and are implemented principally at a national level by governmental bodies. When marketing authorization is granted either by the EMEA or the French Medicine Agency (AFSSAPS), the pharmaceutical company has to apply for reimbursement on positive lists to obtain funding by the mandatory health insurance scheme (*assurance maladie obligatoire*). There are two lists: one for reimbursable medicines dispensed by retail pharmacies (*Liste des Spécialités remboursables aux Assurés Sociaux*) and one for hospital medicines (*Liste des Spécialités agréées aux collectivités*).

Germany

The pharmaceutical industry in Germany is among the most powerful in the developed world and so there has been a tension in the dichotomy between pharmaceutical policy driving quality and access through fair pricing and industry policy driving the economy in Germany. With a large workforce of over 5 million employees, the pharmaceutical industry also plays a key role in labour market policy being such a large and powerful part of the German economy (Döring and Paul, 2010; European Observatory on Health Systems and Policies, 2017c).

Germany's health-care system is a contribution-based social insurance system, which fits the Bismarck model. This model was outlined previously but what this essentially means is that health care is primarily funded by the public sector. The basic principles of social rights are used as the framework for ensuring social security in cases of illness, and these social right principles must be followed by both health insurance companies and the health service providers (Döring and Paul, 2010).

Of the EUR45.3 billion spent on medicines in 2010 in Germany, the majority (84%) was through community pharmacy (European Observatory on Health Systems and Policies, 2017c) and so this sector is not insignificant and plays a vital role in the procurement and distribution of pharmaceuticals. For dispensing prescription-only medicines, pharmacists in Germany are paid a flat rate payment (EUR8.35) plus a fixed margin of 3%. The retail price contains an additional 19% value added tax (VAT), also known as Umsatzsteuer in German. The margin is calculated from the manufacturer's price plus the relevant maximum margin for wholesalers (excluding VAT). For OTC and other nonprescription medicines, the German community pharmacies are free to determine the price.

Aside from procurement and distribution in German Community Pharmacy, cognitive pharmaceutical services have been available for almost one-quarter of a century (Eickhoff and Schulz, 2006). In 2003, a contract was established between representatives of community pharmacy owners and the largest of the nationwide German health insurance funds. This was the first time a nationwide contract had been successfully negotiated. One year later, a very interesting tri-lateral integrated care contract was signed, which brought together "family pharmacy" with "family physician"–family denoting the primary care focus and delivery. The majority of community pharmacies in Germany were registered to participate at that time.

Belgium

There appears to be relatively less publicly available information on Belgium when it comes to pharmaceutical services reimbursement. For example, ISPOR has not generated a Global Health Care Systems Roadmap for Belgium although 22 other European countries have profiles. In Belgium, there are approximately 4950 pharmacies servicing a population of around 11 million inhabitants. Most European nations spend around 10% GDP on health care; however, there is significant variability of pharmaceutical expenditure. Belgium is similar to France in that its pharmaceutical spend is toward the top end of European countries at 16.4% (le Polain et al., 2010). From the same data-set, Belgium also has the highest "out of pocket expenses" for medicines of 22% (among Austria, Belgium, France, the Netherlands, and Sweden). In Belgium, patients pay a co-insurance for pharmaceuticals (a % of the reimbursement basis), and there is an annual income-dependent ceiling for total out-of-pocket expenditure on health care.

Advanced pharmaceutical care in community pharmacy is in its infancy as a formalized process in Belgium. In October 2013, a New Medicines Service (NMS) was introduced to support one chronic illness—asthma management. This is the first initiative that puts this form of pharmaceutical care into practice in Belgium; and as far as the author is aware, it is the first to be evaluated (Fraeyman et al., 2017). Pharmacists register NMS interventions and are able to claim for this but it appears that details of reimbursement are not made publicly available on policy websites.

Sovereignty Funding Models

USA

The United States appears to be the most complicated of the pharmaceutical systems reviewed in this chapter. This is largely the result of the whole health-care system being rather complex (from a funding viewpoint) and quite different from most other systems

around the world. The literature describes the pharmacy system as a "supply chain" from supplier to market—the consumer being the patient. There does not appear to be a Government imposed price for medicines or the cost of dispensing and this is how health pricing is determined in a Sovereignty-based system. The United States is as close to "free-market" as any of the health systems analyzed in this chapter.

Joey Mattlingy (2012) suggests one of the most confusing markets for the consumer is located at the pharmacy counter in the United States (Mattingly, 2012). He adds that the rise of health-care costs has lawmakers and employers scrambling to find ways to provide access to care without going bankrupt. Numerous policies at different levels of government and in the private sector have further complicated this market, creating a system nearly impossible for the average person to navigate.

When thinking of the pharmaceutical system and its associated policies as a supply chain, there are four main touch points: pharmaceutical manufacturer, wholesaler, community pharmacy, and the consumer, but in the United States, there is a third party involved (the insurer) and they have pharmaceutical supply managers to monitor pricing. It is not an entirely free market with Congress establishing average sale prices (ASPs) as the primary basis for Medicare Part B Drug reimbursement (Murrin, 2015).

ISPOR in their global health-care systems roadmap (USA) state that Medicare, for Part B prescription drugs, pays the average sales price (ASP) plus 6% for drugs administered in the physician's office or clinic, whereas for Part D and Medicare Advantage Prescription Drug (MA-PD) plans, Medicare negotiates rebates and discounts with the pharmaceutical industry. Under the Medicaid program, the State (since Medicaid is managed by individual States) will pay pharmacies or managed care plans for medicines dispensed using rates based on wholesale acquisition cost (WAC) for branded medicines, and maximum allowable cost (MAC) for other brands and generics. WACs are set by manufacturers and are an estimate of the manufacturer's list price for wholesalers or other direct purchasers, not including discounts or rebates (International Society of Pharmaceutical Outcomes Research (ISPOR), 2017b).

Medicare Part B (Medical Insurance) generally does not cover most prescription medicines used at home but it does cover a limited number of outpatient prescription medicines under certain conditions. Generally, medicines covered under Part B are those that would not usually be self-administered, like those obtained from a doctor's office or hospital outpatient setting. Medications not covered under Part B may be covered under Medicare prescription medicines coverage (Part D). The official US Government site for Medicare outlines the following regarding Part B scheduled items (US Government, 2017a).

- **For covered Part B prescription medicines that patients obtain in a doctor's office or pharmacy**, they pay 20% of the Medicare-approved amount, and the Part B deductible applies. Patients must accept assignment for Part B medicines, so they should never be asked to pay more than the co-insurance or co-payment for the medication itself.
- **For covered Part B prescription drugs obtained in a hospital outpatient setting**, patients pay a co-payment. If patients are given medicines not covered under Part B in a hospital outpatient setting, they pay 100% for them, unless they have Part D or other prescription drug coverage; what is paid depends on whether the drug plan covers the drug, and whether the hospital is in the drug plan's network.

Each Medicare medicines plan has its own list of covered medicines (called a formulary). Many Medicare medicines plans place medications into different "tiers" on their formularies. Medications in each tier have a different cost. A medicine in a lower tier will generally cost less than a medicine in a higher tier. Sometimes, if prescribers think patients need a medicine that's on a higher tier, the patient or prescriber can ask the plan manager for an exceptionto obtain a lower copayment (US Government, 2017b). A Medicare medicines plan can make some changes to its formulary during the year, within guidelines set by Medicare. If the change involves a medicine the patient is currently taking, the plan must do one of these:

- Provide written notice to patients at least 60 days prior to the date the change becomes effective.
- At the time the patient requests a refill, provide written notice of the change and a 60-day supply of the medicine under the same plan rules as before the change.

Congress mandates the Office of Inspector General (OIG) to compare ASPs with average manufacturer prices (AMPs) and directs the Centers for Medicare & Medicaid Services (CMS) to substitute payment amounts for medications with ASPs that exceed AMPs by a threshold of 5%. To comply with its statutory mandate, OIG has completed over 30 quarterly pricing comparisons. In April 2013, CMS began substituting payment amounts in accordance with its published price substitution policy, which currently applies to only certain medication codes with complete AMP data that exceed the 5% threshold in two consecutive quarters or three of the previous four quarters.

In the United States, pharmacists have been called to actively participate in the new primary care era following a period of transformative legislation in the Affordable Care Act (ACA) alongside the broadening of health-care insurance coverage. A very high percentage of the US population (92%) live within 3 km of a pharmacy, and there are now over 67,000 pharmacies within the United States, suggesting access to pharmacy services is in fact very good. Part of the reform movement is to lever community pharmacy into helping meet two key goals of the ACA—expanding care to the insured and uninsured and providing greater access to care (Munger et al., 2016).

With the complexity already outlined regarding the US health system and changes in Medicare payment structures, Johnson and colleagues have highlighted the need for pharmacists to keep up with changes (such as the considerable policy changes over a dozen years ago) and the complexities of pharmaceutical reimbursement to help them improve the financial viability of their organizations (Fijalka et al., 2008; Johnson, 2006, 2008).

Community-based pharmacies in the United States began incorporating convenience clinics also known as "retail clinics" into their business models in 2000 (Munger et al., 2016). Retail clinics are medical clinics located in pharmacies, grocery stores, and large retailer outlets such as Target and Walmart (RAND Corporation, 2016). They provide just one primary care function: first-contact care although there has been criticism that these clinics have failed to meet expectations in transforming health-care systems (Hwang and Mehrotra, 2013). Again this highlights the complexity of the US health system, especially when we think about how pharmacy might impact health outcomes through colocation with physicians compared with when these clinics are also found in large retail stores.

Australia

Australia is perhaps the most difficult nation to categorise in terms of overall health system type. At the macrolevel of the "whole of system", Australia is perhaps closest to operating like the USA; in a sovereignty market. When one considers the pharmaceutical system (funded by the overarching system as a whole); however, it operates much more like a Bismarck system. Funding is through national insurance but there is significant linkage between Government, Pharmacy Guild and University Schools of Pharmacy.

Pharmacy Funding Policy Reform

A long-term strategic program of pharmacy practice research has produced a substantial evidence base to underpin proposed new community pharmacy services funded by the Australian Government (Anderson et al., 2008). Tripartite arrangements between Schools of Pharmacy, the Australian Government, and the Pharmacy Guild have supported this through the Community Pharmacy Agreement Research and Development Program. This has been used to inform the priorities of the Sixth Agreement (6CPA) (Commonwealth Government of Australia, 2005). The 6CPA took effect on July 1, 2015. It is a significant jump in investment in community pharmacy by the Australian Government of AUD2.4 billion over the 5-year period 2015–2020. This figure increases to AUD2.8 billion when including chemotherapeutic products and services. The Government will provide AUD825 million over 3 years, from 2017 to 2018 to community pharmacies. This is expected to support and improve the access to medicines by Australians. Over AUD600 million will be through the 6CPA agreement allowing pharmacists to deliver new services or expanded programs. This funding covers the evaluation of the following:

- Dose administration aids
- Staged supply
- MedsCheck
- Diabetes MedsCheck
- Home medicines review program
- Pharmacy trial program

The key features of the 6CPA include:

- A new Administration, Handling and Infrastructure (AHI) Fee, which replaces the previous pharmacy mark-up,
- Dispensing remuneration indexed to the Consumer Price Index,
- An increased investment in Community Pharmacy programs and services,
- A government commitment to extend the Location Rules until mid-2020, with an independent review to be conducted during the 6CPA to inform future arrangements. The rules relate to the establishment of a new pharmacy or the relocation of an existing pharmacy. The rules set out location-based criteria, which are intended to provide further stability of the community pharmacy network and patient access.

The tripartite arrangement in Australia signals a strong and long-term commitment by the Australian Government, the Pharmacy Guild, and the academic community to develop community pharmacy services and to evaluate service provision in a robust manner.

The tripartite agreement has resulted in a positive approach toward community pharmacy development, practice evaluation, and organizational research by all three parties (Anderson et al., 2008). The academic focus has been on identifying facilitators to the successful provision of extended services in Australian community pharmacy. This is a different focus to the barrier identification reported in other high-income countries. Seven facilitators to the implementation of cognitive clinical services in Australia have been identified (Roberts, 2005; Roberts et al., 2006). These include relationships with doctors, remuneration, communication and teamwork, pharmacy design, positive patient expectation, external support, and assistance with change management. The inverse of the first three facilitators reported by Roberts and colleagues were reported by New Zealand pharmacists as potential barriers in the Ten Year Vision study and this is discussed further in the section below (Scahill et al., 2009b).

The downstream benefits have been realized through development of sustainable research programs evaluating and supporting community pharmacy (Feletto et al., 2010a, 2010b, 2011; Roberts, 2005; Roberts et al., 2003, 2006). So, clearly, remuneration is one of the facilitators for pharmacy service uptake, and the following section outlines the current status of funding in Australia.

Administrative handling and infrastructure (AHI)

The Pharmacy Guild of Australia states that the AHI substantially delinks pharmacy remuneration from the price of medicines and is in recognition of the nonprofessional costs of delivering the Pharmaceutical Benefits Scheme (PBS) to patients on behalf of the

Panel 6 Continuing Community Pharmacy Programs in Australia (2015-2020)

- Medication Adherence Programs – Dosage administration aids (DAAs) and Staged Supply with periodic instalments of a full prescription period
- Medication Management Programs – Clinical Interventions, Home Medicines Reviews, Residential Medication Management Reviews and MedsCheck
- Rural Support Programs – Rural Pharmacy Workforce Program and the Rural Pharmacy Maintenance Allowance
- Aboriginal and Torres Strait Islander Program

Government. This does not occur in large parts of Europe and is a significant and positive move for the Australian Community Pharmacy sector. Compared to the existing mark-up structure, which would have continued to trend down over the 6CPA period due to falling PBS prices, the AHI provides an immediate overall increase compared with current mark-up and will increase each year during the 6CPA as a result of indexation. The trending down of remuneration with the mark-up structure and falling pharmaceutical prices is certainly what is happening in parts of Europe.

Importantly, the AHI Fee has been tiered such that the fee applicable to the most expensive medicines on the PBS will remain in line with the current mark-up (AUD72.43 maximum).

The value of this fee from 1 July 2017 was:

- Where the Approved Price to Pharmacist (wholesaler PBS list price) is up to AUD180.00: AUD3.94 per prescription
- Where the Approved Price to Pharmacist is between AUD180.00 and 2089.71: AUD3.49 plus 3.5% of the amount by which the price exceeds AUD180
- Where the Approved Price to Pharmacist is AUD2089.71 or above: AUD72.43

The "AHI Fee" is indexed annually on 1 July by the Consumer Price Index (CPI). From 1 July 2017, the dispensing fee will increase to AUD47.15 for ready-prepared prescriptions. As with the AHI Fee, it is indexed annually on 1 July by CPI. The Pharmacy Guild of Australia highlights that a remuneration review is to be conducted to inform possible pharmacy remuneration arrangements for the 7CPA (July 2020 onwards). The review will not be able to be used to change pharmacy remuneration during the 6CPA. What is clear though is that the Australian Government is prepared to negotiate suitable remuneration packages.

There has been an increase in the total funding allocated to community pharmacy programs in the 6CPA to focus on evidence-based, patient-focused services. This includes programs that benefit Aboriginal and Torres Strait Islanders, and people living in rural and remote areas. This is a significant change from previous agreements and represents a change in the focus of the Government toward the health of these peoples. There is a strong focus on diversity. The Pharmacy Guild of Australia notes that the Government has increased its funding for Programs by over 70% equating to AUD1.26 billion apportioned to the following:

- Continuing Community Pharmacy Programs (AUD613 million) (see **Panel 6**)
- Pharmacy Trial Program (AUD50 million)
- Additional funding to support new and expanded Programs (AUD600 million)

There are major steps forward in terms of funding and support for clinical programs. For the first time, pharmacies are directly remunerated for the provision of diabetes products under the National Diabetes Services Scheme (NDSS).

On the technology front, pharmacies will continue to be funded for electronic transfer of prescriptions and are encouraged to be more involved in e-health through the 6th Agreement and this is likely to be a significant aspect of future agreements.

In summary, in Australia, information is freely available, and the remuneration contract is supported by evidence of pharmacies' value proposition through years of well-funded collaborative research.

Other Systems

South Africa

In 1996, the South African Government released the South African National Drug Policy (NDP) (South African Government, 1996). The aim was to ensure an adequate and reliable supply of safe, cost-effective medicines of acceptable quality to all citizens of South Africa and the rational use of medicines by prescribers, dispensers, and consumers (Section 2, pg 3). The policy had a focus on health, economic, and national development objectives, and the WHO highlighted that the policy was expected to serve the health needs of South Africa by:

- Providing a clear description of the management of the pharmaceutical system,
- Steering key stakeholders with respect to what they can contribute in achieving policy aims,
- Systematic reduction of inefficiencies and waste through development of pharmaceutical infrastructure,
- Design through implementation of suitable programs for human resource development in health care related to pharmaceuticals (World Health Organisation (WHO), 2017).

The policy was a high level one that provides a platform for the development of a robust pharmaceutical system. There is a specific (special as per WHO) place for the pharmacist in this policy in ensuring the supply, distribution, and rational use of medicines. The

aim with respect to procurement and distribution was to promote cost-effectiveness in the public sector and to utilize private-sector facilities as appropriate. It was made clear that a system of joint responsibility between the government and the patient for the financing of medicines was what the government wanted. At this time, financing was related to the procurement and distribution of essential medicines which were provided free of charge at the point of service, at the primary care level. Further policy has been developed and on 19th January 2015 a national policy for the establishment and functioning of Pharmaceutical and Therapeutics committees in South Africa was generated by the Department of Health of the Republic of South Africa (Department of Health: Republic of South Africa, 2017).

A recent review of health-care systems and pharmacy practice in South Africa has been undertaken by Andy Gray at the University of KwaZulu-Natal in Durban (Gray et al., 2016). It is clear that there has been significant change and there is ongoing reform since the transition to democracy in 1994, when the system was fragmented and primary care services underdeveloped. There remains private-sector medical scheme reimbursement policies (health insurance) with no pharmaceutical surcharge for those who can afford to pay (Gray et al., 2016; Malangu, 2014).

In South Africa, there is almost complete separation of private and public sector provision of services. In the public sector, all services at the primary care level are free, and pharmacists in the public sector facilities are salaried. At this point, apart from a centralized dispensing service for chronic medicines (which is provided by large distance dispensing contractors but with some pick-ups being from private-sector community pharmacies), the private sector does not service public sector-dependent patients (Personal communication A Gray, 18th September 2017). Pharmacists in the private sector provide services predominantly to those who are members/beneficiaries of medical schemes (i.e., insured; approximately 8 million out of 55 million population).

In the private sector, pharmacists are reimbursed by means of a regulated maximum dispensing fee and the dispensing fee is not divorced from the price of the medicine (Gray and Suleman, 2015; Gray et al., 2017; Suleman and Gray, 2015), which is the same for most of the European countries investigated in this chapter. The current fee structure for dispensing in South Africa is outlined as below:

- where the single exit price of a medicine or scheduled substance is less than ZAR97.06, the dispensing fee shall not exceed ZAR9.25 plus 46% of the single exit price in respect of that medicine or scheduled substance;
- where the single exit price of a medicine or scheduled substance is greater than or equal to .06 but less than .88, the dispensing fee shall not exceed ZAR22.50 plus 33% of the single exit price in respect of that medicine or scheduled substance;
- where the single exit price of a medicine or scheduled substance is greater than or equal to .88 but less than .10, the dispensing fee shall not exceed ZAR69.00 plus 15% of the Single Exit Price in respect of that medicine or scheduled substance;
- where the single exit price of a medicine or scheduled substance is greater than or equal to ZAR906.10), the dispensing fee shall not exceed ZAR160.00 plus 5% of the Single Exit Price in respect of that medicine or scheduled substance (South African Department of Health, 2017).

The Single Exit Price (SEP) is the factory-gate price (which includes any logistics fee paid to wholesalers or distributors), is delinked from volumes, and cannot be discounted. It is paid by all private-sector purchasers (pharmacists, dispensing practitioners, hospitals). A maximum SEP increase is allowed each year.

South Africa is in the process of implementing universal health-care coverage through a National Health Insurance scheme (National Department of Health: Republic of South Africa, 2017). It is not clear at this point how cognitive (enhanced clinical) pharmaceutical services will fit into this scheme, which could take up to 15 years to fully implement. Having said this, pharmacists will need to play a central role in the move to a single financing approach; certainly specialist clinical pharmacists are suggested to be vital to this transition as it relates to medicines use (Gray et al., 2016).

Another interesting change in the South African pharmaceutical system is the Authorized Pharmacist Prescriber Qualification (South African Pharmacy Council, 2011). This is a postgraduate diploma in Pharmacy proposed by the South African Pharmacy Council, which dovetails with the National Human Resources Strategy for Health and the National Drug Policy. Pharmacists will treat patients with medicines listed in the Primary Healthcare Essential Medicines List (EML) according to standard treatment guidelines. There are, however, no publically available details regarding service remuneration at the time of writing.

Summary

This chapter explored the funding mechanisms of selected nations in the international community pharmacy sector. The focus is on developed countries—those high-income nations that have health system infrastructure in place and for which there is a strong and definable pharmaceutical subsystem. The chapter is framed by grouping nations with the same or similar "whole of health systems" model—rather than by geographic location or affiliation with such jurisdictions as the British Commonwealth. Community Pharmacy structures and funding have been framed in terms of levels including medicines pricing, dispensing/counseling fees, and payment for enhanced cognitive (clinical) services.

This analysis highlights several global issues for the community pharmacy sector when it comes to funding and remuneration. First, there appears to be a dearth of publicly available information on not only strategy but also payment mechanisms to community pharmacies for dispensing and enhanced services in many countries. Medicines "pricing" seems to be more freely available. Second, where information is available, there is often a relationship between medicines pricing and pharmacy services remuneration. There needs to be a substantial "delinking" of pharmacy remuneration from medicines price—mark-up structures

linked to price are tracking downward as pharmaceutical policy puts pressure on the pharmaceutical industry to reduce prices. Switching to generics is also causing a significant reduction. Third, although countries can be grouped into like "whole of health systems," the variation in pharmaceutical subsystems within these countries is more obvious and significant than the system as a whole. A strong overall system if required to strengthen the pharmaceutical system but there is much variation in the pharmaceutical systems of these developed nations.

Although pharmaceutical care was implemented a long time ago in parts of Europe, a number of countries are yet to gain appropriate direct (free from medicines pricing) funding for these professional services. In late 2018, Australia and Canada have the most advanced remuneration systems.

Abbreviations

ACA—Affordable Care Act
AEMPS—Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicinal Products and Medical Devices Agency)
AFSSAPS—Agence Française de Sécurité Sanitaire des Produits de Santé (French Agency)
AMP—Average Manufacturer Prices
ARRC—Age-related Residential Care
ASP—Average Sale Prices
BSMC—Better, Sooner, More Convenient Primary Health Care
CEPS—Economic Committee for Health Products
CMS—Centers for Medicare & Medicaid Services
6CPA—Sixth Community Pharmacy Agreement
CPA—Canadian Pharmacists Association
CPI—Consumer Price Index
CPSA—Community Pharmacy Services Agreement
CRC—Community Residential Care
DAA—Dose Administration Aids
DHBNZ—District Health Boards New Zealand
ECP—Emergency contraceptive pill
EMA—European Medicines Agency
EML—Essential Medicines List
FIP—Federation Internationale Pharmacists
GVS—Geneesmiddelenvergoedingssyteem (Dutch Drug Reimbursement system)
ISPOR—International Society of Pharmaceutical Outcomes Research
LTC—Long-term conditions programme
MA-PD—Medicare Advantage Prescription Drug
MedNZ—Medicines New Zealand
NDP—South African National Drug Policy
NDSS—National Diabetes Services Scheme
NMS—New Medicines Service
NZPHCS—New Zealand Primary Health Care Strategy
OECD—Organisation for Economic Cooperation and Development
OIG—Office of Inspector General
PhAS—Pharmacy Access Scheme
PHOs—Primary Health Organisations
SEP—Single Exit Price
VAT—Value Added Tax
WHO—World Health Organization

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Generic Drug Policies

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Definitions of Generic Drugs

The definition of a "generic drug" varies across countries, based on differences in legal requirements in the generic drug approval process and if the definition includes the original drugs with expired patents. Several countries have an official country-level definition while others refer to definitions by the World Health Organization (WHO), the European Medicines Agency (EMA), or the US Food and Drug Administration (FDA) (Alfonso-Cristancho et al., 2015). Common for most definitions is that a generic drug is a medicinal product that can be manufactured and put on the market by companies, other than the company that invented it, because the original patent[1] has expired.

WHO's definition of generic drugs comprises all multi-source pharmaceutical products that are therapeutically equivalent and interchangeable, including original drugs for which the patents have expired. A multisource pharmaceutical product is a drug that can be purchased under any of several trademarks from different manufacturers or suppliers. After the patent has expired, an original drug, also denoted "single-source drug," becomes multi-source. The WHO definition is different from those of the EMA and the FDA, which do not include the original drug.

According to the EMA, which is responsible for the drug marketing authorization process in the European Union (EU), a generic drug is "a medicinal product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference drug,[2] and whose bioequivalence with the reference drug[2] has been demonstrated by appropriate bioavailability studies" (EMA, 2004). In the USA, the FDA's Center of Drug Evaluation and Research (CDER) is responsible for approval of generic drugs (FDA, 2018). Their definition of a generic drug is "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use."

Bioequivalence is the main regulatory principle for generic drug approval in the EU and the USA. For two drugs to be approved as bioequivalent, they have to be pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) at the site of drug action, after administration in the same molar dose under similar conditions, have to be similar to such a degree that their effects can be expected to be essentially the same (WHO, 2016). The term "pharmaceutical equivalence" requires that the two products have identical amounts of the same active ingredient in the same dosage form and route of administration, and meet the same standards of strength, quality, purity, and identity. Despite this, the active ingredients can be in different chemical forms (salt,

[1] Patents are described in "The Regulatory Process From Invention to Generic Competition" section.
[2] The reference drug is usually the original drug which was granted a marketing authorization by an authority on the basis of submitted quality, pre-clinical and clinical data (often referred to as the "brand-name drug"). Sometimes other generic drugs are used as reference drugs, for instance if the original drug has been withdrawn from the market.

ester, ether, isomer, mixture of isomers, complex or derivative of an active substance) unless they differ significantly in properties with regard to safety and/or efficacy (EMA, 2010; FDA, 2018).

The parameters used to measure bioavailability are the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (C_{max}). Average bioequivalence is established if the 90% confidence interval for the geometric mean of both the AUC and C_{max} for the generic drug is within 80% and 125% of the corresponding parameters of the drug used as reference (EMA, 2010; FDA, 2018). Measurement of these parameters is usually performed in 20–30 healthy volunteers (usually both women and men) under standardized conditions regarding food, exercise, other drug intake, smoking, and alcohol. The volunteers receive both the original (reference) and the generic (test) drug to be compared in a randomized order. If the plasma levels achieved for the two drugs are equal and the tissue distribution is equal, the original's formulation is irrelevant, and the drugs are pharmacodynamically alike.

In most countries outside the EU and the USA the legal requirements that generic drug manufacturers must follow to obtain approval for their products are less rigid. This is often reflected in the country-specific definitions, which may state that a generic drug needs to be "similar" to a reference drug. To be similar usually implies that the products contain the same active ingredient in the same amount, but that there is no hard evidence of bioequivalence or the products being manufactured under the same industry standards (Alfonso-Cristancho et al., 2015).

Naming of Generic Drugs

During the process of research and development, a new pharmaceutical substance is given a generic and "Internationally agreed Non-proprietary Name" (INN), in addition to the proprietary, or brand, name. The INN is the shortened scientific name based on the active ingredient. Names of pharmacologically related substances demonstrate their relationship by using a common "stem." The INN system was introduced by WHO in 1950 as an internationally recognized nomenclature for pharmaceutical substances. The INNs are available in the public domain, hence their designation as "non-proprietary." According to WHO, an international nomenclature for pharmaceutical substances is important for the clear identification, safe prescription and dispensing of drugs to patients, and for global communication and exchange of information among health professionals and scientists. By the use of common stems the physician, the pharmacist, or anyone dealing with pharmaceutical products can recognize that the substance belongs to a group of substances having similar pharmacological activity (WHO, 1997).

INNs are used by default as generic names in major national and regional pharmacopoeias, such as the British Pharmacopoeia and the European Pharmacopoeia. The use of INNs is normally required by national or, as in the case of the European Union, by international legislation.

Generic drugs can be either branded or unbranded products. Branded products are registered with a specific "invented" trade name while the unbranded drugs often go by their INN combined with the name of the company. Generally, most of the scientific literature uses INNs, whereas brand-names dominate the commercial information. The brand-name is designed by the pharmaceutical firm with the intention to promote brand loyalty and facilitate recognition among health professionals and patients.

The Regulatory Process From Invention to Generic Competition

Development of new drugs is a complex and resource intensive process including pre-clinical and clinical studies. It is estimated that the average cost of bringing a new drug to the market is about USD2.6 billion (2013 dollars) (DiMasi et al., 2016) and that one in six new drugs that enter clinical testing is eventually approved for marketing (DiMasi et al., 2010).

New original drugs are usually protected by patents, which are exclusive property rights that exist in the laws of sovereign states to prevent other than the innovative company from manufacturing, marketing, and selling generic versions of the drug. Patent rights are limited in duration, with the global standard being 20 years from when the application was submitted. In the area of drug development, early disclosure of inventions is seen as necessary, usually long before a resulting product is marketed. The pharmaceutical industry is, in most countries, regulated by government agencies requiring documentation of safety and efficacy, which adds time to the pre-marketing process. The time between patent submission and having the product ready for sale can therefore be longer than the sales period under patent. Of the 20 years with patent, the sales period may typically constitute 7–10 years. The legislation in some countries permits a patent holder to apply for an extension of the patent period to compensate for the loss of marketing time due to safety and efficacy regulation.

The period of market exclusivity is meant to compensate for the cost burden incurred by years of research and development. Once the patent of an original drug has expired, however, and there are no other intellectual property rights associated with the drug, other companies are allowed to start the manufacturing of generic equivalents and sell these on the market for a lower price. A lower price is anticipated for multiple reasons. Since generic drugs are bioequivalent to already approved products,[3] the manufacturers of

[3] Extensive reviews of bioequivalence data submitted to the FDA (from 1996 to 2007) have clearly demonstrated that generic drugs are pharmacologically equivalent to the original counterparts (Davit et al., 2009; Kesselheim et al., 2008). An assessment by Davit et al. showed that the average difference in absorption between the original and generic drug was 3.5% which is comparable to differences between two different batches of an original drug (Davit et al., 2009).

generic drugs do not have to repeat the pre-clinical and clinical studies that were required for the original drug and the costs associated with generic drugs are therefore less than for their original counterpart. Furthermore, the costs of manufacturing an original or a generic drug will probably not differ significantly, as they have to be manufactured under the same industry standards. In fact, it is not uncommon that the original drug and a generic equivalent are being manufactured in the same facilities. This becomes possible when innovative-based companies buy or develop their own generic department in order to pursue access to both the patent and the off-patent pharmaceutical market (Probyn, 2004). The generic manufacturers also benefit from the existence of an already prevailing market, which was developed by the previous patent holder, and can spend less economical resources on market establishment. In addition, multiple applications submitted by different manufacturers are often approved to market a single drug, creating a potential for lower prices due to competition in the market.

The Need for Generic Drug Policies

Along with rising drug expenditures, the role of economics in pharmaceutical policy has evolved drastically during the last decades. Generic drug policies, which refer to any regulation, measure or initiative, typically undertaken by the government authorities to promote the use of generic drugs, have been important in this context. The cost-saving potential for generic drugs has been attractive to health authorities worldwide as a means to tackle the long-term challenges of an ageing population, increased incidences of chronic diseases, and budgetary constraints compounded by the high cost of new drugs. The ultimate aim of generic drug policies is, however, not only to reduce drug costs but also to increase the access to and regulation of generic drugs and prevent drug shortages and supply disruption. The availability of low-priced generic drugs is especially important to increase the economical access to drug treatment in low- and middle-income countries, where the pharmaceutical market is regulated to a limited extent.

Although economic theory indicates that it should not be necessary to create policies for the generic drug market, there are several features of this market that makes regulation favorable from a payer's perspective. Due to patent protection, pharmaceutical companies may have some market power to be used in price setting, at least within certain therapeutic areas and for a certain period of time. The prices of patented drugs are therefore generally higher than what would have been the case in a market with several suppliers of the same product. In addition, the patent period allows the companies to provide physicians with brand-name specific information which may establish a brand-name loyalty that persists after the product's patent has expired (Lundin, 2000). This "first mover advantage," in combination with the fact that physicians are not economically responsible for their prescribing, makes it possible for brand-name manufacturers to maintain a high-price strategy after patent expiry, instead of engaging in price competition with generic suppliers. This phenomenon, known as the "generic competition paradox" (Kong, 2009), implies that the brand-name manufacturers may continue to target the market segment that remains loyal to the original product.

In many countries, a third party, in the form of a private or public insurer, is paying the main share of the drug costs. This significantly affects the demand elasticity and restricts prescribers' and patients' incentives for economically rational drug use. When individuals are exempted from the financial consequences of their consumption, the price sensitivity in the market falls and the demand is not reflected in the prices. Presuming that patient demand is initially responsive to the drug price, third party payment has an unquestionable positive effect on the access to drug therapy. There is, however, a negative effect known as "moral hazard" which implies that if a patient is shielded from the total costs of the drug therapy, he/she might choose differently than if he/she was fully exposed to the costs (Lundin, 2000). This might result in an undesirable increased utilization of drugs in general or an increased utilization of more expensive drugs than strictly necessary.

Regulatory authorities and third party payers have implemented various policies to directly or indirectly regulate availability and access to lower-priced generic drugs. There are in broad outline two main categories of such policies: supply side and demand side policies. These will be described in the next sections.

Supply Side Policies

Generic Drug Approval and Market Access

The most important competitive advantage for the suppliers of generic drugs is that they do not have to bear the costs of years of research and development. In addition, the substantial scientific evidence for the original drug from clinical trials as well as from real-life can be used to simplify the market authorization process for generic equivalents.

A simplified approval process for generic drugs was first introduced when the *Drug Price Competition and Patent Term Restoration Act* (known as the *Hatch-Waxman Act*) was passed in the USA in 1984. The Act included a statement that pre-clinical and clinical testing does not have to be repeated for generic equivalents of original drugs approved after 1962. Hence, it created an abbreviated pathway for approval of generic drugs. The first coherent set of bioequivalence standards was also presented in the Act. It was put in place to ensure that generic drugs would be less expensive than the original drug and thereby make it easier for generic drugs to enter the market and expand access to important drugs. In practice it means that pharmaceutical companies can submit an abbreviated new drug application (ANDA) to the FDA when they apply for market approval of a generic drug. In the application they must demonstrate that the generic drug contains the same active ingredient as the original drug (inactive ingredients, denoted

"excipients," may vary), is identical in strength, dosage form, and route of administration, is manufactured under the same strict standards as the original, and is sold in an appropriate container with the correct labeling. Generic drugs manufactured by the original companies, i.e., the previous patent holders, are exceptions from this. These so-called "authorized generics" are approved under the same new drug application (NDA) as the original drug and marketed and distributed by an authorized generic drug distributor with a generic drug product label. Authorized generics contain the same excipients as the original drug and do not differ in taste, color, size, or shape.

An abbreviated pathway similar to the one in the Hatch-Waxman Act was later included in the EU legislation by the generic market authorization application (generic MAA) described in the Directive 2004/27/EC of the European Parliament and of the Council. The generic MAA is applicable to generic equivalents to original drugs that have been approved for at least 10 years in an EU member state. If the generic drug is found to be bioequivalent to the original drug, the efficacy and safety data that formed the basis for approval of the original drug apply to the generic drug.

Another effort to increase market entry of generic drugs is to prioritize applications from companies that want to deliver generic drugs in markets where the availability of generic alternatives is scarce. In addition, it is possible to reward the company that brings the first generic alternative to the market with a time-limited market exclusivity. The shortcoming of this is, of course, that it holds other suppliers away from the market, possibly also in the long run.

The time spent to get a generic drug on the market can be reduced by permitting legal exemptions from the patent law, often referred to as Bolar provision.[4] The exemption allows other than the patent holder to use the technology of a patented drug to perform work that would assist in the marketing or regulatory approval of the generic product, while the original's patent is still in force. It includes permission for the generic manufacturer to set up and test the manufacturing and delivery capacity before entering a market, enabling marketing of a generic drug as soon as the patent expires. This legal exemption has been put in place worldwide but its nature and scope varies significantly from country to country.

Pricing and Reimbursement

Many countries, especially in Europe, have implemented price control on prescription drugs. Price control can be applied either on all prescription drugs or only on those that are included in a reimbursement scheme. A common pricing practice for generic drugs is to set the price in reference to the original drug, for instance, by giving generic drugs a price that is a certain percentage lower than the original drug—a policy called "generic drug linkage" or internal reference pricing. The policy design varies between countries with respect to the size and timing of the price reductions (e.g., immediately after patent expiry or when a generic market is established), and if the price of the original drug is subject to the same price reductions as the generic alternatives. In some countries, it has been decided that the first company to market a generic version must set a price at a certain percentage below the price of the original drug at the time of patent expiry and that subsequent market entry of other generics must be prices at or below this level (Vogler, 2012). Another approach is to incrementally reduce the price of a drug according to predefined rates, depending on sales volume (Dalen et al., 2011).

There are also pricing practices that do not directly restrict the companies' freedom to set drug prices but affect prices in a more indirect manner. The intention is to decrease the sales of more expensive drugs by encouraging patients to opt for more cost-effective drugs. Indirect price controls can also be denoted as "incentive-based" systems since they depend on how the different stakeholders behave in response to the incentives in the system. In such a system the stakeholders (i.e., patients in the role as consumers and pharmacists in the role as sellers) are rewarded (positive incentives) or punished (negative incentives) depending on whether they behave in accordance or deviation with how the makers of the system want them to behave.

A generic reference price system is a typical example of an incentive-based strategy. This strategy is based on the premise that drugs are generically interchangeable and can be clustered into "reference groups" of similar drugs. Each group is assigned a reference price, which is the reimbursement price for the drugs in that particular group.[5] For drugs that are more expensive than the reference price, the patient has to pay the cost above the reference price. The reference price is often set around or below the average price of the generic drugs, or at the lowest price in the cluster. A "not too low" reference price has been advised for a brief, initial period, to provide incentives for more generic suppliers to enter the market.

It is also possible for the third party payer to reimburse only one of a few drugs within a certain cluster, typically the least expensive drug in the group. This stimulates a price competition when new generic drugs enter the market because the companies compete to be the preferred supplier within the cluster. An undesired consequence, however, might be that some generic drug suppliers, whose products have not been selected for reimbursement, are forced out of the market, thereby reducing the generic competition. Another strategy is to offer patients low-cost generic drugs without co-payment. If generic drugs are available free of charge, the presumption is that patients' demand will shift away from expensive brand name drugs toward cheaper generics.

[4] Named after the case Roche Products versus Bolar Pharmaceutical in 1984, a court case in the USA related to the manufacturing of generic pharmaceuticals.

[5] Other levels of reference-based pricing exist where the reference groups constitute drugs that are analogues (chemically different) and drugs that are therapeutically similar and used to treat a particular condition. Most countries, however, have adopted the "generic" approach which has relatively small implications for patients' drug therapy but thereby also limited cost saving potential (Ioannides-Demos et al., 2002).

Tendering

Tendering is another way to encourage price competition in the pharmaceutical market. In the context of drugs, tendering can be explained as any formal and competitive procurement procedure through which tenders (offers) are requested, received, and evaluated for the procurement of drugs and where the contract is granted to the pharmaceutical company/importer who submits the most advantageous offer.

Tendering has traditionally been applied in the hospital sector, for separate hospitals or for groups of hospitals at a regional or national level. The latter is a form of tendering referred to as joint procurement. Joint procurement enhances the hospitals' purchasing power over the pharmaceutical companies by stimulating the companies to lower the prices of one or more drugs to obtain the exclusive right to distribute these to the hospitals.

More recently, several countries have made use of tendering also in the outpatient off-patent sector, effectuated by governmental authorities or private health insurance companies. WHO reports that even supranational initiatives have been suggested to make the procurement process more efficient and strengthen the supply management systems in countries which are facing financial challenges in the healthcare sector. In the WHO European Region report on improving access to drugs through public tendering, three main groups of tenders to be used for generic drugs are described: open tender, restricted tender, and competitive negotiation (WHO, 2016). An open tender implies that bids are invited from any supplier which fulfills the terms and conditions specified in the announcement. This is in contrast to a restricted tender where interested suppliers need to be approved in advance, for instance through a prequalification process that takes into account adherence to good manufacturing practices, past supplier performance, financial viability, and similar. Restricted tenders can also be conducted in a step-wise manner where the lowest price offered is published without announcing the name of the bidder before other qualified bidders are invited to submit lower offers. In a competitive negotiation, a preselected number of suppliers are invited to submit price offers, followed by negotiation to achieve a better price or particular arrangements.[6]

To win a tender can imply large delivery requirements that some suppliers have problems fulfilling because they are unable to keep up with manufacturing to meet the demand. To minimize the risk of supply disruptions and secure sustainability, the contracts can be divided between two or more companies.

Demand Side Policies

Generic Prescribing

An important way to try to control drug expenditures is to influence prescribing patterns. Generic prescribing, or prescribing by INN, implies that the prescriber writes the active ingredient name instead of the brand name on the prescription. This may be enforced as an indicative or mandatory prescribing practice. Generic prescribing is supposed to contribute to rational drug utilization and prevent prescribing and dispensing errors.

Since mandatory generic prescribing was introduced in the UK in 1968, many countries worldwide have little by little put in place a similar practice for either a selection of therapy groups or all groups where generic drugs are available. No matter if generic prescribing is indicatively or mandatorily enforced, important additional measures are to teach practicing physicians as well as medical students to prescribe by INN and implement prescribing software that supports such prescribing. From the 2000s onwards, more and more countries have installed electronic prescribing systems which can be designed with a default generic drug choice. This has been found to give an immediate and sustained increase in the proportion of generic drug prescriptions (Malhotra et al., 2016). Applied in hospitals, generic prescribing does not only stimulate generic drug use in the hospital, it also affects the use after discharge. If the hospital physicians prescribe generic drugs upon patient discharge, these drugs are quite likely to be dispensed at retail level and possibly also affect prescribing in primary care.

It is crucial to note, however, that generic prescribing in itself does not stimulate generic drug use unless pharmacists choose to dispense a generic drug. Therefore, incentives for pharmacists to sell less expensive drugs should also be implemented (described in next section).

Generic Substitution

Generic substitution is the practice where pharmacists substitute a prescribed drug with a generically equivalent drug. This kind of substitution is economically rational in situations where the prescribed drug is more expensive than the generic alternative that is available in the pharmacy. It also has positive effects beyond the economic argument because it makes it legal to switch to a different brand if the prescribed one is unavailable.

In countries with mature healthcare systems, the national drug authorities normally decide if a drug is substitutable with another drug based on generic interchangeability. In the same way as for generic prescribing, this policy may be indicative or mandatory. For generic substitution policies to be successful, it is of principal importance to have in place proper incentives for pharmacists to dispense generic drugs. This can for instance be in the form of a system that financially rewards the pharmacists for dispensing

[6] This method has for instance been used in the negotiation of reduced prices for antiretrovirals conducted by the United Nations Children's Fund (UNICEF) and the Clinton Foundation.

generic drugs, by extra dispensing fees or higher margins for generic drugs. Pharmacy-owners may be offered discounts by generic drug suppliers who want to enter the market or increase their market shares, something that may increase the pharmacy's profit. To prevent the entire discount from being retained at the retail level, and to ensure economic benefit to the patient and/or the third party payer, generic substitution can be combined with other policies, for instance generic reference pricing (described in "Pricing and Reimbursement" section). The opportunity to perform generic substitution is considered important for a successful outcome of a reference price system. If the pharmacist is not allowed to select the cheapest/reimbursable drug in a reference group, the consumer shift mechanisms will easily be undermined. On the other hand, a reference price system, which is combined with generic substitution, allows the pharmacist to retain some of the difference between the price of the drug and the reference price if they dispense a drug below the reference price. This makes, in many situations, an attractive financial incentive for pharmacists.

Financial incentives for pharmacists, however, are of limited value if patients do not accept the substitution. In most countries, patients are provided with an opportunity to refuse generic substitution and request a specific brand (often the brand specified on the prescription). The decisive point is whether patients are financially punished by having to pay an additional cost (a "brand premium") if they refuse substitution. In some countries, the patient has to pay the full price of the drug if they are unwilling to accept the generic drug that the pharmacist has to offer. In addition, the physician may also have the opportunity to exempt the patient from generic substitution and, possibly, the extra payment.

It is an evidence-based argument that policies that allow generic drug companies to set their own prices, while giving physicians and pharmacists incentives to prescribe and dispense the least expensive product, are more effective at reducing prices over time than direct regulation of prices (Wouters et al., 2017). Despite being rewarded with higher margins on generic drugs, pharmacy-owners are not necessarily collaborative when the aim is to bring down prices in the long-term (Håkonsen et al., 2009). It is therefore of importance to get the incentives right in both short and long perspectives, properly adjusted to the distribution power in the market, so that market actors do not sideline the strategies.

Targeted Information and Academic Detailing

Physicians play an important role in the uptake of generic drug use since they make the final decision of what to prescribe. They also have a more indirect role because their views on generic drugs may be reflected in the views of their patients. Patients generally prefer exactly the drug prescribed by their physician but tend to accept generic substitution if they perceive that the physician is positive toward generic drugs (Håkonsen and Toverud, 2012). Physicians might, however, be unaware that generic drugs are available and/or that they are sold at a lower price. They might also have scarce knowledge about the bioequivalence requirements for generic drugs and hold opinions that generic drugs are inferior to brand-name drugs. Particularly in countries with less mature healthcare systems, physicians are concerned about generic drug suppliers' trustworthiness (Toverud et al., 2015), sometimes with good reason.

To raise the acceptance of generic drugs among physicians, it is crucial to provide them with appropriate information, which will also prevent potential misconceptions and increase the extent of generic prescribing (if allowed). This can be achieved by targeted information campaigns or academic detailing involving meetings with clinical consultants (e.g., physicians and pharmacists) who give the physicians unbiased, evidence-based information about generic drugs. A follow-up measure is to combine this with feedback on their prescribing behavior. The feedback can include detailed information about the prescribing rates of generic and original drugs, the costs per defined daily dose of drugs prescribed in each category, the rate of reservation against a generic being dispensed and the potential savings if generic drugs are being consistently used.

Academic detailing can also be organized as sessions where physicians discuss their prescribing patterns, with or without the presence of pharmacists. So-called "pharmacotherapeutic discussion groups" or "quality circles for pharmacotherapy" give physicians the opportunity to exchange information and experiences which eventually can change their prescribing behavior. These sessions also have the potential of changing physicians' knowledge and perceptions of generic drugs and increase the proportion of generic drug prescriptions (Spiegel et al., 2012).

Finally, a principal measure to increase familiarity with generic drugs is to focus on INNs instead of brand names in health professional education systems. The education curricula should also make sure that students gain sufficient insight into the principles of generic equality and interchangeability.

Prescribing Budgets and Indicators

The abovementioned policies to stimulate generic prescribing are sometimes combined with financial incentives for physicians. For instance, physicians can be given a prescribing budget (or a quota) that puts restrictions on how much they can prescribe (Rashidian et al., 2015). If they choose to prescribe low-cost generic drugs instead of more expensive brands, their budget will cover more prescriptions and minimize the chances of running financially short during the budget year.

Another approach is to implement a pay-for-performance policy, whereby prescribers or their organizations are financially rewarded for their prescribing behavior (Rashidian et al., 2015). As a generic drug policy, this could take the form of additional payment for increased generic prescribing or reduced payment for prescriptions of expensive original drugs. As an indicator for rational prescribing, the percentage of prescriptions for certain generic drugs versus more expensive drugs within different drug classes can be monitored by the third party payer. In addition to increasing the share of generic dispensing, this facilitates the understanding and evaluation of the prescribing practices for the policy maker and forms the basis for prescriber feedback.

Public Information Campaigns

Although generic drugs are equivalent to the original drug, they may have other names, colors, and shapes because of the other excipients. Patients may have specific preferences for using a certain brand and be opposed to substitution to a drug they are unfamiliar with. For instance, patients who know their drugs by name and appearance might find it more demanding to keep track of their drugs if they are dispensed a different brand of generic. A review of studies from high-income countries showed that although generic substitution and generic drugs are well accepted by most patients, about one-third report negative experiences with generic drugs (Håkonsen and Toverud, 2012). Patients of higher age and/or low educational level seemed more likely to hold negative views toward generics while the results were inconclusive regarding variables such as sex and income.

There are many potential reasons why someone might hold negative attitudes toward generic drugs. It is a common notion that lower prices imply poorer quality and this applies to drugs as much as for other products. Studies show that patients make tradeoffs between price and perceived quality in relation to the seriousness and complexity of the condition they are treating when choosing among original drugs and generics (Al-Gedadi et al., 2008; Ganther and Kreling, 2000; Heikkilä et al., 2007). Particularly, when patients have to bear only a small share of the cost themselves, they tend to choose perceived quality over cost. Even in countries without public healthcare and limited access to private health insurance, patients tend to choose the most expensive brands, which they can afford within their budgets, in attempts to avoid counterfeit and substandard drugs. Although counterfeit and substandard drugs can be available under different names, brand-names as well as INNs, and be offered at any price, there is general skepticism toward the cheapest generics, especially if they are labeled with unknown names (Håkonsen and Toverud, 2011).

Lower prices, however, are a double-edged sword. Price differentials have also been shown to have considerable effects on peoples' decisions to opt for the cheapest alternatives (Dalen et al., 2011; Rizzo and Zeckhauser, 2009). Personal economic benefits, in terms of reduced co-payments or avoidance of an additional cost, are decisive factors in patients' acceptance of generic drugs regardless of income. In addition, patients' choices are influenced by knowledge, previous experience with the drug and information from friends, family, and media.

Hence, policies to improve the knowledge of and attitudes toward generic drugs in the general population are crucial supplements to the other presented generic drug policies. Information campaigns through mass media have resulted in public awareness of important health-related topics (e.g., more rational use of antibiotics, how to quit smoking, what to do in case of a heart-attack) and could be a useful channel for unbiased information about generic drugs. Physicians, pharmacists, and other healthcare personnel should also provide information, on the condition that they possess appropriate information themselves.

Evaluation of Generic Drug Policies

The objective of generic drug policies is to promote the use of generic drugs and thereby maximize health gain for the population by efficiently allocating limited resources. Price reduction and market share of generic drugs after patent expiry are commonly used indicators for the success of generic drug policies. It has been argued, however, that a methodological framework should also take into account the robustness of the generic market, which is operationalized as the availability of generic drugs and the time of generic entry. The main argument is that patients may already be switched to other therapeutic options that are still under patent protection if generic drugs are brought to market months after the original brand lost its exclusivity. In a framework by Kanavos (2014) the following five indicators are proposed to address the robustness of a generic market: (1) availability (whether a generic is available after loss of patent exclusivity); (2) time delay and speed of generic entry (i.e., how soon a generic enters the market); (3) number of generic competitors (i.e., is there a sufficient number of competitors to stimulate price competition; (4) generic volume share evolution (i.e., does generic volume increase its share relative to the originator brand); and (5) price developments (i.e., do prices decline significantly post-patent expiry, is the amplitude of price reduction following generic entry related to the price level at patent expiry, and is there a link between the magnitude of price reduction post-patent expiry and generic market share).

In the evaluation of generic drug policies and the robustness of the generic market, it is important to consider the possibility of price segmentation within a country. Particularly in low- and middle-income countries, drugs may have higher prices in private pharmacies targeting wealthier customers while lower prices are offered in public pharmacies (WHO, 2016). In some low- and middle-income countries the price level on selected drugs in the private sector is higher than in high-income countries. Therefore, studies should report prices in private versus public sectors in relation to international reference prices.

Multiple factors might attenuate the efficiency of generic drug policies related to health outcome and subsequent health expenditures. Drug non-adherence and medication errors might be unintended consequences of generic drug policies leading to lost opportunities to improve or maintain a patient's health status and increased costs of therapy. The costs can be divided into direct costs due to increases in drug use, physician visits, and/or hospitalization rates, health benefits forgone (human cost and opportunities lost), and indirect, productivity costs (personal and social economic burden). In total, the economic consequences of these problems might be substantial; potentially counterbalancing some of the savings gained. In the pursuit of short-term decreases in costs, there is a concern that the result could be increased long-term costs, e.g., costs due to increased morbidity and mortality resulting from suboptimal drug use. There are also other costs involved in implementing and managing the different policies including the development of a feasible regulatory framework, implementation of necessary changes in administrative and computer systems, and education of healthcare and administrative personnel. It is, therefore, important that savings are compatible with administrative costs in the short and long-term.

Global Considerations

In low-income countries, particularly, low-cost generic drugs have made medical treatment possible for large parts of the population. Despite this, it is estimated that about one-third of the world's population lacks sustainable access to essential drugs (WHO, 2008). Most of the generic drug policies described in this chapter are examples of policies implemented in mature healthcare systems in high-income countries. In less developed countries, where essential drugs are not always available or affordable to those who need them, pharmaceutical markets are relatively unregulated and free from pharmaceutical measures to enhance generic drug use. Prescribing guidelines and prescribing facilitators (such as electronic prescribing systems) are scarce and so are policies for drug pricing and maximum mark-ups. It is also a challenge that generic drugs manufactured in countries that do not have stringent regulatory authorities can create product-quality risks due to improper control routines and lack of bioequivalence requirements. Other challenges in the implementation of generic drug policies in low- and middle-income countries include legal barriers associated with regulatory and intellectual property policies (lack of harmonized regulatory provisions among stakeholders, data exclusivity, patent linkage, patent extensions) and financial barriers to the uptake of generic drugs (Kaplan et al., 2012). Low salaries for prescribers and dispensers, ownership of pharmacies by physicians, low mark-ups for the dispensing of generic drugs, or dispensing fees as a fixed percentage of price are examples of the latter (Kaplan et al., 2012). As described in "Generic substitution" section, proper incentives for pharmacists to dispense generic drugs are a prerequisite for a successful outcome, otherwise generic drugs would only be offered to the poorest patients.

To promote the use of quality assured generic drugs also in less mature healthcare systems, WHO has developed a guideline for low- and middle-income countries on how to implement effective pharmaceutical pricing policies (WHO, 2015). Besides policies to promote uptake of generics via an increased number of market authorizations and reduced timelines, the guideline focuses on policies to ensure quality and safety, including the monitoring of good manufacturing practice (GMP), publication of inspection reports, post-market surveys, sanctions for false quality claims, and documentation of bioequivalence.

Conclusion

Although the definition of a generic drug varies between countries, there is a universal understanding that generic drugs are medicinal products that can be manufactured and marketed by companies other than the innovator company after the original patent has expired. The ultimate aim of generic drug policies is to increase the global access to and regulation of generic drugs, reduce drug costs, and prevent drug shortages and supply disruption. The availability of low-priced generic drugs is important to increase economical access to drug treatment in low- and middle-income countries. Despite this, most of the existing policies, which are described in this chapter, remain unimplemented in the less mature healthcare systems.

Healthcare professionals, particularly physicians and pharmacists, have important roles in the uptake of generic drugs since they make the final decision on what to prescribe and dispense. They also have important roles in their encounter with patients whose confidence in generic drugs often depends on proper information from health professionals.

Glossary

Active substance: A substance that alone or in combination with one or other substances is considered to fulfill the intended activity of a drug.
Bioavailability: The rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.
Bioequivalence: When two drugs contain the same amount of the same active substance(s) in the same dosage forms and the bioavailabilities of the two drugs after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.
Generic drug: A drug whose original patent has expired (various definitions are presented in the text).
Generic drug policy: Any regulation, measure or initiative, typically undertaken by the government authorities to promote the use of generic drugs.
Internationally agreed non-proprietary name: A unique public drug name, usually similar to the name of the active substance, that is globally recognized.
Market exclusivity: Exclusive marketing rights granted by the government authority upon approval of a drug. Can be granted if statutory requirements are met.
Multisource product: A drug that can be purchased under several trademarks from different manufacturers or suppliers.
Patent: Exclusive property rights to prevent other than the innovative company from manufacturing, marketing, and selling generic versions of the drug.
Pharmaceutical equivalence: When medicines contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.
Price control: When government authorities set the price of a drug and/or indirectly influence it.

Reference drug: A marketed drug used as comparator in the assessment of bioequivalence and market approval of generic drugs.
Third party payer: A public or private organization that pays or insures health or medical expenses on behalf of beneficiaries or recipients.

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The Social Determinants of Health Inequalities: Implications for Research and Practice in Social Pharmacy

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Introduction

The causes and consequences of health inequalities (and their implications for research and practice) have not, it is fair to say, been a notable feature of the body of work that we refer to as social pharmacy. By contrast, the previous three decades have witnessed a burgeoning number of empirical studies, numerous reviews, and growing political awareness about the social determinants of health inequalities (Wilkinson and Pickett, 2009; Wilkinson and Pickett, 2018). The field of epidemiology and public health, focusing on health inequalities, has risen in prominence with a finding that an individual's social position (whether this is measured by social class, education, or deprivation) profoundly shapes their health outcomes. To illustrate this using deprivation as a marker of social position, the recent Global Burden of Disease study showed that males who lived in the most deprived areas of England in 2013 could expect to have a life expectancy which was 8.2 years shorter than those living in the least deprived areas (Newton et al., 2015). If we were to look at social class or education, we would also see wide differences in health outcomes (Wilkinson and Pickett, 2009). There are, of course, huge inequalities in health outcomes when we compare health outcomes within and between different countries. For those who want to know more about this literature, there are numerous reviews (Dorling, 2010; Graham, 2007; Wilkinson, 1996; Wilkinson and Pickett, 2009, 2018).

While the cumulative effects of a lifetime of disadvantage and poverty are well known and well researched, the focus of the debate in recent years around the causes of health inequalities has moved towards understanding the health consequences of living in an unequal society, as measured by levels of income (or wealth) inequality. For example, Richard Wilkinson and Kate Pickett argue that the greater the level of social inequality within a country, the more likely that the country is to experience a worsening of a range of health and social problems(Wilkinson and Pickett, 2009, 2018). Their proposition is that it is inequality, per se, as well as poverty, disadvantage, and education that impacts on health (through what are referred to as bio-psycho-social processes). This set of arguments has gained considerable traction among researchers, commentators and epidemiologists, and even amongst politicians. However, as indicated, health inequalities have not been a particular focus of concern within social pharmacy.

This lack of attention to the macro determinants of health and illness, I will argue, is a feature of the wider landscape of social pharmacy and pharmacy practice research, focused as it is on the micro-determinants and organizational features of health services, rather than looking up-stream towards those factors that shape health outcomes at the macro level (Bissell and Traulsen, 2005).

In this chapter, I will describe some of the key arguments that have led to focus on social inequality as a key determinant of health inequality, while also seeking to make clear the relevance of these arguments in the world of social pharmacy and pharmacy practice research.

The Historical Background

As noted earlier, contemporary social epidemiology has shown that unequal societies have worse health and well-being than those that are more equal (Wilkinson and Pickett, 2009). In some ways, this is not a new argument. From Friedrich Engels onwards, many commentators have shown how the external world impacts our bodies. It is not difficult to appreciate (at least historically) how the cumulative impact of lack—for example lower levels of income, education, lack of employment, a lack of high-quality housing, environmental pollution, etc.—impact both physical and mental well-being. For example, back in the 19th century in Europe, the massive social changes that accompanied industrialization and urbanization, gave rise to a set of living conditions that condemned

some sections of the population to short and dangerous lives, while at the same time enriching a small number of the population. The impact of these changes on health in England is vividly described here:

> "the rates of smallpox, typhus, typhoid fever, diphtheria and scarlet fever all increased: two cholera epidemics swept through the warrens of the Great Towns, a third was on its way . . . industrial capitalism gave rise to novel physical arrangements for working and dwelling (the factory, the company, the town) that created new patterns of economic exploitation (mass displacements from land, urban migration in unprecedented numbers, wage labour) . . . hazardous and fatiguing work, damp cold, and stifling living quarters, cheap gin and adulterated foods, demoralisation – the legacy of disease bequeathed by early capitalism stems from such an environment." (Susser et al., 1985)

It is easy to understand how the working conditions characterizing capitalism in the 18th and 19th century shaped broader health outcomes, given the massive transformations that were taking place at this time. However, bringing this up-to-date, researchers now argue that it is the pyscho-social experience of living in an unequal society (rather than simply the material impacts of poverty, poor housing, hazardous working conditions as described earlier) that fundamentally shapes health experiences and outcomes.

This chapter describes the evidence and 'causal mechanisms' with respect to this literature, focusing in particular on Wilkinson and Pickett's ground-breaking work "*The Spirit Level*" (published in 2009) and their second book "*The Inner Level*" (published in 2018). This is a compelling set of arguments and has relevance to all researchers working in the field of health and illness––and to pharmacy practice researchers. Michael Marmot put it starkly:

> "Health inequalities result from social inequalities. Action on health inequalities requires action across all the social determinants of health" (The Marmot Review, 2010 Executive summary).

Before setting out the evidence, it is worth making the point that much of the work in social epidemiology is focused on socio-economic aspects or classed aspects of inequality. It is of course recognized that inequalities arise from other axes of difference (gender, age, ethnicity, region, etc), and the intersections between these are hugely important to understanding health outcomes. However, for reasons of space and in order to make clear their core arguments, this study focuses on socio-economic aspects of inequality.

Core Debates and Arguments Within the Social Determinants of Health

The starting point for much writing on health inequalities goes back to seminal research from the 1980s. The Black Report, published in 1980 in the United Kingdom, noted that the causes of health inequalities should not be attributed (as was common within political parlance at the time) to failings in the National Health Service. With the benefits of hindsight, this is a good example of focusing on the proximal cause rather than the distal causes of health inequalities. Having a comprehensive health service, free at the point of use, politicians (and epidemiologists) initially found it hard to understand why health inequalities in terms of outcomes arose since treatment was available to all. The Black Report, although initially ignored by the incoming Conservative administration, focused its attention on many of the 'upstream' social factors that 'get under the skin' and shape outcomes–such as poor housing, diet, income, and education.

In other words, the argument was that if one wants to understand health outcomes, one not only need to understand failing in health service provision, but also to understand how a range of socio-economic factors that disadvantage individuals and populations, shaped these outcomes. As many readers will know, the Black Report adopted four broad types of explanation for health inequalities. These were (in shorthand) a materialist explanation, a cultural/behavioral explanation, an explanation framed around social selection/drift, and the artifact explanation. It is important to bear in mind that the types of explanations framing health inequalities were very much a feature of their time, but they still provide a solid framework that facilitates understanding. The "artifact" explanation, that the inequalities were a product of the data collection strategies, has largely been rejected. The social selection argument, for which there is some support, argued that people who experience poorer health in early life end up being poorly equipped in terms of skills for the jobs market, which then results in ill health. The evidence suggests that some conditions, such as schizophrenia, do result in downward social mobility but the numbers of individuals experiencing this is small and insufficient to account for the patterns we saw earlier.

By contrast, materialist and cultural/behavioral explanations were more avidly taken up and have provided the starting point for frameworks that identify the underpinning factors, and hence, what might be the best approaches to tackle health inequalities. But before teasing out the nature of these explanations, some general comments on the history of the epidemiology of inequalities in health are given.

Contemporary debates about the root causes of inequality have often involved making moral judgments about those who have the poorest health outcomes. For example, it was commonplace to hear that those who lived in 'squalor' in the 19th century were responsible for their poor health outcomes and political commentators repeat a similar pattern today. The health of the poorest is still often referred to as an outcome which reflects suboptimal and deficient decision making and today the term 'lifestyle decisions' is often pointed to when seeking to make sense of the health outcomes of the poorest in the UK population. Something of the same argument can be seen in discussions about the social determinants of health inequalities. Jenny Popay and others have referred to this as the 'lifestyle drift' argument, common within many health policies, where the behavioral choices impacting chronic diseases are held to be the core reason for poor health outcomes, denying the salience of material living conditions, or the wider social determinants. Popay et al. (2010) note:

"'lifestyle drift'—the tendency for policy to start off recognizing the need for action on upstream social determinants of health inequalities only to drift downstream to focus largely on individual lifestyle factors."

To move onto some of the key issues here, debates about the role of environmental factors versus the role of individual, behavioral and biological factors has most extensively been studied in countries that have passed through the "epidemiological transition," and some understanding of the epidemiological transition is important for pharmacy practice researchers who may not be familiar with this.

The epidemiological transition refers to the point in the development of a country when the epidemic diseases of poverty, such as water-borne and infectious diseases, cease to be the major causes of mortality and are replaced by the cancers, cardiovascular, and other degenerative conditions familiar in the developed world (Wilkinson, 1996), which require both a functioning health system and some level of self-management of life-style to effectively manage them. An easy way of understanding this is that once national income (usually described through per capita income) rises, there is a very clear and rapid increase in life expectancy. However, at a particular point or threshold (and this is typically seen above around $25,000 per capita), any further increase in national income per capita do not typically feed into higher levels of life expectancy. Prior to this point, increase in income per head, produces increase in life expectancy. For example, as per capita income increases, basic public health infrastructure (better nutrition, better sanitation, and education) all feed into increased life expectancy. Mortality patterns at this point prior to the epidemiological tradition, see high rates amongst the most vulnerable––infants, under-fives, and the elderly––these groups being most sensitive to basic public health measures and infrastructural developments. But once beyond a certain point (the epidemiological transition), the picture changes.

The key point to understand here is that social inequality in health is the level of inequality in a given society. Health in the richer, more affluent societies loses its linear relationship with national income per capita, but within a given country the familiar gradient from rich to poor is maintained, and the health and a range of social problems show a relationship with the extent of inequality and not with average income. What is entirely clear, is that if we look at a country like the United Kingdom, what is seen is wide and increasing levels of inequality, which have clear health consequences.

There is substantial evidence about both the size (and the increasing size) of the gap in incomes and health consequences of such inequality. In the recent years there have been debates about the strength of the relationship between social and health inequality.

Inequality, Health and Social Problems

One of the most impressive aspects of the work of Wilkinson and Pickett, in *The Spirit Level* is their construction of an Index of Health and Social Problems, which extends their perspective beyond inequality and its association with health, using a wide range of studies and national and international datasets. This index uses data on levels of trust, mental health, life expectancy, infant mortality, morbidity, obesity, educational performance, teenage births, homicide, and imprisonment rates and social mobility to argue that what appears to be the underpinning variable for *all of them* is income inequality. In other words, inequality is the *fundamental causative factor* not simply one of many variables (Wilkinson and Pickett, 2009).

It is this argument that represents a shift, and one reflected in the Marmot report that has implications for public health policy and research. *The Spirit Level* was widely criticized for its methodological underpinnings, including data selection methods, statistical techniques, but perhaps most importantly, its central argument––that inequality is bad for all of us and that addressing problems one-by-one and leaving the income gradient untouched, would have little impact on health and social problems. However, their work is extended in their most recent book *The Inner Level* (2018), and backed up by an independent review of the evidence (Rowlingson, 2011) that concluded that the evidence for these claims and the underlying explanatory framework was strong. Indeed, although authors may have been critical of their central claims, it is also the case that there have been attempts to support and extend their arguments (Bissell et al., 2016).

Moving on, what accounts for the impact of inequality on health. this study sets out Wilkinson and Pickett's explanations below, alongside those that have taken a different approach. The study starts with the neo-material explanation that is often counter-posed to that adopted by Wilkinson and Pickett (2009). An understanding of this is important to understand how their explanation deviates from this.

Neo-Material Explanations

Neo-material arguments for health inequalities, follow the Black Report's emphasis on the absence or presence of material resources and have an obvious salience. They are perhaps best understood through some straightforward explanations. Neo-materialist explanations for inequalities in health emphasize the *"combination of negative exposures and lack of resources held by individuals, along with systematic under-investment across a wide range of human, cultural and political-economic processes"* (Lynch, 2000, p. 1001). This is a fairly straightforward explanation to understand. What is being said here is that the cumulative, life-course exposures to negative circumstances (for example, repeated experiences of unemployment, under-employment, poor housing, exposure to pollution) along with a lack of resources (a regular income and other economic resources) to manage these negative exposures, are clearly and obviously detrimental to health in the long term. What is often added into this argument, is the consequence of a lack of investment

in a welfare state that might ameliorate the worst effects of these negative circumstances, particularly for the poorest populations. The neo-materialist explanation focuses on the practical, tangible economic resources and circumstances faced by individuals, and it is these, authors argue, that accounts for the majority of the inequalities in health.

In many ways, this is a straightforward argument since it emphasizes on some obvious strategies that people deploy in order to manage their health. For example, if there are delays in obtaining health care (long waiting times for a particular treatment), then it is an obvious point that those with resources can obtain faster treatments by skipping waiting lists and taking services of the private sector. Similarly, they may find it easier to purchase those goods and services that offer health benefits (gym membership, physiotherapy services, counseling, etc.) Of course at the same time, this argument also assumes that all population groups are equally oriented to health and the prevention of ill-health but we know that this may not be the case (Bissell et al., 2016).

On the other hand, however, it is difficult to see how ownership of some of the goods that the neo-materialists argue have an impact on health and well-being could do so by exclusively or primarily material pathways. For example, possession of more than one car is unlikely to have a direct positive effect on health particularly for those who personally own more than one car (Dorling, 2010). Indeed, it could be argued that the effect could be a negative one resulting in reduced incentives to walk or take exercise. In contrast, it could be argued that any health gain is more easily explained by the prestige or status attached to owning two cars (Marmot, 2004). This issue of status is at the heart of the psychosocial argument of the study discussed in the next section.

Psychosocial Explanations

Psychosocial explanations––associated with Marmot, Wilkinson and Pickett (2009), have always recognized that access to goods and services, for adequate health and safety at work and comprehensive health care are key social determinants. However, their argument picks up from a point largely over-looked by neo-materialists. The evidence demonstrates that when behavioral risk factors and these material determinants are controlled for studies, they typically only explain less than half of the gradient in mortality. In other words, there remains an excess of mortality not explained by material factors alone. In order to situate and explain this finding, the psychosocial explanation focuses on three areas: the damaging effects of stress in early life, lack of friends or social engagement, and the focus here, shaming or invidious social comparisons that aggravate the consequences of greater social inequality. This, it is argued, has a key impact on health across the life course and is not taken into account by those espousing neo-materialistic explanations.

Arguments around social status and the deleterious impacts of shaming social comparisons loom large in their account. Wilkinson and Pickett (2009, 2018) argue that what is central to the experience of living in an unequal society is a process of social status differentiation involving shaming evaluations of the self in relation to socially salient others, up and down the income ladder. This is crucial to grasp, and is a very different argument to that advanced by neo-materialists. What Wilkinson and Pickett (2009) are arguing is that humans are constantly weighing up, both consciously and unconsciously, their place in the social hierarchy and this involves making finely tuned assessments of one's status in relation to others. In order to feel shame or shame related discomfort, we need to be in a position to care about or value the opinions or views of another. Wilkinson draws extensively on the work of sociologist Thomas Scheff who viewed shame as *"**The** social emotion"* (p.79 emphasis in the original). According to Scheff, who was supported by a few other sociologists, humans are intensely evaluative beings and on a day-to-day level this means we are constantly monitoring threats of exclusion from the bonds and connections with others which are central to our lives. To understand this, Wilkinson and Pickett (2009) describe this in the following way:

> "Greater inequality seems to heighten people's social evaluation anxieties by increasing the importance of social status. Instead of accepting each other as equals on the basis of our common humanity as we might in more equal settings, getting the measure of each other becomes more important as status differences widen . . . If inequalities are bigger, so that some people seem to count for almost everything and others for practically nothing, where each one of us is placed becomes more important." (Wilkinson and Pickett 2009 p. 43–44).

Their argument, therefore, is that contemporary unequal societies present more opportunities for people to feel shame, both chronic and acute and there are limited resources, particularly for the poorest, to protect themselves from these shaming social comparisons (unlike those further up the social hierarchy). These comparisons are often a source of considerable anxiety especially amongst those with the least resources in society, and one of the impacts as individuals ruminate on and seek to manage these, is an increase in 'othering' (Peacock et al., 2014). Indeed, in the latter paper, I have sought (with others) to extend their ideas about shame in the context of inequality that emanate from Wilkinson and Pickett (2009) work. In particular, we have sought to incorporate what Andrew Sayer refers to as low level shame, or, drawing on the work of the sociologist Pierre Bourdieu, shame that might be part of the *habitus*. For example, we might think of the impacts of shaming social comparisons in terms of acute, high level actions, which result in burning shame. However, as Sayer argues, it is more likely that shaming social comparisons are woven into the fabric of daily lives and are experienced in rather more prosaic ways. For example, we argue in the above paper:

> "The most harmful shame in the context of depression is chronic rather than acute. This may be similar to what Sayer (2005: 153) has described as 'low level shame', characteristic of unequal societies and far more difficult to access than acute shame, forming not just a backdrop to life but a sense of being woven into everyday experiences, and experienced as part of the habitus. For the least advantaged this can mean repeated exposure to numerous minor and major incidences of disrespect, mis-recognition or symbolic violence, starting in childhood and running throughout the life-course" (Peacock et al., 2014, p. 392)

To be clear, Wilkinson and Pickett (2009) are arguing here for a very different sort of explanation than that of the neo-materialists; their point is that a society which focuses on hierarchy holds those at the top as the most successful, most valuable and worthy, which can have very deleterious health impacts for others. As Wilkinson and Pickett (2009) argue, living in these types of societies produces social stressors that enter the body through particular pathways and it is these stressors that have an impact on health and well-being. This study briefly outlines these pathways in the final section below.

The Biology of Stress- How Inequality Gets Inside the Body

There is a growing body of evidence, drawn from evolutionary psychology and from other disciplines, which has shown bodily responses, and in particular blunted and raised level of cortisol in the blood (Wilkinson and Pickett, 2009). In short, their argument is that the anxieties about social status (in an increasingly stratified and unequal society) find their way into the body through heightened awareness of others social position. Social comparison and shame, they argue, are fundamental to this process and there is a literature from evolutionary psychology that supports their position. Awareness of these inequalities, it is argued, is a process of ruminating and reflecting on these inequalities that produce blunted and raised cortisol level that further impact on the working of the immune system (Wilkinson and Pickett, 2009).

Conclusion and Relevance to Pharmacy Practice

Health inequalities and their social determinants form the framework in which pharmacists operate and provide services—dispensing medicines, prescribing, giving advice, and treatment. Understanding how the 'outside gets inside' provides important contextual information for pharmacists, even if they feel there is little they can directly do as practitioners to impact these wider determinants. Of course, one area where they can be involved and make an impact, is through advocacy work, alongside other health professionals and policy makers at the local and national level. This is certainly an area where other health professionals have been focusing their activities. This is no different for the profession of pharmacy.

The new evidence described in this study shows that inequality has an "independent" effect on health that cannot be tackled without narrowing the gap between rich and poor. Interventions at the level of providing information or trying to persuade individuals to change practice can impact, but only at the local level and will leave the wider social determinants unaffected. Indeed, there are currently many initiatives seeking to address health inequalities that prefer to focus on "nudging" individuals into making better choices. There is limited evidence these will have a positive impact.

However, by contract, placing inequality at the center of policy and practice opens up the possibility of both advocacy and auditing for public health practitioners, including pharmacists. This chapter has sought to extend knowledge about how these inequalities manifest themselves, and awareness of this can be brought to bear on specific issues advocacy may extend to challenging some of the approaches of government if there is no evidence base to sustain them.

What does this mean for pharmacy practice researchers and why is it important to know more about the social determinants of health inequalities? Too often, pharmacy practice researchers make assumptions about the lifestyles of the poor without an appreciation of the macro factors shaping health outcomes. It is important for pharmacy practice researchers to be aware of these factors (Bissell and Traulsen, 2005). Pharmacists can act as advocates for change at the level of the social determinants. This chapter encourages this transformation and wider awareness of the social determinants of health inequalities.

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Managing Cultural Diversity in Pharmacy Practice in the United States

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Nomenclature

Culturalkinetics—movement along the Cultural Competency Continuum as new patients or cultures are encountered

> *"America's health care system is neither healthy, caring, or a system"*
>
> Walther Cronkite

Challenges patients face in accessing the health-care system generally that originate in early experiences of life. These obstacles include difficulties with literacy level, numeracy comprehension, cultural estrangement, and problem-solving skills. It is a paradox being a patient, moving from everyday life into the mysterious realm of the sick role is an enormous change. As a person enters into the "patient world," numerous aspects of his or her existence change (Bleidt et al., 2018), some examples are as follows:

- You have to engage, and you may not understand who you are;
- You hear many strange and ominous sounding words, and phraseology may be difficult to understand;
- You enter the health-care culture; there are idiosyncratic ways of doing things and strange rules;
- You have to adapt to a distinct time perspective; tasks run on specific time with significant waits to then rush to do something or you are asked to wake up in order to take your medicines;
- You are enclosed in a small place with little room for an extended or larger family to visit;
- You have to don strange garb that makes you feel more vulnerable and makes you look unappealing and immodest;
- You are not sure what the expectations of you are, creating an uncomfortable situation.

Being a patient is complicated. You come into a realm that is very different from your daily routine. You have to remain in this strange realm during the length of treatment, which, in the case of a severe chronic condition, may be for the rest of your life. This new existence usually runs parallel with day-to-day life; thereby, making it more involved. This intricacy can be considerably exacerbated in a patient with numeracy or low health literacy (Bleidt et al., 2018).

As the population changes in the United States and worldwide, the pharmacy profession must adapt to these transformations of a motley society in order to serve our patients better. To manage diversity successfully in our practice settings, we must become more

[1] Dr. Bleidt does not believe in race as a subdivision of humankind. When asked, he identifies himself as a member of the human race. The concept of race was an artificial construct developed by British sociologists used to justify slavery and treating others with less dignity than deserved. This chapter reflects these views.

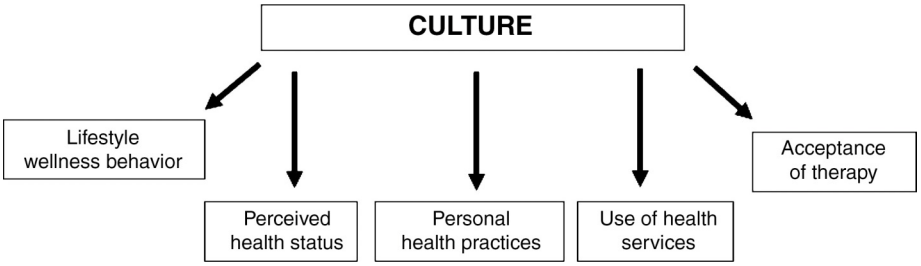

Figure 1 Influence of culture on a patient's health beliefs and health. *Source: Adapted from Bleidt, B., 1992. Understanding multicultural pharmaceutical education. In: B. Bleidt (Ed.), Multicultural Pharmaceutical Education. Pharmaceutical Products Press, New York, NY, pp. 141–150.*

familiar with the concepts of health (what is it), of culture (what does it entail), time (as a construct of culture), and of other social determinants of health. Health was defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" by the World Health Organization (WHO, 1948, p. 1).

The culturally competent delivery of patient-centered care involves the recognition and understanding of cultural differences between pharmacists, as caregivers, (including pharmacy staff) and their patients. This process involves acquiring and utilizing specific tools and skills to gain mastery over these dissimilarities. A patient's cultural influences have an impact on his or her health-care choices and the ultimate outcome.

Introduction

In order to illustrate a key point, I often ask people "what is the most popular condiment in the United States?" Without fail, I receive the same answer—ketchup. This answer would be correct, if it were earlier than 1993. The sales and use of ketchup were surpassed by salsa in 1992. Thus, signaling a tremendous change in the taste buds of Americans and demonstrating the impact of cultural influences on society. Much has changed in the years since in society, in health care, and in food. Now, tortillas outsell burger and hotdog buns and tortilla chips are more popular than potato chips (Hirsch, 2013).

The 2001 Institute of Medicine (IOM) report, Crossing the Quality Chasm, described several components that need to be present to ensure high-quality care for all (IOM, 2001). Among these factors were that health care should be patient-centered, timely, and equitable. Fig. 1 illustrates the influence of culture on a patient's health beliefs and health. Health disparities among different groups are attributed to poorer overall health and decreased health outcomes.

In this chapter, culture will be defined, its role and influence as a social determinant of health will be explored, and the concepts of cultural awareness and cultural competency, which are the foundation of a patient-centered approach in pharmacy practice, will be examined. Managing cultural diversity in all practice settings, through a culturally competent awareness and approach, will lead to better outcomes and wellness. The chapter will also present the necessity for culturally competent services delivery, along with an exploration of what is involved in a practitioner's cultural integration journey.

What is Culture?

Culture is defined as "the totality of socially transmitted behavioral patterns, arts, beliefs, values, customs, life-ways, and all other products of human work and thought characteristics of a population of people that guide their worldview and decision-making" (Purnell and Paulanka, 2012, p. 2). In pharmacy, culture plays an essential role in patient–pharmacist communication. The health literacy and numeracy level of your patients are also strongly influenced by culture (Bleidt et al., 2018). "Even though culture is only one part of health literacy, it is a very important piece of the complicated topic of health literacy" (Office of Disease Prevention and Health Promotion, 2007).

In an individual patient, their culture is probably a significant determinant (AHRQ, 2015; Bleidt and Coleman, 2018) in:

- How they perceive illness overall
- How they interpret their current condition (serious or not)
- What the family's role will be in their care plan
- What their expectations are from the health-care system
- Why they may be distrustful of systems
- How medical or pharmaceutical decisions are made
- What their beliefs about medicines are
- How adherent they will be to their prescribed treatment(s)
- What the role of alternative therapy will be
- How traditional healing practices will impact care

Table 1 Health-care scenarios affected by culture

Cultural domain[a]	*Potential domain components*	*Pertinent health-care scenario*
Overview, inhabited localities, and topography	Heritage, residency, migration patterns, educational status, occupation	A group of people of a similar culture could live in areas where residents may not have easy access to fresh food or local grocers ("food deserts").
Communication	Language, dialects, cultural interaction patterns, temporal relationships, format for names	Colloquialisms may not be familiar to the health-care provider causing the provider to have difficulty perceiving common social cues from their patients.
Family roles and organization	Decision makers, matriarchal versus patriarchal priorities, alternative lifestyles	Family hierarchy of gender roles may dictate who receives patient counseling information or who the caregiver is for a patient.
Workforce issues	Conflicts in the workplace, professional autonomy	Immigration status may affect the patient's eligibility to receive employee health benefits.
Biocultural ecology	Client's physical, biological, and physiological variations	Specific ethnic groups may have an increased risk to be afflicted by a certain disease state, such a hypertension or cancer.
High-risk behaviors	Use of alcohol, tobacco, and other recreational drugs	It may be permissible to engage in promiscuous heterosexual encounters, but unacceptable to have a monogamous homosexual partner in certain cultures.
Pregnancy and childbearing practices	Sanctioned vs. unsanctioned fertility practices and practices related to pregnancy, birthing, and postpartum care, nursing/breastfeeding	Certain cultures may have no concept of the need for prenatal or postnatal care.
Death rituals	Death, euthanasia, burial practices, bereavement	Some cultures may require touching of remains although highly communicable disease could be present (e.g., Ebola). Others need to dispose of the body before sunset or within a certain timeframe (Winslow, 1920).
Health-care practitioners	Status, use and perceptions of traditional, magico-religious practitioners, and biomedical health-care professionals	Some cultures may consult advisors or healers prior to or instead of seeking treatment from health-care practitioners.
Health-care practices	Health-seeking behaviors, folklore practices, beliefs regarding blood transfusions, organ donation	A patient could employ alternative healing practices such as cupping or coining instead of or in addition to Western medicine modalities.
Spirituality	Religious practices, use of prayer, meaning of life, individual sources of strength, health-care practices related to these beliefs	A patient could require the presence of a spiritual advisor as a member of their health-care team or see their illness as part of God's plan.

[a]Cultural Domain headings expanded from: Purnell and Paulanka (2012).

Source: Bleidt, B., Coleman, C., 2018. Culturalkinetics: Cultural perspectives in public health. In: Introduction to Public Health: A Primer for Pharmacists, second ed. Jones and Bartlett Publishers, Sudbury, MA.

As ethnic diversity continues to expand, it becomes more important to understand that cultural considerations must be recognized as an integral factor in patient care to a greater extent than in past years. Cultural values and norms can be a determining factor in self-management of a disease, health-seeking behaviors, and cross-cultural communication with health-care practitioners. Health-care providers who fail to recognize that culture is the background for many of the decisions made relating to health will most likely encounter mistrust from the patient in addition to possible professional frustration from the lack of impactful patient outcomes due to patient nonadherence (Purnell and Paulanka, 2012). In **Table 1**, *Health-care scenarios affected by culture* contain material from the 12 domains of culture discussed by Purnell and Paulanka with an adapted situational aspect related to patient care in the Pertinent Health Care Scenario column from Bleidt and Coleman (2018).

Culturally Competent Care in Pharmacy Practice

Providing culturally competent care is a major contributor to reducing the more expansive concern of health disparities (U.S. Department of Health and Human Services, 2010). Disparities in health outcomes exist; they affect groups of patients who may experience more or larger obstacles to access or participate in the health-care system. These discrepancies in care, many of which will be discussed in more detail later, may be based on, among others (Surgeon General, 2014):

- Ethnicity
- Gender
- Gender identity
- Age
- Rurality
- Socioeconomic class

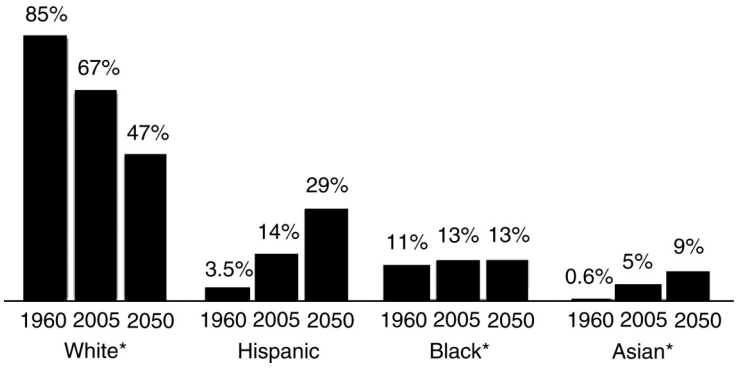

Figure 2 Population by ethnicity 1960, 2005, 2050. Note: All races modified and not Hispanic (*); American Indian/Alaska native not shown. *Source: From Passel, J.S., Cohn, D.V., 2008, February 11. U. S. population projections: 2005–2050. Washington, DC. Retrieved from http://pewhispanic.org/files/reports/85.pdf.*

- Religious beliefs
- Disability

There are other nuances to comprehending culture and its influences. The first is that each person is a member of numerous cultures. The dominant culture manifested may depend upon the circumstances. There may also be contradictory messages sent due to competing dominant cultures.

Second, some aspects of culture are more visibly obvious in an individual (such as ethnicity, gender, or religion), while other aspects may not be as readily apparent at all (such as religion, sexual orientation, or gender identity). Third is that there can be tremendous diversity within a defined culture. For example, Latino or Hispanic cultures are incredibly diverse, representing customs, beliefs, and values from different hemispheres and many countries. Fourth, some cultures to which a patient may identify may not be immediately recognizable as a distinct culture by a novice during his or her cultural-integration journey (Bleidt and Coleman, 2018). Examples of these cultures may include:

- Lifestyle (vegan, cross fit, couch potato); and
- Health professional (versus lay person);
- Generational (to which generation does a patient belong);
- Disability (psychological, mobility, emotional);
- Primary spoken language (e.g., English, French, Creole, Arabic, Spanish);
- Gender (transsexual, questioning).

Delivering culturally competent care that is respectful to a heterogeneous patient population is a very complex proposition. The complexity of this situation will multiply as both the United States and world populations become more diverse. Historically, the failure of the U.S. health-care system to recognize the influence of culture has had a negative impact on the health and well-being of the populace and has challenged how we value the individuality and autonomy of a patient.

The cultural composition of the U.S. population is evolving continuously and rapidly expanding. By 2050, the population is expected to increase to nearly 440 million people, showing an approximately 48% growth since 2005. Projections indicate that those who are now considered minorities will be a collective majority in 2050. Fig. 2 provides a graphical representation and ethnic breakdown of the U.S. population for the years 1960, 2005, and 2050 (Passel and Cohn, 2008, February 11).

The rapid growth and substantial changes projected over a 90-year timeframe provide a clear road map of how and why culture has become such a huge influence on health. Also of interest is that 20% of the 2050 population will include new immigrants to the United States.

The Need for Cultural Competence in Pharmacy Practice

To serve an increasingly diverse population better, it has been suggested that there is a need to increase the ethnic and gender diversity among health-care practitioners (National Academies, 2016). Much of this need is born from the fact that minority clinicians are notably more inclined to practice in minority and medically underserved areas than their nonminority colleagues (Smedley et al., 2004). Across the United States and other countries, there are many medically underserved communities and populations. Most reported health inequities and disparities can be found in these Medically Underserved Populations (MUPs) located within Medically Underserved Areas (MUAs) and also in places designated as "Health Professional Shortage Areas" (HPSAs) (Health Resources and Services Administration, 2016, July 1).

Medically Underserved Populations are comprised of clusters of people who face cultural, linguistic, literacy, and other obstacles to accessing health care. A *Medically Underserved Area* is defined as a region "designated by Health Resources Services Administration as having too few primary care providers, high infant mortality, high poverty or a high elderly population" (U.S. Department of Health and Human Services, 2018). MUAs can span an entire county, several adjoining counties, or multiple urban census tracts. HPSAs are

SNPhA is an educational service association of pharmacy students who are concerned about the profession of pharmacy, healthcare issues, and the poor minority representation in these areas.

The purpose of SNPhA is to plan, organize, coordinate, and execute programs geared toward the improvement of the health, educational, and social environment of minority communities.

Figure 3 SNPhA Mission Statement. *Source: Student National Pharmaceutical Association, 2018.*

locales that have shortages of primary medical, mental health, or dental providers. There areas cut across rural and urban settings, different types of populations, or a variety of medical facilities. The defining factor is that patients within a HPSA have difficulty accessing needed medical, dental, and mental health services due to a shortage of primary care clinicians (Health Resources and Services Administration, 2016, July 1).

Facilities having a greater diversity among health professionals have been shown to have an increase in patient satisfaction, more choices for the patient of clinicians, improved patient–pharmacist communication, and greater access to care for minorities (LaVeist and Pierre, 2014; Smedley et al., 2004; Williams et al., 2016). Pharmacy is privileged to feature a student professional society, Student National Pharmaceutical Association, whose mission is "to improve the health of the medically underserved and increase the number of minority pharmacists" (SNPhA, 2016). The SNPhA was formed by students in 1972 as an independent organization (SNPhA, 1972) to promote these interests among student pharmacists. SNPhA's Mission Statement is presented in Fig. 3; it explains the many clinical initiatives and activities undertaken and targeted at improving the health outcomes of medically underserved people.

SNPhA operates six (6) core patient outreach initiatives; among them are chronic kidney disease, HIV, AIDS, and diabetes. As part of its diligence, SNPhA measures and records the number of clinical events and patient interventions. In 2016, there were more than 108,000 patient encounters, primarily performed in MUAs showing that the student pharmacists in SNPhA have a significant impact on the health and wellness of the population they serve (SNPhA, 2018).

Cultural Competence

The delivery of effective and efficient pharmacy, patient-centered care necessitates a keen awareness of the similarities, nuances, and differences of the different cultures to which a patient identifies. Fig. 4 presents the stages involved in one's personal journey toward a proficient level of cultural integration (Bleidt, 1992). A practicing pharmacist can be at several different points along this continuum; his or her location depends on which culture(s) she or he is encountering at that point in time. This journey has no set starting gate, because learned techniques, practices, and skills gleaned from one cultural engagement advances the pharmacist along the continuum as new cultures are encountered. A pharmacist evolves toward a proficient mastery of cultural integration with each new and repeat cultural experience.

This continuum can be applicable to both organizations and individuals. The five demarcations along the continuum are meant as benchmarks to self-assess progress. Stage 1, *Cultural Insensitive*, can be considered as not being aware of cultural differences and their impact on health or not wanting to learn about diverse cultures. *Cultural Awareness* begins with a self-examination of one's own cultural background, what makes it unique, how it compares to the encountered culture, and what bearing these findings may have. In the *Cultural Sensitivity* stage, pharmacists build on the growing awareness and begin to develop a deeper cultural knowledge about others, but have not yet assimilated this knowledge into practice successfully. In the penultimate stage, *Cultural Competency*, the pharmacist becomes more proficient at identifying cultural influences and acquires a competent level of knowledge-based skills so that he or she is able to communicate more appropriately with patients of other cultures. The pharmacist is aware of valued norms and rules and the pharmacist–patient relationship is valued from the patient's perspective. In the last stage, *cultural integration*, the learned cultural knowledge and skills are easily placed into practice to serve the patient more efficiently and bring about better outcomes (Bleidt and Coleman, 2018).

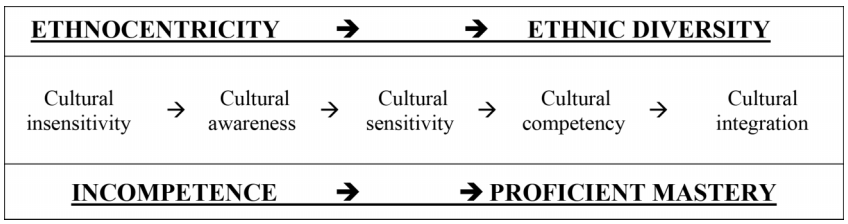

Figure 4 Journey toward cultural integration based upon the Cultural Competency Continuum. *Source: Adapted from Bleidt, B., 1992. Understanding multicultural pharmaceutical education. In: B. Bleidt (Ed.), Multicultural Pharmaceutical Education. Pharmaceutical Products Press, New York, NY, pp. 141–150; Bleidt, B., Coleman, C., 2018. Culturalkinetics: Cultural perspectives in public health. In: Introduction to Public Health: A Primer for Pharmacists, second ed. Jones and Bartlett Publishers, Sudbury, MA.*

A proficient, culturally integrated pharmacist has possession of sufficient skills, knowledge, abilities, and attitudes to deliver optimum patient-centered pharmacy care to a broad array of ethnic and cultural backgrounds. Organizations, facilities, or practitioners may be able to progress through the stages more rapidly due to greater support and resources; this progression makes patients feel more comfortable.

Culturalkinetics

The process of Culturalkinetics is "defined as the movement along the Cultural Competency Continuum as new patients or cultures are encountered" (Bleidt and Coleman, 2018). It involves understanding that other cultures may not share the same views or values as you do. This process starts with using established cultural baseline norms, being vigilant of the very small distinction between these norms and stereotyping. These models are used with each new encounter until sufficient data can be obtained from a cultural assessment of the patient. Then, the more relevant, individualized information is used in partnering with the patient on his or her care. With each patient encounter, more data can be gathered until a more complete understanding of who he or she is can be achieved.

The Culturalkinetics process, when applied correctly, results in better patient bonding. It is a continuous process of self-awareness and self-improvement. As more specific knowledge is gained about a culture or a patient, this information about cultural nuances and how they affect attitudes and health behaviors can be utilized. Through this process, one becomes more sensitive, understanding, and empathetic about cultural variances. Finally, cultural integration is reached when a practitioner is truly skillful in adapting and responding to those differences within appropriate contexts and circumstances.

The Golden Rule, "do unto others as you would have them do unto you," is derived from the Holy Bible; "as ye would that men should do to you, do ye also to them likewise" (Luke 6:31). It is a very common maxim relating to patient care, among other things. A much more patient-centered approach to care can be established using the Culturalkinetics process; this involves using the Platinum Rule, which states "do to others as they would have you do unto them" (Popper, 1966). This approach is more culturally competent, more sensitive to others, and more empathetic. This philosophy adjusts for the fact that different people want to be treated differently in similar circumstances. By accommodating the feelings of others, you are stating that you want to understand what they want, before initiating care.

Culturalkinetics utilizes a set of developed aptitudes needed to culturally assess a patient. According to Bleidt (1992), these skills include:

- identifying and empathizing with ethno-specific problems (such as bigotry, acculturation);
- respecting the person as an individual and his or her rights to be treated as a unique human being (autonomy);
- respecting those who appear to be different as equals (acceptance);
- being able to communicate at the patient's literacy level without appearing to be condescending;
- being an active, empathetic listener, and being courteous;
- appreciating, without prejudgment, contrasting value systems and beliefs that a patient may hold;
- being able to relate to the medically underserved;
- discovering something unique in a patient's background and using this connection to establish a rapport with them;
- using cross-cultural approaches to solve individual problems; and
- valuing cultural differences.

From the above list of essential skills, the behaviors and values most relevant to culturally competent organizational policies and processes can be embodied within standards and guidelines of the institution. Standards developed in this manner would, by definition, include an expanded definition of culture beyond race or ethnicity and a broader perspective on health, settings, and services provision. This philosophy is reflected in the 2016 National Center for Cultural Competence recommendations. To achieve cultural competence, an institution must:

- have a defined set of values and principles and demonstrate behaviors, attitudes, policies, and structures that enable them to work effectively cross-culturally;
- have the capacity to (1) value diversity, (2) conduct self-assessment, (3) manage dynamics of difference, (4) acquire and institutionalize cultural knowledge, and (5) adapt to diversity and the cultural contexts of the communities they serve; and
- incorporate the above in all aspects of policymaking, administration, practice, and service delivery and involve systematically consumers, key stakeholders, and communities (NCCC, 2016, para. 3).

Culturally and Linguistically Appropriate Services Standards

Public health is differentiated from health-care delivery in that it is concerned with issues that impact the health outcomes of populations in contrast to the health of an individual. A population can be defined as a small number of people within a community or as widespread as the people moving among different countries. Today, the burden, both financial and personal, of preventable, chronic diseases and the existence of world-wide communicable diseases substantially affect and challenge the public health and health-care systems. Winslow (1920), described Public Health as the "science and art of preventing disease, prolonging life and

promoting health through organized efforts and informed choices of society, organizations, public and private, communities and individuals" (Winslow, 1920, p. 30).

When public health issues arise that could affect health negatively, it is paramount to both identify and prioritize these concerns using a realistic framework that leads to positive action and solution. Dr. Silvia J. Rabionet, Associate Professor of Public Health at Nova Southeastern University College of Pharmacy, identified eight conditions that must be met for an issue to be defined as a public health problem (Bleidt and Coleman, 2018). These criteria are:

1. Does it affect the health and well-being of the population?
2. Is it widespread and increasing in scope and magnitude within a population or in a subgroup of a population?
3. Does it affect health-related and other societal resources (e.g., economic and social impacts)?
4. Does it challenge cultural norms and/or raise questions about core values?
5. Does its solution rest in collective measures and interventions based in disease prevention, health promotion, and education?
6. Does it require interprofessional collaboration?
7. Does it call for organized government intervention? and
8. Does it merit urgent action?

In the 1990s, the issues of health disparities and culturally ignorant care brought about many discussions and calls for action to find solutions to these now-better-defined public health problems. Activities undertaken to resolve the deficiency in culturally competent care in the past have included interprofessional teamwork, accrediting body guidelines, and governmental action, both regulatory and legislative. As a result of these factors, culturally competent care delivery has the criteria to be classified as a public health problem.

In response to the calls for action, the Office of Minority Health (OMH) released the National Standards for Culturally and Linguistically Appropriate Services in Health Care (CLAS Standards) in 1999. Since then, they have been the foundation for health-care organizations' endeavors to reduce health disparities, improve quality of care, and improve health equity (Office of Minority Health, 1999, 2001).

The relationship between the social determinants of health (SDH) and health was emphasized in the Introduction Section to the 1999 CLAS standards. The SDH include "those conditions in which individuals are born, grow, live, work, and age" (WHO, 2016), such as level of education, socioeconomic status, and the accessibility of health services.

Although the original 14 guidelines have been modified several times, the primary aim of these standards is unwavering: to facilitate health-care delivery for minority populations. These standards are targeted toward health-care organizations and the types of services that these organizations should provide in a culturally competent environment. Some of the particular services include:

- staff education in cultural and linguistic service delivery;
- language assistance provision including interpreters;
- strategic plan promotion, highlighting goals and policies in providing services to diverse populations; and
- collaborative partnerships development within the community.

OMH updated the CLAS Standards in 2012 to elucidate their meaning and expand their scope. In this revision, the former Standard 1 was designated as the Principal Standard, to "[p]rovide effective, equitable, understandable, respectful, and quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs" (OMH, 2013, p. 31). If the other 14 standards were successfully adopted and sustained, then the Principal Standard would be achieved. The remaining standards were divided into three categories. **Table 2** lists the standards for each of these categories.

The Joint Commission developed a document to reveal more clearly how their standards and performance elements match with the CLAS Standards. This crosswalk of CLAS Standards to Joint Commission Standards was developed for hospital accreditation and ambulatory care, among others. The latest version was released in 2014 (Joint Commission, 2014).

The principal goal of Western medicine is to provide optimal care for ALL patients. To realize this objective, health-care practitioners need to acknowledge and understand the existence of cultural variations and beliefs among their patients. The ethos of patient-centered care in pharmacy practice (pharmaceutical care or pharmacy care) is very compatible with delivering personalized care. This process considers how a patient's culture impacts her or his illness, as well as how the patient will accept the therapy. It is also cognizant of the relationship between the pharmacist and patient and how you communicate with them.

As the last century was ending, several agencies of the Federal Government began work on an ambitious project aspiring to decade-long targets designed to improve the health of the nation. Similar projects were being initiated in the European Union and other places. The U.S. Department of Health and Human Services (DHHS), in September 1990, released the first version of its strategy for improving the overall health of American citizens by the turn of the millennium (US DHHS, 1991). *Healthy People 2000*, National Health Promotion and Disease Prevention Objectives, set over 300 objectives that were proposed to be met in 10 years. Subsequently, *Healthy People 2010* and *Healthy People 2020* have been developed, approved, and implemented (US DHHS, 2000, 2010). A key target of *Healthy People 2000* was to decrease health disparities in America. *Healthy People 2010* took a step further and set a goal of eliminating health disparities. The current version, *Healthy People 2020*, went even further and set a goal to achieve health equity. These reports associate a patient's health with the broader social determinants of health espoused by the World Health Organization (WHO, 2016) and the United States (Secretary's Advisory Committee, 2010, July 6).

Table 2 National standards for Culturally and Linguistically Appropriate Services (CLAS) in health and health care

Principal Standard: Provide effective, equitable, understandable, respectful, and quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs.	
Theme 1: Governance, Leadership, and Workforce	1. Advance and sustain governance and leadership that promotes CLAS and health equity
	2. Recruit, promote, and support a diverse governance, leadership, and workforce
	3. Educate and train governance, leadership, and workforce in CLAS
Theme 2: Communication and Language Assistance	4. Offer communication and language assistance
	5. Inform individuals of the availability of language assistance
	6. Ensure the competence of individuals providing language assistance
	7. Provide easy-to-understand materials and signage
Theme 3: Engagement, Continuous Improvement, and Accountability	8. Infuse CLAS goals, policies, and management accountability throughout the organization's planning and operations
	9. Conduct organizational assessments
	10. Collect and maintain demographic data
	11. Conduct assessments of community health assets and needs
	12. Partner with the community
	13. Create conflict and grievance resolution processes
	14. Communicate the organization's progress in implementing and sustaining CLAS

Source: Office of Minority Health, 2013. National standards for culturally and linguistically appropriate services in health and health care: A blueprint for advancing and sustaining CLAS policy and practice. Washington, DC: Retrieved from https://www.thinkculturalhealth.hhs.gov/pdfs/EnhancedCLASStandardsBlueprint.pdf, 30 March 2018, pp. 30–32.

Culture and Time

One major characteristic of unique cultures that seems to baffle one's understanding of it is the concept of time. Time has a unique significance within each culture. Having an appreciation of how a patient views time can be very beneficial to the pharmacist–patient relationship. In general, time can be viewed as mono-chronic (linear) or poly-chronic (multiway, nonlinear). A past, present, and future exist in the linear concept of time (Lewis, 2014).

Patients from Northern Europe and the US tend to be linear in how they experience time. In general, they view it as a priceless, continuous, limited commodity (Lewis, 2014); it can be lost (wasted), banked (saved), transferred (given), or used (spent). Linearly, time can also be described as spare (free) or overtime (bonus). In countries inhabited by linear-active people, time is money; it is both clock- and calendar-related (Helman, 2005). Behaviors are inclined to be based on the premise that the past is done and the present can be used to plan, so that time can be worked more efficiently in the immediate future.

Patients from Southern Europe and the Middle East tend to view time as nonlinear (Lewis, 2014). In general, patients from these regions may be more multiactive and manage their time differently from linear time followers. In these cultures, the best way to invest time is generally considered to be engaging and completing in a human transaction. They consider time to be less important than the closeness of the relationship and their interaction between parties; sometimes, these transactions are so important that the actual time of the meeting or appointment is irrelevant (Lewis, 2014). To people part of these cultures, time is considered as an event or as a commodity that can be shaped, allotted, or manipulated (Helman, 2005). To linear time followers, nonlinear time followers seem to pay very little attention to promptness or schedules.

In many Eastern cultures, time is generally seen as cyclic and is considered cosmological (Lewis, 2014). In cyclical time cultures, there is a limitless supply of time; therefore, it is not considered as a scarce commodity. As the sun rises and sets every day, seasons follow from one to the next, people age and die, but their children live on; these cultures view this as a form of timelessness (Lewis, 2014). A health-care professional from a mono-chronic culture may take a cyclic culture patient's action, or lack thereof, as either not understanding the severity of the medical situation or as being apathetic when dealing with his or her ailments. Neither assumption would be correct. A patient from a cyclic culture may be slow to follow-up on an appointment and only seek assistance when something is awry. After all, life begins at some points, ends at another, and the passage is slowly paced. Managing cultural diversity with cyclic-minded patients requires that a pharmacist comprehends that past and present decisions, must harmonize with the patient's future, and that medication may only be needed when the body "calls for it" (Helman, 2005).

There are other cultural concepts of time and with limited space allotted to this chapter, they will not be further discussed. For further information on this topic, one useful reference is *Cross-Cultural Concept of Time: Chronemics* from Communcaid, which can be found at the following URL: https://www.communicaid.com/cross-cultural-training/blog/chronemics-concept-of-time/. However, another example of a time perception cultural difference that really stands out involves the Malagasy culture, people from Madagascar. They envision their future as passing them from behind. The future becomes the past as it unfolds in front of them. That, which is visible, what is in front of them, is considered the past. Both the past and the present are observable and understood; "the future is totally unknown and therefore it is 'behind' or as some put it: 'none of us have eyes in the back of our head'" (Dahl, 1995). It is time that moves from behind and moves past you, you do not move through time.

Implications for Pharmacists and Pharmacy Practice

Pharmacists play many roles in delivering patient-centered pharmacy care. It is our responsibility to recognize that culture is not simply defined by ethnicity. It is a labyrinth that can only be navigated when factors such as customs, wellness values, health beliefs, language, gender identity, sexual orientation, among others are fully grasped (Bleidt, 1992).

An individual pharmacist's journey along the Cultural Competency Continuum can be made easier or more difficult by the organization or facility in which he or she practices. The following recommendations are presented to show what can be done to foster a more culturally-competent environment within practice sites. These suggestions are an excellent place to begin the ongoing voyage toward the proficient mastery of cultural integration (adapted from Brown and Nichols-English (1999)):

- Respect and value the differences and similarities in people and cultures;
- Establish an environment that is supportive to practicing multicultural, patient-centered, pharmacy care;
- Work to ensure that adequate resources are allocated to build a foundation for these purposes, such as staff and clinician training on an ongoing basis (including attendance at courses and workshops) and patient education materials;
- Help build an atmosphere where pharmacists and other practitioners are able to adapt their practice in response to changing patient demographics and differences in the population they are serving;
- Accept techniques, tactics, and approaches for dissimilar cultures; and
- Build better patient-care teams by reinforcing collaborative relationships with other health-care providers.

By identifying, acknowledging, and comprehending the factors that can lead to health disparities, pharmacists are able to make changes in their practice and service delivery in a more culturally competent manner to all their patients. By using the culturalkinetic process, the pharmacy environment can be made more welcoming for different groups and by incorporating health promotion and disease prevention initiatives, pharmacists will be able to enhance the overall health of local communities. Through minimizing or eliminating communication barriers, the quality of care improves (Vanderpool & Ad Hoc Committee on Ethnic Diversity and Cultural Competence, 2005).

Several national pharmacy organizations have adopted policies in support of culturally competent, patient-centered, pharmacy care. Acknowledged by the House of Delegates and Board of Directors of two of the most influential professional societies, these policies, which directly relate to cultural competence, for the American Pharmacists Association (APhA) are located in Appendix I and for the American Society of Health-System Pharmacists (ASHP) in Appendix II.

Wrap-Up

As presented throughout this chapter, there is a need for practicing pharmacists to understand that diversity and culture are not simply defined by a patient's ethnicity. Culture is a complex labyrinth that can only be solved when aspects such as customs, language, literacy level, values, health beliefs, religion, among others, irrespective of ethnicity, are understood. To be an excellent manager of diversity in pharmacy practice, one must first move forward sufficiently on the Cultural Competent Continuum and apply what has been learned to each patient encounter. Throughout this chapter, the process of Culturalkinetics and how to journey toward cultural integration were detailed to provide a template of a roadmap along this quest.

In the absence of culturally competent care, the dearth of understanding of the values, priorities, time, and fears of patients more than likely will lead to miscommunication between clinician and patient. Medical misadventures, poor diagnosis, and inadequate responses to medications and other treatments follow. Possessing the abilities, techniques, and skills to be able to interpret and comprehend patient-specific nuances are indispensable for those seeking pharmacy services.

Being culturally competent at the highest levels encompasses the abilities, attitudes, collective knowledge, and aptitudes of pharmacists to provide optimum services to a wide variety of ethnically and culturally diverse patients. This journey begins with developing the proficiencies to assemble and organize relevant cultural information. The first step is to ascertain if the patient needs a cultural assessment. Then, if the answer is yes, collect cultural information along with the other data that is needed to serve a patient well.

At the proficient mastery level of *cultural competency*, cultural integration, pharmacists consider individual differences in each patient worthy of recognition. These skills are becoming more valuable in an increasingly diverse society and more important as pharmacists encounter more patients who are immigrants or visitors from other countries. Pharmacists who use these abilities to help their patients also welcome people from other cultures not covered in this chapter, such as, to name a few:

- Disabled persons
- Lesbian, gay bisexual, transgender, intersex, and questioning (LGBTIQ) persons
- Speakers of English as a second language
- People from various religions
- People from different generations
- People from diverse geographical location (e.g., rural versus suburban or urban)
- People of all socioeconomic status

Many of the above-mentioned groups have been marginalized by the health-care system for too many decades.

One of the best philosophies for managing diversity in pharmacy practice is to follow the Platinum Rule, a more culturally competent variation of the Golden Rule (Popper, 1966). "Treat others the way they want to be treated." The Platinum Rule distinguishes among personal and cultural preferences and engages the patient as an autonomous being with the right to be treated as he or she feels is appropriate.

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- https://www.pharmacist.com/policy-manual
- http://www.who.int/social_determinants/sdh_definition/en/
- http://www.dimensionsofculture.com

Appendix I American Pharmacist Association Cultural Competence Policies

APhA Policy: Cultural Competence (2005)

1. Recognizing the diverse patient population served by our profession and the impact of cultural diversity on patient safety and medication use outcomes, APhA encourages pharmacists to continually strive to achieve and develop cultural awareness, sensitivity, and cultural competence.
2. APhA shall facilitate access to resources that assist pharmacists and student pharmacists in achieving and maintaining cultural competence relevant to their practice.

(JAPhA NS45(5):554 September/October 2005) (reviewed 2006) (reviewed 2011) (reviewed 2016)

Cultural Health Beliefs and Medication Use (2006)

1. APhA supports culturally sensitive outreach efforts to increase mutual understanding of the risks and other issues of using prescription medications without a prescription order or using unapproved products.
2. APhA supports expanding culturally competent health care services in all communities.

(JAPhA NS46(5):561 September/October 2006) (Reviewed 2009) (Reviewed 2014)

Source: https://www.pharmacist.com/policy-manual

Appendix II ASHP Cultural Competence Policies

1613 Cultural Competency

Source: Council on Education and Workforce Development

- To foster the ongoing development of cultural competency within the pharmacy workforce; further,
- To educate healthcare providers on the importance of providing culturally congruent care to achieve quality care and patient engagement.

This policy supersedes ASHP policy 1414.

Rationale

The United States is rapidly becoming a more diverse nation. Culture influences a patient's belief and behavior toward health and illness. Cultural competence can significantly affect clinical outcomes. Research has shown that overlooking cultural beliefs may lead to negative health consequences (Administration on Aging, 2018). According to the National Center for Cultural Competency, there are numerous examples of benefits derived from the impact of cultural competence on quality and effectiveness of care in relation to health outcomes and well-being (Goode et al., 2006). Further, pharmacists can contribute to providing "culturally congruent care," which can be described as "a process of effective interaction between the provider and client levels" of healthcare that encourages provider cultural competence while recognizing that "[p]atients and families bring their own values, perceptions, and expectations to healthcare encounters which also influence the creation or destruction of cultural congruence (Schim and Doorenbos, 2010)." The Report of the ASHP Ad Hoc Committee on Ethnic Diversity and Cultural Competence (ASHP, 2005) and the ASHP Statement on Racial and Ethnic Disparities in Health Care (ASHP, 2008) support ways to raise awareness of the importance of cultural competence in the provision of patient care so that optimal therapeutic outcomes are achieved in diverse populations.

Marketing of Pharmacy Services

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> Marketing pharmaceutical care [and other professional services] is not the responsibility of the few innovative pharmacists who try it first. Rather, it is the responsibility of everyone in the profession.
>
> Charles D. Hepler

Introduction

When one hears the word marketing different thoughts come up, such as the advertising of alcohol and tobacco, or those telemarketing calls that you find irritating, and how it can disrupt life, or how it leads to overconsumption. While we need to recognize that marketing can be and has been used in less than ideal ways, it has also been used to better society. For example, marketing is used in public education campaigns, such as the importance of getting the necessary vaccinations, to ways that tobacco harms the user and others around, or the dangers of consuming too much alcohol; this method is what is referred to as social marketing.

When people talk of marketing they have many misconceptions, such as it is just the promotion part; as an analogy, this is similar to the misconception many have that pharmacists simply count pills. According to Kotler (n.d.) marketing is defined as " . . . the science and art of exploring, creating, and delivering value to satisfy the needs of a target market." In layperson's terms, marketing is the process of determining the needs and/or wants of potential users/buyers and then providing products (goods and/or services) that meet or exceed expectations. Marketing occurs only when there is an exchange among two or more parties in which something of value is exchanged; for example, when a patient comes to your pharmacy to have a prescription filled, you provide the good (medications) and service (professional counselling) in exchange for payment (this can be out-of-pocket, government insurance, third-party insurance, etc.).

There are two ways to view marketing exchanges in your pharmacy: isolated, individual transactions where there is no expectation for future exchanges, commonly referred to as transactional marketing; or a series of transactions over time where a relationship is formed and is nurtured, and this is commonly referred to as relationship marketing. In most out-patient and community pharmacies relationship, marketing should be the goal as you want to form long-term relationships with your patients and therefore earn their loyalty; it is much more efficient and cheaper to retain customers than it is to continually try and attract new ones. Transactional marketing may be used in an in-patient setting where the patient has an acute illness and is less likely to interact, if at all, with the hospital pharmacist. For a more in-depth discussion on relationship marketing and its uses in pharmacy, see Doucette and McDonough (2002).

There are parallel characteristics between relationship marketing and pharmaceutical care:

Relationship Marketing		*Pharmaceutical Care*
Develop a relationship with customer	→	Establish therapeutic relationship
Collect and manage customer information	→	Assess and record patient needs
Individualize your services to customers	→	Create an individualized care plan
Involve front-line personnel	→	Delegate clerical tasks to free up time for professional duties
Emphasize long-term outcomes	→	Monitor impact on patient outcomes

Ultimately a patient seeks health care because of a known illness (acute or chronic), accident, or injury. Where they seek care depends on ones' previous experiences, family and friends, employers, etc. This is where pharmacists can play a greater role in having patients' and others they have formal or informal relationships with aware of what pharmacists can do to help treat or prevent a need for health care. In this chapter, you will learn about the basics of marketing and how it can be used to enhance practice.

NOTE: patient, consumer, client, and customer may be used in this chapter—ultimately, they all refer to the individual(s) that are the focus of a pharmacists' professional roles.

As highlighted by Holdford (2015), there are some issues in marketing community pharmacist services, including:

- Control of practice by non-pharmacists;
- Product (tangible good) orientation;
- Conflicting professional and business roles; and
- Poorly defined image of pharmacists among the general public.

Marketing to most is synonymous with promotion, but promotion is one of the "4 Ps"; that is, marketing consists of the marketing mix, or "4 Ps", of product, price, place, and promotion. Ultimately marketing is about getting the right goods and/or services, to the right people, at the right place, time, and price, using the right promotional methods.

With the ever-changing scope of pharmacy practice it is becoming increasingly necessary for pharmacists to promote professional services they can offer. Just because you have advanced education in cardiology and provide the most comprehensive patient care does not mean that people will seek out your services; you need to design your services with the patient in mind and then communicate the benefits of your service offering. "If you build it they will come" for the most part does not work in health care, especially when patients do not always know what is best for them, particularly in the more preventative, public health role many pharmacists assume that does not seek to treat a condition but prevent it. Added to this is that many outside of the profession ascribe to the old model of pharmacy, its distribution function, and tangible products.

It must be acknowledged that most patients do not want the products (goods and/or services) they receive; this is called negative demand, and many times a patient does not want to take the metformin or atorvastatin prescribed, those are negative products. Yes, they can improve one's health and reduce the likelihood of disease progression, but one does not typically want to take medication; however with good counseling they will see why they need to take the medication.

Pharmacists that can demonstrate their value are much more likely to succeed in practice. Marketing is a tool that pharmacists can use to demonstrate value by understanding their target market. A market is a group of people that share a need or want that can be satisfied through exchange relationships formed when using the tools of marketing. Target marketing focuses on the target market, which is the set of actual (current) and potential patients/customers for your product(s).

It is essential to avoid marketing myopia that occurs when an organization, like a community pharmacy, focuses on what they want to provide patients/customers instead of figuring out what the market (patients/customer) needs or wants (Levitt, 2004). When you focus on what you want to provide myopia (shortsightedness) may occur and as a result the target market is not having its needs and wants met.

Another factor to consider when examining your product offering and how you serve your target market is the concept of value and satisfaction. As many patients/customers cannot completely evaluate the service provided by a pharmacist they may look for other aspects that they can evaluate, such as the tone of voice of the pharmacist, the physical infrastructure of the pharmacy, the clothing worn by the pharmacy team, etc. If a patient/customer visits a pharmacy and expects the pharmacist to be friendly and the service delivered is above the expectation, then the patient/customer is highly satisfied; however, if because of previous interactions with the pharmacist the patient/customer expects a high level of service and it does not meet expectation, then satisfaction will be low.

Therefore, pharmacy as a profession should work to educate the general public on what pharmacists do and can do. There is still the common misconception of the "count, pour, lick, stick" image of pharmacists that primarily centers on the distribution functions of pharmacists and the role pharmacists played in the past. In most jurisdictions, however, where community pharmacies are businesses, most of the promotional efforts to enhance the image of pharmacists' center on the image of the pharmacist practicing for a specific employer, and not what pharmacists as a whole do and can do; for example, "your Company pharmacist can prescribe for . . . " instead of stating that "pharmacists can prescribe for . . . " As a result, it is up to individual pharmacists and professional advocacy organizations to educate the public on the role of pharmacists.

Marketing Research

Before undertaking a change in one's practice or wanting to promote a product offering, one must conduct marketing research so that what is offered to the market is what the market needs or wants; otherwise, one risks suffering from marketing myopia and not meeting the needs of the market. Marketing research involves the analysis of markets, current and/or potential, to determine what is currently offered, any opportunities and challenges, and to obtain the requisite information to make strategic decisions for marketing programs.

In collecting data there are two main forms to consider: primary data and secondary data. When conducting primary data research information is collected directly from the original source to solve a problem. Primary data are collected when there is no current, or sufficient, data to inform your decision making. Whereas secondary data are information that has already been collected for a purpose other than what you want information for, but it can be used to inform your decision. The benefit of primary data is

that you can ask very specific questions that require answers in order to make decisions; as a result, primary data are more expensive than secondary data. The benefit of secondary data is that the data has already been collected and therefore is cheaper than primary data; however, the downside is that because the data were collected for another purpose it may not adequately answer the questions you have. There is a good likelihood that you may have to obtain both primary and secondary data. Of note is that the patient database you have in your pharmacy is a rich source of data; it can allow you to see what medications are dispensed most often, how often patients have prescriptions filled (adherence), what conditions patients have, etc. and you can better target a specific segment of patients.

In obtaining secondary data you will want to understand how the data were collected; was it collected as part of a government census, were focus groups used, for what reason(s) was the data originally collected, etc.? Once you make the decision that primary data will need to be collected as there is no or insufficient existing secondary data, there are three broad methods of primary marketing research: survey; observation; and experiment.

Survey data collection involves gathering data, usually via a questionnaire, directly from respondents to obtain facts, opinions, and attitudes. If your organization does not have employees that are able to perform a survey you will likely want to hire a marketing research company to develop the survey questions and collect the data. Data may be collected via a telephone survey, through a mail self-administered survey, when interacting with patients at the pharmacy, or even a consumer intercept where consumers in the pharmacy are asked to fill out a questionnaire. There are other considerations to take into account when collecting data via survey, such as will there be an incentive to participate.

Observation primary data collection occurs by observing participants' actions without directly interacting with them. This can be done in person or could also be done by watching collected video. Observation can be useful when wanting to see the route customers take, once they have entered the store, to arrive at the pharmacy counter; this data can help in how you merchandise the route most often taken so that you can "encourage" other purchases. You may also want to understand whether a patient that drops off a new prescription stays in the store, and if so, what do they do, such as sit in the patient waiting area or wandering the store.

The final method of primary data collection is an experiment where you change one or more variables while observing the impact of the change on another variable. For example, you may want to see how workflow changes when you have pharmacists counsel patients when they drop off a new prescription, as opposed to when they pick up their medication; when conducting the experiment you may ask for feedback from patients and pharmacists on how they were affected by the changes and if the changes were generally positive or negative. Once that data is collected you can analyze it to inform your strategy.

In general, market research should: define the issue/problem; analyze the situation and choose a method of research; get problem-specific data, analyze and interpret data; and solve the problem/make recommendations. When conducting your marketing research, you should also include an environmental scan of the practice environment. The five factors in environmental scanning are: political and legal factors (e.g. regulations); technological factors (e.g. technical infrastructure in place); socio-cultural factors (e.g. demographics, culture, values, etc.); competitive factors (e.g. nearest competitors, speed, etc.); and economic factors (e.g. boom or recession, GDP, unemployment, third-party insurance, etc.).

One needs to consider the market that will be targeted with marketing efforts. A market is the set of actual and potential consumers of a product; these people share a need or want. For example, you may target patients who have been recently diagnosed with Type II diabetes for a program provided by a Certified Diabetes Educator pharmacist from your pharmacy; while those outside of your target market may find benefit, such as patients who have had Type II diabetes for a while, when targeting your marketing efforts you want to best communicate with your target market – those you recruit from outside your target market are a bonus! Some variables to consider in defining your target market include: the size and potential for growth of the target market; how "easy" is it to reach this target market; if the goal is profitability, is it going to be profitable; the nature of the market, such as highly competitive; and the nature of the organization (if you are a pharmacy that is a part of a discount retailer you are not going to try and charge a premium price as this will not match the nature of your organization).

The Marketing Mix

Marketing is about getting the right goods and/or services (products), to the right people (target market), at the right place, time and price, using the right promotion techniques. This can be achieved by using the marketing mix, or what is commonly referred to as the "4 Ps": product, price, place, and promotion (see **Table 1**). The 4Ps of Marketing were first introduced in 1967 by Philip Kotler in his book *Marketing Management* (Kotler and Keller, 2014). When the product is a service, there are three additional Ps: people, processes, and physical evidence (Kotler et al., 2002).

Another way to view the 4Ps is to remember that products provide consumer solutions, price represents consumer costs (financial and non-financial), place provides convenience, and promotion enables two-way communication.

Product

Many use the marketing term "product" in reference to a tangible item, however, products can be tangible and/or intangible items. If one remembers that in marketing a product can be anything satisfying a need or want, tangible and/or intangible, the application of marketing in pharmacy is better aligned.

Table 1 The Marketing Mix

Term	*Definition*
The 4Ps	
Products (service and/or good)	Provide customer/patient solutions to a need or want. For example, in a community pharmacy the products offered are a combination of goods, tangible items such as prescription medications, and services, intangible items such as tobacco cessation counselling. As well, a product can also mean an experience someone has, such as going to an amusement park, a community pharmacy, or a Cirque du Soleil show; however, for the purposes of this chapter a product will refer to a good and/or service.
Price	Represents consumer/patient costs, such as the financial cost to obtain a product (both for the patient and potentially other payers, such as insurance companies), but one needs to consider non-financial costs of obtaining a product, such as time and convenience.
Place	Provides convenience for the target market. For example, providing services at the community pharmacy may be convenient for pharmacists providing the service; however, it may be more advantageous to provide the service at a community center, or in the patient's home. Another example of place, primarily in regard to community pharmacies in the US, is drive thru pharmacies. While many within the profession view this as negative since drive thru windows are associated with fast food restaurants, it may be more convenient for the parent of an infant to pick up a prescription for amoxicillin to treat a bacterial ear ache at a drive thru window than taking the unwell infant into the pharmacy to pick up the prescription.
Promotion	Enables two-way communication where the provider/organization seeks to communicate, to the market, why the market should choose their organization over others. For example, the convenience of providing flu shots without an appointment versus at a public health clinic. As well, one must be aware of the regulations surrounding promotional efforts as there are restrictions for professionals, including pharmacists, in what is okay to include and what cannot be done, such as direct comparison between two competitors.
Additional 3Ps of services	
People	Are those such as the patient and the service provider, but also includes the customers waiting in line at the pharmacy, the other members of the pharmacy team, etc. For example, if you are counselling a patient on sildenafil, the likelihood of that patient retaining the information increases if it is just the pharmacist and the patient in a private counselling room, and not at the normal pick up counter where other pharmacy staff and customers are in close proximity.
Processes	Involve the policies and procedures that go into providing services to patients. For example, your pharmacy may find it cuts down on errors and costs by having a patient counselled when they drop off their prescription than when they pick it up. As well, many community pharmacies have protocols that the employer wants pharmacy team members to follow so that there is consistency among what a patient will expect among team members but also at other locations of the same pharmacy chain. While we cannot discuss them in this chapter, a good way of understanding the processes of your pharmacy is to create a service blueprint (see Holdford, 2015).
Physical Evidence	Is a key factor in marketing services since the intangible nature of services means that the patient cannot see, touch, or feel the service like they can when the product is a tangible item. As a result, patients will use the physical evidence to evaluate the service, pre- and post-consumption, such as the clothing worn by the pharmacist, how the pharmacy is organized, how easy is it to find parking, etc.

Consumer products can be divided into four types: convenience; shopping; specialty; and unsought. Convenience products are items that an individual buys frequently, immediately, and with little to no comparison and buying effort. These products tend to be priced low, mass advertising is used to be top of mind to consumers, and there are many purchase locations (i.e. there are little to no restrictions on where they can be sold). Examples of convenience products that are available through community pharmacy and other retailers are throat lozenges, regular strength pain relievers, adhesive bandages, etc.; many times these items are placed in locations where a consumer makes an impulse buy, such as beside the cash register or on the bunk-end of an aisle.

The next consumer product type, shopping products, are ones for which the consumer makes the effort to search out alternatives; they tend to be higher in price, bought infrequently, and there are limited locations in which a consumer can buy the product. Within a community pharmacy there are a limited number of shopping products, but an example would be blood glucose meters; some examples of shopping products not directly related to pharmacy are furniture, appliances, vehicles, etc. Specialty products are items that have unique characteristics that require the consumer to go to select few places to obtain the item and are likely to have one place to purchase the item within a given geographic area; these items tend to be higher in price and consumers are willing to expend considerable effort to obtain the specialty products. While there are few examples in pharmacy, specialty products that one can identify would be high priced, imported sports cars, a specific kind/brand of watch, etc.

The final type of consumer products are unsought products. For unsought products the consumer may not know about the product or has heard of it but does not normally think of buying it. Unsought products tend to require significant advertising and personal selling as they are new innovations or are products consumers do not want to think about. Within a community pharmacy examples of unsought products are pregnancy tests and emergency contraception; outside of pharmacy examples include life insurance and cemetery plots.

Products, in particular tangible products, tend to be part of a larger product offering by an organization. An item is simply a specific version of a product, such as cough suppressant for dry coughs. A product line is a group of closely related products such as all

formulations of cough suppressant. Product mix involves all product lines an organization sells, such as cough suppressant, oral pain relievers, first-aid products, etc.; organizations tend to have a portfolio of product mixes that are closely aligned.

The next product consideration is branding; this topic can be quite complex and to completely understand and appreciate branding one subsection of a chapter is not sufficient, but a general overview is provided. A brand is a name, term/slogan, sign, symbol, design or a combination that identifies the seller/maker of a product. Branding is about creating, maintaining, protecting and enhancing goods and services. Branding is defined as "the process involved in creating a unique name and image for a product in the consumers' mind, mainly through advertising campaigns with a consistent theme. Branding aims to establish a significant and differentiated presence in the market that attracts and retains loyal customers" (Business Dictionary, 2018).

There are some brands that are so strong that when one sees an image or even font style that most people would know what brand it is; for example, the big "M" is for McDonalds, the silhouette of a shaped bottle is recognized as Coca-Cola, or the image of an apple with a bite out of it is the Apple logo. Community pharmacies, especially chain pharmacies, have distinct brands and use branding to maintain and enhance the brand. Some aspects that represent a brand are the colors used for signage, the uniform that members of the pharmacy team wear, the labels on prescription vials, and others. Branding is even a consideration when developing the protocol pharmacy team members follow when a patient drops off a prescription. When an organization has multiple pharmacies the way a patient is greeted, the questions asked of them, the layout of the front store, etc. are used at all locations as it provides a recognizable way that an interaction will follow in any location. Ultimately the pharmacy wants to maintain brand loyalty, which represents commitment to a specific brand.

Two other aspects of branding to consider are brand awareness and brand recall. Brand awareness is the ability that someone can identify a particular product/brand by viewing the product/logo, packaging, or advertising campaign; for example, if shown the logo for a chain pharmacy and you are able to name the brand it implies brand awareness. Brand recall is the ability of someone, when prompted, to correctly name a brand from memory; for example, asking individuals what brand comes to mind when you say name the first community pharmacy you think of.

The ideal brand is one that is used in reference to all products in that category, a generalized brand/trademark. For example, many people will ask "where can I find a Band-Aid"; however, Band-Aid is a brand of adhesive bandages. Another familiar generalized brand is Q-tips, which is a brand of cotton swabs, not the name of all cotton swabs.

Products go through the four stages of a product lifecycle: introduction; growth; maturity; and decline. This is not to say that all products will experience a decline, but it does make one recognize that a product line or product mix should be maintained to have a diverse portfolio of products that will be in various stages. A brief, general overview of the product lifecycle is discussed below.

The initial stage is the introduction stage; during this time profits are below zero because of the costs involved in bringing the product to market and sales are just beginning. If it is a completely new product the adoption of the product is likely to be slow because you need to promote to your target market about the features of your product and its benefits. In health care consider the introduction stage that occurs for a new to the market branded pharmaceutical—efforts are immense to get the message out to the target market and encourage product trial (many times this may be done through samples of the medication given to physicians).

Next is the growth stage where sales rise quickly as do profits (sales and profits are used here, but it could be product adoption that is the goal of a non-profit organization). In this stage, if first to market or the leader in the category, one needs to constantly be monitoring how competitors are reacting to increase the chances that your product will survive long term; as well, in this stage sales continue to grow and profits peak and begin to decline as competitors enter the market.

In the maturity stage, sales reach peak and then begin to decline as more competitors enter the market; as well, profits decrease during this stage. As a result, if a product is doing well in the market an organization, to maintain market share, will have to invest in promotional efforts which also contribute to decreasing profits. The final stage is the decline stage when sales and profits fall rapidly. At this point one has to consider making improvements to products to stay in the market, especially if there are advancements made by competitors. Another reason for a product to fall out of favor is if it was part of a trend that is no longer relevant.

Two other product considerations are product differentiation and product positioning. Product differentiation occurs when a product is created and designed so that consumers perceive it as different from competitors. For example, product differentiation in some drug categories occurs when the drug is approved for a new indication when others in the category are not, or when a company combines two medications to create a combination drug that reduces the number of tablets a patient needs to remember to take. In product positioning, the organization works to create and maintain a certain persona in the consumers' mind; for example, when evaluating the pain reliever products on the market one may consider what the product is used for (body aches or headaches) and the price of the product (expensive versus inexpensive). Where an organization positions its products will depend on many factors, including the overall brand the organization maintains (e.g. low price, high value, prestige, etc.) and how it is relative to competitors in factors such as how fast it works, how long consumers can expect it to last, etc.

Price

Pricing is a crucial factor in marketing and is also one of the most challenging aspects to control. Each product will require a unique pricing strategy. Some examples of pricing strategy would be wanting to achieve a target profit or ROI (return on investment), building traffic in your pharmacy, achieving a specific market share, creating or maintaining an image, etc. While it is easy to recognize the financial price of a product, one must not forget about the other components of price, including time, energy, and

opportunity costs; it is important not to lose sight of price when offering a product in a non-profit environment as, just because there may be no financial costs to the patient, there are other costs to consider.

Some ways to determine a price are to create a cost-based pricing strategy where price to the consumer is set based on a desired profit margin. There is also demand-based pricing that comes into play when one, through market research, determines the price that the market is willing to pay for your product. Competition-based pricing occurs when prices are set above or below what the competition is charging. Another consideration is a break-even analysis, the point where net income is zero and any profit will come when sales are above the break-even point. When introducing a new product to the market a skimming strategy may be used where prices are set high to maximize profits while there is less competition; on the other end would be penetration pricing strategy where prices are set low to attract consumers and at the same time discourage potential competitors from entering the market.

Place

Place, or distribution, covers the activities that make a product available to consumers when they want to purchase them. In having a narrow view of place, many community pharmacists may only consider place to refer to the pharmacy itself; however, one should consider place in relation to what is best or ideal for the market. In some ways it may be more convenient for you to offer a medication assessment service in the counselling room of your pharmacy, but is that the most convenient place for your patients? For example, your target market is seniors not living in a nursing/care home who could benefit from a medication assessment. Given potential mobility issues, why not go to the patients by renting out a room at a retirement community center where you come to your patients?

In assessing market coverage, the three strategies are intensive, selective, or exclusive. In intensive market coverage the organization puts products in as many places as possible; this provides maximum exposure. The second strategy is selective in which only a select few locations would offer the product; for example, you may only have 4 of 10 community pharmacies in a city dispense vaccinations as intensive coverage would not be the best use of the organization's resources. The final strategy is exclusive market coverage where only one pharmacy in a geographical region offers the product; for example, only one of your pharmacies is given the license to conduct genetic screening to optimize medication use by patients.

Promotion

In its simplest form, promotion is communication that facilitates exchanges among two or more parties by influencing the audience to accept a product. As a reminder, while many examples in this chapter focus on the for-profit community pharmacy environment, all aspects of the marketing mix, including promotion, can be used within a non-profit environment.

The goal of promotion is to stimulate demand for your product(s). For example, a pharmacist at your pharmacy recently became a Certified Respiratory Educator and would like to offer spirometry testing to patients; since most patients would not know what spirometry is and why it would be good to get tested, there will be little to no demand if you do not promote the service. Whether your pharmacy is for- or non-profit promotion is required to inform many stakeholders, including patients, physicians, carers, etc.

Promotion is used to communicate effectively with the market leading to engagement. As a result your promotional strategy must align with the target market so that you are "speaking their language", otherwise you will simply be spending time and money on a flawed strategy. Objectives of promotion are numerous including creating awareness and stimulating demand for your product(s), retaining loyal customers, combating competitors' promotional efforts, reducing sales fluctuation, etc.

A common misconception is that promotion is really advertising; however, advertising is one of the four strategies that make up the promotion mix, which also includes sales promotion, public relations, and personal selling. Advertising is paid, non-personal communication that uses various types of media to communicate with the target market. Mediums used for advertising, with varying costs to consider, include television, direct mail, radio, online social media platforms, etc. Sales promotions are done when an organization promotes certain products, many times offering the products for a discounted price; for example, in winter months many pharmacies have sales promotions for vitamin D supplements.

Public relations are when an organization attempts to earn public understanding, acceptance, and trust in the organization or specific products offered by the organization. Publicity is any information about the organization or its products distributed through the media that is not directly paid for; when seeking publicity, the subject matter must be interesting, relevant, and newsworthy. For example, an organization may put out a media notice that a new professional service is being offered with the hope that media outlets will pick up the story and spread the message; publicity is also used by regulatory and advocacy organizations to inform the public of changes to regulations, increased scope-of-practice, etc. Some advantages to publicity are that it is free, more believable than advertising, and can reach those who may not see or pay attention to commercials; however, the disadvantages to consider include that the media may not pick up the story, they may alter the message, or it could be negative.

Personal selling is when an organization, or its employees, search for prospective customers, and can include face-to-face presentations, service after the sale, etc. Another promotional tool, that is the best form of promotion, is word-of-mouth advertising as it is the cheapest, most believable and most effective; word-of-mouth occurs when a satisfied customer sees value in the product and informs others in their social circle about the product.

Social media platforms are now a major medium for promotional messages. In using social media there are several ways to advertise to specific geographical areas, people of a select age range, people of specific genders, etc. There are some ethical issues that can arise when promoting a product using social media, such as advertising to people that do not realize the message they see is paid advertising. Furthermore, rules and regulations for promotional methods for pharmacists and pharmacies must be understood and followed. For example, most jurisdictions do not allow direct, head-to-head comparison advertising.

Products as a Service

A service is any activity or benefit that is offered to another that is intangible and does not result in the ownership of anything besides the knowledge gained through the service encounter. Services marketing is the component of marketing that focuses on the intangible components of a product. In considering the purchase of tangible products the majority of the time there is a service component to it. When the service is the main component of the transaction this is referred to as the core service, such as a medication review; whereas when the service is performed in support of the sale of a tangible product, it is referred to as supplementary service, such as the expected patient counselling provided when a medication is dispensed.

The goods–services continuum is the recognition that the vast majority of the time products contain components of both goods and services. On the mostly goods side of the equation there are products such as canned foods, whereas on the mostly services side of the equation there are products such as insurance, consulting, or teaching.

Physical evidence centers on where the service is provided. The environment in which the service is delivered can help distinguish your pharmacy from competitors. Depending on the physical evidence provided it may allow you to charge a premium price for your services, or it may reinforce the discount nature of the organization and therefore services are set to reflect the strategy and environment.

Process is the aspects that are involved in providing the service, the systems used. An organization will have its standard operating procedures that allow services to be provided in a relatively consistent manner. Understanding and defining the processes involved in service delivery will help to reduce confusion and promote a consistent service; essentially this lets everyone on the pharmacy team know who does what and when.

The final, obvious component is the people involved in service provision. The employees that interact with customers are the face of the organization and as a result customers evaluate the service based on how the employee(s) deliver it. The people providing the service are essentially the only component of a service that customers can see and interact with.

There are four characteristics of services: inseparability; intangibility; inconsistent; and non-inventoried. Inseparability is the result of the fact that services cannot be separated from providers; as a result the staff providing the service(s) are essential in the provision and quality of the service to patients. Intangibility occurs in the provision of services as they cannot be seen, tasted, felt, heard, or smelled before the service is provided; as a result, it makes it difficult to sample and evaluate a service, and even more so when the service is provided by a professional, such as a pharmacist. The inconsistent nature of service delivery means that the quality of services depends on who provides them and when, where, and how; therefore, you need to acknowledge that almost every time a service is offered it is going to be different and as a result services are difficult to standardize in terms of quality. The final characteristic of services is non-inventoried, meaning that services, unlike goods, cannot be stored for later sale or use; the fluctuating demand for some services can be a challenge to ensure services are provided when required, while at the same time preventing wasted resources by having a supply that exceeds demand. For example, you may provide influenza vaccinations without an appointment, but there will be greater demand at certain times of the day or even days of the week, and time of year so it is key to try and predict demand as best you can to have the optimal number of pharmacists on shift.

There are difficulties for those outside of a profession to adequately assess a professional service. When we examine qualities of a service there are non-search and search considerations (Nelson, 1970; Darby and Karni, 1973; Zeithaml, 1981). Search qualities are factors that one can identify and assess prior to choice and/or consumption; being able to evaluate the qualities ahead of time may be the result of reviews of the service provider (e.g. pharmacist) from past clients. Whereas non-search qualities are ones that cannot be evaluated prior to purchase/consumption. The non-search qualities are broken into experience qualities and credence qualities. Experience qualities are ones that can only be evaluated during or after a service has been provided. Whereas credence qualities can never be meaningfully evaluated even after use/consumption; these credence qualities relate to most aspects of professional services.

On one end of the spectrum of the ability to evaluate products are those high in search attributes, such as clothing, food, a motor vehicle, etc. In the middle, there are attributes high in experience qualities, such as a haircut, yard care, restaurant meals, etc. On the other end of the spectrum, are products hard to evaluate as they are high in credence attributes, such as pharmacy services, legal services, complex surgery, etc.

One method to help reduce fluctuations when providing professional services would be to develop service scripts. As outlined by Holdford (2015), service scripts describe a service performance in a written list of actions; that is, the steps that should be followed in a given circumstance. In the service script you should establish expected actions and responsibilities, standardize procedures, and base it on the best methods available. Service scripts can be developed for a variety of reasons, such as when there is a dispensing error, a patient complains about the cost of a prescription, a prescribing error, and the like. While service scripts attempt to standardize the actions taken during a particular encounter, as health care professionals pharmacists will still do what is right for the patient and use their professional expertise.

A strategy that may be linked with a service script, but can also be separate, is a service blueprint. Service blueprints are flowcharts/diagrams used to design service operations (Holdford, 2015). In the development of a service blueprint around interactions with patients, the point of view of the patient is taken into account; this can then give pharmacists a well-rounded perspective when designing a new service or changing current operations. Service blueprints concurrently illustrate the process, patient roles, service provider roles, and support service roles (Holdford, 2015). As an example, you could design a service blueprint for your current dispensing practices; in developing the blueprint you would consider the physical environment of the pharmacy, patient actions, contact employee (those directly serving patients) actions, and invisible processes that occur, such as interaction with insurance providers.

The final area to be examined in this chapter when providing a professional service is the service-profit chain that links a service organization's profits (if that is the goal of the organization) with employee and consumer satisfaction (Heskett et al., 1994). "The service-profit chain establishes relationships between profitability, customer loyalty, and employee satisfaction, loyalty, and productivity" (Heskett et al., 1994). The concept explains the connections that exist among the organization, employees, and consumers to manage a service experience.

The relationships among the organization, employees, and customers are connected in three ways: external marketing; internal marketing; and interactive marketing (Heskett et al., 1994). External marketing is the relationship that exists between the organization and its consumers; this relationship is the one that is developed and nurtured through various mechanisms discussed in this chapter including product design and promotional efforts. Internal marketing is the relationship that exists between the organization and its employees; this relationship is key as employees are the organization's direct link with customers. If employees do not feel they are a part of the decision-making process and are simply "told" what to do, not only will the relationship between the organization and its employees suffer but so will the relationship between the employees and customers. The relationship between employees and customers is the interactive marketing component of the service-profit chain; the interaction that occurs between employees and customers is directly linked with the contact between the organization and its employees.

The internal marketing environment is the direct link between the organization and its employees; the employees in this relationship are the internal customers. And just like you want to maintain a good relationship with external customers, so should you between the organization and its internal customers. If employees are treated like internal customers, the organization wants to make sure they are satisfied and are being heard. An organization should monitor the internal customers' satisfaction through methods such as surveys, exit interviews, anonymous feedback, etc. and use that information to continually evaluate ways to increase satisfaction.

Summary

An overview of marketing and its role in pharmacy practice was provided in this chapter. While the broad overview is a base from which to work, you are encouraged to examine the subject more deeply; the list of references provided is a good place to start. Marketing is a tool that can enhance pharmacy practice by better meeting the wants and needs of patients to optimize their health.

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Medication Narratives

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Medication narratives are stories told about medicines in people's everyday lives as they are embedded within broader stories of illness and health (Bissell et al., 2006; Ryan et al., 2007). They can be stories about taking medicines, experimenting with them, trying new medicines, stopping ones that are no longer needed or desired, and of resisting or refusing medicines. They can be stories about how people subjectively feel about their medicines, how they make sense of taking them, and the meanings ascribed to them in stories of living with illness or engaging in health-enhancing or risk-averting behaviors. They may also be stories of the social interactions with others—doctors, nurses, pharmacists, carers, family, and friends—as they engage with medicines in their everyday lives. Medication narratives, as stories about people's subjective experiences with medicines, particularly outside of the doctor's office or the pharmacy, provide a window into the lived experiences of health and illness.

Such stories are often referred to as offering a lay perspective on illness and medicines. In fact, Frank (2013) has argued that the biomedical model marginalizes those living with illness, and telling stories is one way that the voice of the experiencer of illness can be re-claimed. The concept of medication narratives works to center medication users' ways of representing their lives, drawing attention to how they offer something new, while also countering and complementing narratives created by doctors, nurses, pharmacists, midwives, and other health professionals about patients and their bodily experiences. The concept of medication narratives was originally developed by Bissell et al. (2006; see also Ryan et al., 2007) with the goal of catalyzing interest in utilizing narrative data—that is, stories told by people about their subjective experiences—to stimulate new ways of studying individual experiences of medication use in the field of pharmacy practice.

What are Narratives?

Not all speech acts or text, whether collected through research interviews, spoken in a public forum or in a YouTube video, or written in a diary or in an online blog, are necessarily narratives. Narratives attend to change and succession in a sequence, usually in time (Brockmeier, 1994; Bruner, 1990; Ricoeur, 1984). Narratives have a plot, with a beginning, a middle, often a turning point or narrative high, and an end that link together a series of events or experiences, involving the narrator or one or more other actors, often within a specific time frame. According to Riessman (2008, p. 3).

> In everyday oral storytelling, a speaker connects events into a sequence that is consequential for later action and for the meanings that the speaker wants listeners to take away from the story. Events perceived by the speaker as important are selected, organized, connected, and evaluated as meaningful for a particular audience.

French philosopher Paul Ricoeur (1984) described the construction of a story through a series of events in time as *emplotment*, a concept further elaborated on by Mattingly and Garro (2000). Narratives are not only about a series of events emplotted in a story but they are also about the emplotment of the narrative within the broader context of the teller's life history, told to make sense of and order lived experiences. Narrative gives external expression to internal representations of events, experiences, thoughts, and feelings (Squire et al., 2013).

Narratives are also performative, and they are engaged in the production of identities (Bruner, 1987; Riessman, 2008). Through narratives, people craft who they are and how they appear to others in social interaction. They are not told in a vacuum, but often are crafted for a specific audience, allowing the narrator to present a version of her or himself to others. This presentation of the self to

others through narrative may change over time and also may be crafted differently for different audiences (Squire et al., 2013). Lastly, narratives are rarely value neutral. They perform adherence to a set of values and tend to have a moral motive, a moral reason for being told, which often has to do with the values of the teller in her or his broader social and cultural milieu (Bissell et al., 2006; Riessman, 2008; Squire et al., 2013). They can be used to persuade others, to deceive, to mobilize for social and political change, and can be a source of social connection and entertainment (Riessman, 2008).

Narratives of Illness and Health

Scholarly work on narratives of illness and health underpins the conceptual development of medication narratives. Illness is an individual's own subjective experience of being unwell. People can experience an illness, even when doctors are unable to diagnose a definitive disease state as the underlying cause of the illness. Narratives are one way that people living with illness can make sense of being ill and share this experience with others (Frank, 2013). Mike Bury (1982) was one of the first scholars to study illness narratives and he conceptualized them as a form of biographical disruption. This involved disruption in taken for granted assumptions and behaviors, disruption in explanatory systems, and also the mobilization of resources to cope with this disruption caused by illness. Gareth Williams (1984) explored how narratives are involved in processes of narrative reconstruction. Narrative reconstruction involves not only making sense of the disruption caused by illness but also making sense of why the illness happened to them in the first place. He posits that narratives can be engaged in reconstructing individuals' lives amid the ruptures and fragmentation created by illness, making the present experience of illness make sense in terms of the biography of an individual's life.

Lars-Christer Hydén (1997), drawing on the earlier work of Mike Bury (1982) and others, posits five functions of illness narratives. First, illness narratives allow for the transformation of events and experiences of illness that make sense out of illness, giving form and coherence to the new life lived with illness. Second, illness narratives allow for a reconstruction of the ill person's life history, giving new meaning to illness in the context of this life history and allowing for a reconstruction of identity—who I am—through illness. Illness narratives also provide a medium for explaining and understanding illness, including making sense of why the illness happened and why it happened when it did. Further, illness narratives can be told strategically, to produce particular effects in social interaction with others, including by explaining or offering up excuses for particular behavior. We might think of this as the performative function of illness narratives. Lastly, illness narratives can collectivize individual experience, using storytelling to link up the personal and private sphere with the realms of the social and political.

People tell stories by drawing on narrative types that are available within their social and cultural milieu. Several scholars have developed typologies or genres of illness narratives that can allow for the sorting of stories about illness into broad categories. These typologies may be useful to pharmacists and others undertaking their own research on medication narratives by offering ways of conceptualizing a typology of medication narratives, or for comparing the differences and similarities in medication narratives, as they are emplotted within different kinds of illness narratives.

Arthur Frank (2013) described three ideal types of illness narratives based upon the plots or general storylines around which they are organized, primarily on how and if they ultimately resolve themselves. What Frank calls *restitution narratives* are stories of living through illness and being restored to health, with emphasis in these narratives being placed on the remedy, the cure, and life after illness. Survivors' narratives about cancer are a classic form of restitution narrative. In contrast, *chaos narratives* are those stories that are characteristically chaotic, lacking in coherence and narrative order. They are stories that are often told when narrators are still swallowed up by the chaos and uncertainty of illness, incapable of reflecting on and making sense of illness in their lives. They are stories of time without sequence, which often makes them uncomfortable listening for others. *Quest narratives* seek to turn illness into a journey that has a purpose, something to be gained from living through the experience, which can become a *boon* that is offered up to others through narrative. While restitution narratives are often about, as Frank (2013) describes it, the triumph of medicine over illness, quest narratives are moral stories about the triumph of the self through illness. They are told to teach others how to live with illness.

In another work, Frank (2007) develops a further typology of five kinds of illness narratives based on the thematic content, or dramas, around which they are organized. An illness narrative that focuses on (1) the drama of genesis elaborates on what caused the illness to happen when it did. Gareth Williams' (1984) work, already discussed, explores these types of narratives. What Frank describes as (2) the drama of emotion work draws on Arlie Russell Hochschild's (1979) conception of emotion work as the labor that people do to modulate their emotions in the presentation of self to others. In illness narratives, emotion work can be seen in those stories of individuals regulating their emotions when disclosing illness to others, or seeking to appear cheerful in the face of a dire prognosis. We can think of emotion work as akin to what Margaret Wetherell (2012) described as *affective practices*. Stories about (3) the drama of fear and loss also involve a sort of emotional work or affective practice in managing loss (of physical functioning, of a professional identity, of relationships, or of a sense of life as it was before illness) and fear (of worsening illness, of the future, or of death). Telling these kinds of narratives can be especially therapeutic for those who tell them. Stories about (4) the drama of meaning allow people with illness to make meaning about their illness and to find new meaning in life through illness. And lastly, for Frank, stories about (5) the drama of selfinvolve the making up a new kind of self, a changed self, but one made new through the experience of living with illness. It is possible to imagine how medicines could be scripted into each of these narrative types. Understanding this scholarly work on illness narratives can inform research on medication narratives.

Medicines are also scripted into stories about health, that is, stories of preserving health and enhancing health (Bissell et al., 2006). Narratives about medicines for the preservation and enhancement of health may include those stories about taking

(or perhaps, resisting) the use of statins by otherwise healthy people at risk for heart disease. They may include stories about the use of cognitive enhancing drugs, such as Modafinil, by students or professionals to reduce sleepiness, increase cognitive performance, and gain an edge in their studies or their profession. They may be found in narratives about the modification of bodies, such as in stories of women who use hormonal contraceptives to cease monthly menstruation. Such medication narratives will likely proliferate in the future as discourses of healthism, healthy living, and aesthetic and performance enhancement become ever more entrenched in popular culture, and as the pharmacogenetics industry continues to flourish. Arthur Frank (2006) wrote about how health narratives do work as both subjectifiers and connectors. They offer up stories around which people can construct who they are and who they ought to become, but they also connect diverse sites, linking doctor's offices, hospital clinics, health consumers, the investment sector with a financial stake in health products, and personal practices of health preservation and enhancement. Medication narratives about health also offer important sites for critique of the extension of (bio)medicine into health and risk (Clarke et al., 2010) and of the pharmaceuticalization of health. As Adrian's story below illustrates, narratives about medication use for health or performance enhancement offer compelling case studies to stimulate discussion during pharmacy education and training.

While narrative approaches to understanding use, resistance to, and meaning making about medicines are only just beginning to make scholarly inroads into pharmacy practice, a number of scholars have taken up similar approaches to understanding human engagements with medicines drawing on qualitative data; their work may serve as meaningful examples of the potential for exploring stories about medicines. Greenhalgh (2017) provides an auto-ethnographic account constructed through narratives of her experiences of adjuvant chemotherapy for breast cancer. Ballantyne (2016) has explored the experiences of medicines users within the broader "field" of medications where their use is constantly negotiated among a number of key actors, including physicians, pharmacists, government regulatory bodies, the pharmaceutical industry, and users themselves. Both Pound et al. (2005) and Murdoch et al. (2013) have explored how medicine taking can be resisted, particularly within the context of adherence discourses.

Medication Narratives as Empirical Exemplars

The exemplars below are designed to help you recognize medication narratives when you see them in the various forms in which they occur. Medication narratives can be embedded in naturally occurring talk or text, or they can be elicited within the context of a research interview or focus group. They can be spoken, written, or even created through images, such as artwork, photographs, or video. Below we explore several examples of medication narratives drawn from our own research and from publicly available sources to demonstrate the breadth in content, forms and media that can be used to tell stories about medications. In the context of pharmacy practice research, medication narratives are likely to be drawn from elicited data: the text of research interviews, focus groups, or from oral accounts told during ethnographic fieldwork. Yet we draw on the examples below to illustrate how medication narratives are, in fact, everywhere, and these publicly accessible sites can be rich sources for data collection and analysis.

The first empirical exemplar is drawn from our own research on narratives of living with and taking medicines to manage postural tachycardia syndrome (PoTS), a dysfunction of the autonomic nervous system that causes an excessively fast heart rate and fainting or near fainting upon standing. Magdalene's story tells of a specific, time-limited event involving medicines, one in which she experienced a sudden onset of symptoms in hospital and was given medication that she did not want when she was unable to consent. This excerpt is drawn from a longer narrative that was originally written for the website of a PoTS patient organization.[1]

> I was admitted to the hospital and, after a day, I was sent to the ICU because my heart rate was up to 180 beats per minute lying down. The staff kept telling me to calm down, and I told them I couldn't. It's not like I could control this!!!! After a couple days and some beta blockers and other meds, I was moved to a normal hospital room. Every time I ate, I passed out. I couldn't move and could barely talk for 2 or 3 hours each time. At this time, I was on a liquid-only diet. Meanwhile, I had 8 doctors all come in one day to see me, including my primary care doctor, a neurologist, and a psychiatrist. Each one told me that this was all anxiety and that they wanted me to take a medicine for anxiety. Also, they said that I was a female and trying to do too much with school and work. I WAS SO ANGRY! After the first 3 doctors, I was so angry that by the 8th, I was enraged! NO ONE WOULD LISTEN TO ME!!!!!!!!!!!!!!!!!! I knew that it wasn't anxiety and that there was something very wrong with me . . . The doctors treated me like complete crap and told me that I was a woman at the age of 23, trying to finish school, and that my body was just shutting down. They said that I was too stressed and couldn't control my emotions, so that was why I was in the position I was in!!!!!!!! At one point I passed out and was unable to talk, and the doctor ordered the nurses to give me anxiety medicine so that I would stop having the episode. I couldn't tell them that I didn't want it because I couldn't talk. They knew that I didn't want to take it because I had refused it earlier. It was unbelievable. At this point, my heart rate was at 120 beats per minute. I could barely walk. I had Parkinson-like symptoms. My breasts had filled with milk from the domperidone. Every time I threw up, I passed out, and every time I ate, I passed out. After 7 days, they told me that since my heart rate was better, there was no reason for me to stay there and that they wanted to send me to a nursing home because I was unable to take care of myself. My mom said no, that she would take care of me. I left the hospital.

Medication narratives can also tell stories about the meanings that medicines have in people's lives lived with illness. These stories can be about specific events, but they can also be more reflective, drawing together multiple experiences, and engaging

[1] Accessible at: https://www.dinet.org/content/member-stories/mystery-magdalene-r85/

social and cultural perceptions of medicine taking. Shelley, who is living with fibromyalgia and Lyme disease, does this in a story posted to her personal blog, Chronic Mom,[2] when she speaks of how taking opioids to manage her pain has changed her life.

> My pain levels had basically gotten so high I was almost bedridden. I couldn't take care of my kids, I couldn't work, I couldn't do anything that required walking or standing of any sort. Luckily for me I had been a patient of my doctor for some time before I broached the subject of pain relief. She knew me well by then and had no problem prescribing a low dose of Hydrocodone.
>
> This changed my life.
>
> Last week I went camping with a bunch of teenage girls. I was walking miles and miles every day. I was staking down tents in rainstorms, I was frantically running around trying to stop a tent from flooding, I was playing physical games, and I was sleeping on an uncomfortable cot without my heating pad. I was in a lot of pain, by the end of the week I couldn't even walk normally because my muscles were so stiff from the pain, but I did it and I had a blast. The reason that I could do it was because I took 1 pain pill each night so I could sleep. Without that pain pill I never would have made it. My pain level would have gotten so high I wouldn't have been able to sleep, especially in such uncomfortable conditions. I would have lost sleep and as I lost sleep my pain levels would have climbed even higher. Once the painsomnia cycle begins there's no ending it, it's an endless cycle of misery that I was able to avoid due to my pain medication.
>
> My camping experience is only one small example of how pain medication has changed my life. Two weeks after my camping trip I'm going on vacation with my family. We're going to 5 different National Parks and we're going to do a lot of hiking. I love being outdoors and I love exposing my city kids to nature. I'm still limited in what I can do (I won't be rock climbing or going on 12 mile hikes anytime soon), but I could never have done even a little of this before pain medication.
>
> Some might consider these activities optional. After all I don't need to be a camp counselor and I don't need to go on vacation with my kids. Is it really worth the "risk of addiction" just so I can have fun once in a while? Anyone with common sense would say yes it is. And for those who have no common sense they can read my story and realize I've been on the same dose of pain medication since 2014 so clearly I'm not an addict. And for those who have no common sense and no empathy and still think I don't need pain medication, I would point out that I can actually be a productive citizen when I have access to pain medication. Instead of being bedridden I have a life.

In our increasingly virtually networked age, social media and video hosting platforms can be sites for the creation and sharing of medication narratives. The popularity of YouTube as a video blogging platform has made possible the proliferation of video blogs, or *vlogs*, about experiences with illness and medications. Claudia's story[3] about her experiences with her antidepressant and anti-anxiety medications illustrates not only how videos have come to offer compelling media for the telling of stories about medicines, but also as her talk about medication pricing and access shows us, medication narratives are sites where the personal can be linked up with the social and the political.

> I think I started taking antidepressants when I was fourteen and I've gone through periods when I haven't been on them and I've tried different ones. And at the moment, the venlafaxine that I'm on, I think it's okay. It's hard to tell. The quetiapine is an anti-anxiety, I believe. I take that at night and it helps me to sleep. It really makes me tired so it helps me sleep. So that's supposed to stop me from having panic attacks, but I'm having a lot at the moment, but I'm not sure if that's to do with the medication or not. The venlafaxine is odd because it's a very unpleasant medication to be on. I don't know if any of you guys are on it. If you are, then tell me your own stories about venlafaxine. But if you forget to take a dose, then it makes me sick. It makes me very sick. It can give you a headache. You feel awful if you forget to, you know if you've forgotten to take your venlafaxine. Also it tastes, mine tastes really bad. They don't have to because sometimes they have a coating, but mine are not really coated very much, so every morning I have to psych myself into swallowing this tablet because if it goes on your tongue it's just disgusting. To get myself to swallow it, I honestly try to think of Daenerys from Game of Thrones when she's eating that heart, and I just think to myself like, 'Keep it down. It's okay. Just keep it down. Swallow it. Keep it down. It's all good.'

The excerpt above from Claudia's story focuses on what it is like to take medicines, the experience of swallowing them, what they taste like, how they make her feel, what they are supposed to do in her body. Later in her narrative, she moves from a focus on the personal to a critique of the structural issues surrounding medication use, particularly of prescription fees under the British National Health Service.

> I only recently found out, I always thought medication in the UK was free because I've always had my antidepressants and stuff free, but I realized that that's actually because we're on a low income. I thought everyone had that, and I've just recently realised that if you're over a certain income then you have to pay for your own antidepressants and things. I think that's quite bad. I feel like they're kind of vital to be honest, and I don't think it's fair that you should have to pay for those. I also heard the other day that apparently sometimes you have to pay for your own cancer medication, and I was so ignorant I didn't even realise. I think that's appallingly bad. So I really wish that there was something that could be done about that.

Our last exemplar demonstrates how narratives about medication can also be embedded within broader narratives of health and bodily enhancement. In recent years, the term "bio-hacking" has emerged to describe various bodily practices of self-experimentation, often drawing on tools of the Quantified Self movement, to maximize personal health and performance. This can involve the consumption of health or cognitive enhancing medicines of various sorts, including natural supplements, functional foods, over the counter medicines, and prescribed pharmaceuticals, including pharmaceuticals purchased through quasi-legal global networks, such as in Adrian's narrative below.[4] Adrian tells the story of how he decided to use Modafinil, a cognitive enhancing medication, how he procured it from a source in India, and his experience of 3 days of self-experimentation. His narrative takes the form of a

[2] Accessible at: http://www.chronicmom.com/2017/07/how-access-to-opioids-changed-my-life.html/
[3] Accessible at: https://www.youtube.com/watch?v=vpNVyLSdPOs
[4] Accessible at: https://www.youtube.com/watch?v=A8jYQqL6oVM

video review, constructing Modafinil as a consumer good, about which information is shared informally amongst users and potential users.

> I first started a couple of days ago. I got it in the afternoon, which wasn't a great idea. I was really excited for it, so basically I just popped a tab then and there. Then I got a Skype call from my mate back in Australia and we ended up just chatted for like two hours, so I didn't even use it for anything productive. So I didn't really test how well it worked on that first day, which is a shame. But the next morning, actually that night, I didn't get to sleep until about 1:30. I just couldn't sleep. While I didn't feel super focused or super energetic or anything. I just couldn't sleep. My mind was still flowing, you know. One o'clock in the morning I felt like I should have just gone and read a book, you know, gone and done some work. I was just still in the zone. This stuff has a really long half life and I started with 200 mg as well. It's a really long half-life. This one here is actually Modalert. [My supplier] actually offers four different ones. Modalert is the fastest acting one that they do sell, so the other ones are going to have an even longer half-life. This is something like around twelve to fourteen hours half-life, which basically means that you're going to have trouble sleeping if you take these like anywhere after midday. If you're going to bed like midnight, you're going to have some real trouble with that. So you should be taking these things first thing in the morning.
>
> How it worked exactly, I'm not one hundred percent sure. I don't know they know all the effects and exactly how it works. But it affects your dopamine receptors, is one of the main things it does, so it does actually wear off after awhile. So basically you build up a tolerance after several days. I do recommend not to use this more than three or four days per week and every so often you should actually cycle it. So I've taken it three days in a row. The first day I didn't really test it much. The second day was yesterday. That was really good. I took it first thing. I got a lot done. I was basically doing things like writing. I wrote a massive blog post yesterday about all my business plans for basically 2016 and beyond, what I've got planned so far and it ended up being nearly 4,000 words long. I normally kind of hate writing. I don't mind it. I think I'm okay at writing, but it's just something I get bored of. It's not bringing me an instant return, so I'll write for half an hour and smash out a quick 1,500, 2,000 word article and post it up there without really reading it. But I took my time with this one. I actually spent two, three hours writing and brainstorming and thinking. I was just focused on this.

Why Study Medication Narratives in Pharmacy Practice?

Studying narratives allows for the exploration of how stories are structured and how they work to produce the effects in the teller and others that they do. It also allows us to be attentive to who is producing narratives, including how and why they are produced, the ways in which they are experienced by others, their effects on their audiences, and how and why particular narratives are accepted, while others may be contested or refused altogether (Squire et al., 2013). According to Squire and colleagues (2013, p. 2), "narratives carry traces of human lives that we want to understand." Being attentive to all the work that narratives do means garnering insight on these aspects of human lives, which can have critical implications for pharmacy education, practice, and research. Bissell et al. (2006) discuss several reasons why studying medication narratives can be important to the field of pharmacy practice, which we elaborate on below.

Improving Patient Care

At the individual level, pharmacists and other health professionals need to be attuned to the fact that they listen to and participate in the creation of narratives in their everyday work. The patient standing at the pharmacy counter telling of their struggles with medication dosing or their strategies for remembering to take their medicines at the right times is engaging in narrative work. Being attuned to listening to narratives in everyday speech can help health professionals to better understand their patients, their medication use experiences, and their beliefs about medicines in ways that can improve patient care. Such stories may convey insights that help to explain individuals' adherence to medication regimens or their resistance to using medicines exactly as prescribed. They may also help health professionals to understand how others, including family, carers or other professionals, are integrally involved in patients' medication use practices.

Enhancing Pharmacy Teaching and Training

The development of a field of "narrative pharmacy" in much the way that the field of narrative medicine (Charon, 2007; DasGupta and Charon, 2004; Greenhalgh and Hurwitz, 1998) has developed in recent decades would be an asset to the professional development and training of new pharmacists and pharmacy researchers at undergraduate and postgraduate levels. Such an approach would encourage more case-based learning and "teaching through stories," which may enhance pharmacy professional education. Attention to narratives may also enhance pharmacists' and pharmacy students' understandings of the role of pharmacists in patients' lives. Pharmacists have their own narratives to tell about medicines in their personal and professional lives, and are cast into the stories that patients tell about medicines. Medication narratives may be especially useful in pharmacy education and training as tools for stimulating reflection and discussion on the roles that pharmacists play in the stories their patients tell and how they might influence how patients create meaning about medicines in their lives. For example, stories like that told by Claudia above that engage with and critique structural barriers to medicines, such as prescription pricing, can help pharmacists and other health professionals to better understand how personal experiences with medicines are mediated by social, cultural, and political factors and may stimulate controversy and debate on pharmacy ethics. The stories posted to the

Health Talk website,[5] created by the charity DIPEx and the Health Experiences Research Group from the University of Oxford's Nuffield Department of Primary Care Health Sciences, may be a valuable resource for drawing narratives about medications into teaching and professional training.

Engaging the Use of Narrative in the Healing Process

Several scholars have posited that narratives have a crucial role to play not only in making sense of illness but also in the healing process itself (Broom, 1997; Frank, 2013; Greenhalgh and Hurwitz, 1998; Kleinman, 1988). Stories about illness may help people to make sense of the disruption in their lives caused by the onset of illness (Bury, 1982) and they may allow them to reconstruct the past in light of the present, making sense of illness in the context of their life stories (Williams, 1984). Storytelling is one form of social interaction, and Frank (2013) asserts that people tell stories not only for themselves, as a means of constructing or reconstructing their own identities in the face of illness, but also for others. Stories told by others may also help people to find their way through illness or through the experience of taking medicine, facilitating healing, recovery, or coping with a long-term chronic illness. Stories about medicines may be beneficial tools to utilize in patient education and support activities.

Engaging Narrative Approaches in Pharmacy Practice Research

There is a long history of narrative research in the humanities and social sciences. Drawing these approaches into pharmacy practice research may not only generate new research questions and initiatives within pharmacy practice but can also engage pharmacy researchers in contributing to theoretical and methodological work on narratives of illness and health that span the disciplines. Such engagement may foster stronger interdisciplinary ties with the humanities and social sciences and may catalyze future interdisciplinary scholarship in social pharmacy.

How Can We Study Medication Narratives?

Narratives are quite literally everywhere. Narratives can be written, spoken, or crafted via images (artwork, photographs, or video). They can be elicited, as in the research or journalistic interview, or they can be collected from extant sources, such as in the text of online blog posts or YouTube videos. They can be lengthy, telling an entire life story, or they may be only a few sentences long and recount a discrete, time-limited event.

The most common form of narrative analyzed in narrative research is that collected in the course of the research interview. Depending on the nature of the interview, the entire interview may consist of one long, sequential narrative, or it may be made up of many different narratives, reflecting the course of the conversation between researcher and subject. One approach for eliciting narratives about medicines in people's lives is the Free Association Narrative Interview (FANI), a method that is described in detail by Hollway and Jefferson (2008). Ryan et al. (2007) discuss an example of the format of a semi-structured interview guide for eliciting medication narratives in research interviews with medication users. They suggest that such interviews ought to seek the elicitation of rich stories about medicines, starting with broad questions about a person's experience of health and illness throughout their life, before zooming into query more specifically their beliefs about and experiences of medicine taking. They should conclude by offering a space for reflexivity and the consideration of medicines' use within the broader social context.

The analysis of medication narratives should not, however, be restricted only to those elicited in the context of research interviews, focus groups, or ethnographic work with medication users. The Internet, particularly the proliferation of social media-based support networks, personal websites, patient organizations, and video sharing platforms, has made a wealth of extant stories about illness, health, and medicines readily accessible. In our recent exploratory research, we analyzed medication narratives embedded within narratives of living with one particular chronic illness, Postural tachycardia syndrome, a form of dysautonomia or a dysfunctioning of the autonomic nervous system. These stories were collected, with permission, from the websites of patient organizations. It is important to note, however, that analyzing qualitative data collected from publicly accessible Internet sources raises a number of important research ethics issues, which must be attended to in much the same ways as in other forms of human subjects research (Grinyer, 2007; Heilferty, 2011).

There is a great deal of variation and debate over the theoretical underpinnings of narrative analysis, and there are multiple approaches to analyzing narratives based on a number of related but divergent theoretical approaches. Some scholars approach narratives with an emphasis on analyzing events (Labov and Waletzky, 1967; Patterson, 2013); others with an emphasis on the narration of experience, social meanings, and representation (Riessman, 2008; Squire et al., 2013). Some have approached the analysis of narratives through the lens of poststructuralism and the work of Michel Foucault (Tamboukou, 2013). Others have sought to analyze visual narratives (Bell, 2013) or the social interactions facilitated by social media as forms of narrative (Davis, 2013). Andrews et al.'s (2013) edited volume on *Doing Narrative Research* as well as Catherine Kohler Riessman's book on *Narrative Methods for the Human Sciences* (2008) may be helpful guides to conducting narrative analyses. Anderson and Kirpatrick's (2016) discussion of narrative interviewing in a clinical pharmacy context and Fraser's (2004) detailed discussion of

[5] Accessible at: http://www.healthtalk.org/

line by line coding and analysis of narratives may also be helpful to understanding how to conduct narrative analyses about medications.

Future of Medication Narratives

Medication narratives (Bissell et al., 2006; Ryan et al., 2007) remain an emergent concept in the field of Pharmacy Practice. Much further theoretical and methodological elaboration remains to be done, as does much empirical application of the concept. Further scholarly work may:

- Explore how various theoretical approaches, from Labovian (Labov and Waletzky, 1967) to more experience-centered and thematic approaches (Riessman, 2008; Squire et al., 2013), as well as Foucauldian, feminist, or postcolonial perspectives may be applied to research on narratives of medication use.
- Elaborate on the methodological strategies for conducting narrative analysis on stories about medications and the meaning of medications in peoples' lives. For example, how is narrative analysis done on narratives about medicines? How may it differ from methodological approaches to understanding illness narratives or other forms of personal storytelling?
- Underpin the development of empirical research on experiences of taking medication for the management of chronic illness, the management of health risks (such as high cholesterol or hypertension), and for the enhancement of health, cognitive performance, or bodily aesthetics.
- Explore how medication narratives may be used to improve patient care in a health care or community pharmacy setting.
- Evaluate student experiences of using medication narratives as a component of case-based learning in pharmacy education.

Multimedia Annex

In this video narrative, Claudia describes her experiences of taking antidepressant and antianxiety medications, including their taste, how they make her feel, and how she manages to swallow them. She also links her personal story up with the broader social and political context through a critique of prescription pricing under the British National Health Service.

Website link: https://www.youtube.com/watch?v=vpNVyLSdPOs

In his video review of Modafinil, Adrian describes 3 days of self-experimentation with the cognitive enhancing medication, including how he procured it from a supplier based in India, how he used it, how it made him feel, and his personal recommendations to other users.

Website link: https://www.youtube.com/watch?v=A8jYQqL6oVM

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National Medicine Policies Impacting on Pharmacy Practice

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The policies concerning and affecting medicines are discussed, debated, and decided on many levels—global, international, national, and local. The majority of policies which impact pharmacy practice can be found at the national level. Previously, policy makers at the national level paid little attention to medicine production by the pharmaceutical industry or the quality or availability of medicines for consumption by their citizens. This meant that most countries did not regulate the safety and efficacy of medicines. Governments trusted the pharmaceutical industry to test their products for safety and efficacy prior to market release. As long as pharmaceutical companies and pharmacies sold unadulterated medicines at prices that the market could bear, it was the market and not the state that had the responsibility for policing pharmaceutical products. In the 1960s all this began to change, mainly as a result of the Thalidomide scandal, in which women who took thalidomide for nausea in pregnancy gave birth to babies with deformed limbs.

The World Health Organization (WHO) has for decades, encouraged nations to take responsibility and to formulate and implement comprehensive national medicine policies (NMPs), and the WHO message has had an effect. Since 1985 NMPs in low-income countries were established and increased rapidly, with the largest increase between 1985 and 1999. It was only in the mid-1990s that wealthier countries began formulating NMPs. Since the late 1990s NMP has become a global concern and a national endeavor and the number of NMPs has been increasing worldwide. Since the early 2000s the highest proportional increase in NMPs has been in high-income countries, providing appropriate medicines of assured quality, in appropriate quantities, at reasonable and affordable prices. The percentage of NMPs increased across all income categories but the highest proportional increase was seen in high-income countries, from 18% in 1999 to almost 80% in 2011 (Hoebert et al., 2013).

Defining National Medicine Policy

What is NMP and why is it important? In brief, a NMP is a common framework used to address and solve problems associated with pharmaceuticals; it is a commitment to a goal, and provides guidelines for action. NMP involves all the major actors in the pharmaceutical field including actors in both the public and private sectors (World Health Organization, 2001). WHO emphasizes that NMPs be designed as an essential part of health policy, fitting into the framework of the health care system as well as already existing national health policies. Developing a NMP is a complex process that must be country specific since every country and national health system is unique. However, one common goal, found in all NMPs, is to ensure equitable access, good quality, and rational use of medicines.

WHO emphasizes that a NMP must have a physical existence, i.e., be presented and printed as an official government statement which serves as a public declaration of the aspirations, aims, decisions, and commitments of the national government. To ensure that the various government measures do not conflict with existing measures, it is important that the goals and responsibilities are clearly defined and understood. In addition, NMPs should be dynamic and not stagnant—they should be written in such a way that they are capable of accommodating changes over time.

Most NMP s prioritize medium-to long-term goals set by the government for the pharmaceutical sector including not only the public and private sectors but also all the main actors in the pharmaceutical field. An effective NMP formulates and identifies major strategies for attaining these goals. It should be mentioned that although NMPs are best to deal with most pharmaceutical problems there are cases/issues that can and should be managed at a global or regional level. These are usually problems which extend beyond the boundaries of national borders, and are better managed, for example, by the European Medicines Agency (EMA) centralized

registration process and/or by regional groups which collaborate to harmonize regulation and pricing information as well as coordinate NMPs across countries within their regions (Hoebert et al., 2013; Vogler et al., 2017).

The politics influencing NMP are complex and influenced by a variety of other policy decisions. Pharmaceutical policy is an overlap of three existing fields of policy: public health policy, health care policy, and industrial policy (Traulsen and Almarsdottir, 2005a). Developing a NMP is a long and complicated process which requires knowledge of public health demands as well as economic goals and objectives. This means that policy makers are faced with overlapping and often competing regulatory tasks. In the first place, the goal of public health policy is to contribute to the overall public health by guaranteeing safe, high quality, and efficacious medicines. Thereafter is the enormous task of balancing health care budgets and controlling health and drug costs, which is the realm of national health care policy. Finally, given the economic contribution of the pharmaceutical sector to the state, policy makers are faced with the task of promoting a regulatory environment conducive to supporting and encouraging business through industrial policy. Taken together these three policy inputs—two concerned with health and one with commercial interests have a tremendous effect on pharmacy practice (Traulsen and Almarsdottir, 2005a).

The complexity does not end here, it must be remembered that the process of designing and planning a NMP is only the beginning: NMPs must be implemented, monitored, evaluated and last but not least there must be mechanisms available for revising and updating the NMP to remain useful and durable.

Policy Makers' View of Pharmacy and Pharmacists

The overall aim of policymakers is to ensure adequate and accessible health care, welfare, and general wellbeing of its citizens. The issues in NMPs that are relevant for the pharmacy sector and pharmacy profession are based on how policy makers view pharmacies and pharmacists. However, on closer inspection we find two conflicting views of pharmacy and pharmacists—they are either seen as part of a commercial business or as part of (and contributors to) the health care sector (Traulsen and Almarsdottir, 2005b).

On the one hand, when the pharmacy sector is viewed as a commercial enterprise it is seen as making a positive contribution to the economic good of the community. It follows that from this perspective policymakers view pharmacists as business (wo)men. On the other hand, when the pharmacy sector is considered a part of the health care sector it is seen as contributing to health services. Here policymakers view pharmacies as local health care centers—the first contact the public has with the health care system and with academically trained professionals. Pharmacists are viewed as the most easily accessible health care professionals, and their role is to use their extensive education about pharmaceuticals (from development to dispensing) to contribute to the overall public health goals of the community.

When analyzing which of these views dominate in a particular policy debate it is important to consider the two perspectives in the context of the policy. In other words, is the emphasis to lower drug expenditures or to increase patient safety and provide new and useful services for patients?

Both of the above mentioned views can be found at the roots of a conflict the profession has been struggling with since its conception: commercial interests versus professional interests. Despite centuries of regulation, there is no universal consensus on how policymakers perceive and regard pharmacy (and pharmacists). When perceived of as a business, policy makers are inclined to legislate pharmacy just like any other commercial enterprise, emphasizing financial and economic frameworks. In contrast, when pharmacies are accepted as part of the health care sector and pharmacists as academically trained health care professionals who provide a public service, they are inclined to regulate and legislate within the framework of other established health care policies and services.

An example of these two views of the pharmacist could be observed in the late 1990s when the liberalization of pharmacy ownership was debated in Denmark. Initially the policy debate focused on the pros and cons of a free market and competition in the pharmacy sector. The debates shifted focus toward the need for responsible public control of medicines which prioritized safety and access to medicines including the role of pharmacies as health care institutions and by default pharmacists as health care professionals (Larsen et al., 2006).

The contrasting views of pharmacies as businesses vs. health care centers are evident in policy decisions concerning ownership of community pharmacies. There is a wide variety of ownership models for pharmacies but the two most common distinctions are between systems where only pharmacists are allowed to own and run community pharmacies (the case in many countries, for example, Denmark, Finland, Spain, and France) and systems with nonstipulated ownership policies such as in the USA, UK, and Norway where pharmacies are often part of a commercial chain (either pharmacy or supermarket chain). Powerful commercial and economic interests have influenced the rhetoric and policymaking regarding ownership and the professional ownership monopoly has been under siege in the past decades especially in the Nordic countries (Almarsdottir and Traulsen, 2006).

When the view of pharmacies as health care centers is dominant, the personnel of pharmacies are highly regulated as to their required competencies. This aspect was quite clear during the recent policy changes made in Sweden which went from a state owned monopoly (quite rare in the pharmacy world) to a free ownership model in 2009. During the debates about the freeing up of the state monopoly, the rhetoric centered quite often on which members of the workforce should be required to fill prescriptions and give advice to patients (Statens Offentliga Utredningar, 2008). A wide variation exists between countries regarding the requirements necessary for becoming a pharmacist (i.e., length of academic study and on the job training). This variation also includes the training and requirements for other pharmacy personnel available in different countries such as assisting or allied professions (i.e., technicians) (International Pharmaceutical Federation, 2006).

In most countries' with free ownership policies NMPs require that the person in charge of the day-to-day running of the pharmacy be educated as a pharmacist (see Chapters 102, 104–112 in this Encyclopedia). The pharmacist can then delegate responsibilities for work tasks to other pharmacists or to assistants with a variety of training and backgrounds (see Chapter 103 in this Encyclopedia). The general trend, in counties with highly liberal pharmaceutical distribution policies, is that the pharmacy owners usually have the power and authority to select the composition of assisting personnel and are able to hire as inexpensive personnel as possible for tasks that have no legislative requirements.

Pharmacy practice in hospitals has not been exempt from this duality between the commercial and professional interests, although it has been developing in a different way. NMPs affect hospital pharmacy practice differently according to country, however, a common thread can be found in that there is increasing pressure to minimize the cost of medicines to the hospital. The pressure comes from policy makers at the highest levels. Their goal is to stop the escalating cost of health care. Hospital pharmacy practice is very much concerned with negotiating tenders and managing staff. In this climate one finds pharmacists working largely on tasks that seek to meet demands for cost containment. How this dual view of policy makers on the national level affects pharmacy practice and the profession's work will be dealt with below.

NMPs and the Sale of Medicines in Community Pharmacies

National policies affect the role of pharmacy practitioners (pharmacists and allied personnel) through a range of mechanisms. The privileges, requirements, and duties of pharmacists have their roots in history (see Chapter 702). Health systems vary tremendously across the globe and this makes for a variety of payment structures for pharmacy services. In national health care systems, national policies have a direct impact on the payment structure, i.e., how much is paid for dispensing medicines. In other health care systems private health insurers have a large say in what is paid for. Nevertheless, all systems have to abide by the overarching goal of health care systems to make medicines affordable and accessible.

The privileges and duties that pharmacies have through NMPs are not static; they are rapidly moving and follow shifts that affect most—if not all—professions. The issues that are on the move will be dealt with below and have to do with the right to sell prescription medicines and the remuneration for doing this or for providing other services. In addition, NMPs regarding over-the-counter (OTC) medicines are rapidly changing as well as the patients' copayment for medicines and insurance costs.

Sale of Prescription Medicines

Most NMPs privilege pharmacies with the procurement and sale of prescription medicines. This centuries old privilege makes for an important part of the viability and raison d'etre for pharmacies—although to a varying degree according to country. This backbone and mainstay of pharmacy is slowly eroding in most countries as health care budgets are strained and other actors in the health care market vie for this privilege.

There are a number of strategies employed by policymakers to curb costs of pharmaceuticals without losing out on safety and effectiveness of medicines in the population. Those NMPs that affect pharmacy practice in the primary sector are setting profit margins on the sale of medicines, reference pricing, and generic substitution, and switching prescription medicines to OTC status.

When policy makers limit margins on medicines they can either do this by fixing margins to certain percentages or by introducing fees per capita and/or prescription in an attempt to reduce the incentive to sell more medicines. Reference price lists for reimbursement of medicines in their simplest form mean that the price of a certain pharmaceutical product within a class of drugs is set as a reference for other similar drugs (generic or therapeutic equivalents). The reference drug is usually the least expensive in the class. If a patient or physician decides to use a more expensive drug, the patient is required to pay the difference between what would have been reimbursed for the cheaper drug and the price of the selected more expensive drug. The use of reference pricing requires a system of generic substitution or generic prescribing. The principle at work here is that pharmacies (often in cooperation with patients and the prescribers), are able to substitute less expensive generic versions of medicines. Generic prescribing also affects pharmacy practice in the hospital sector.

Positive lists (also called formularies) are lists of pharmaceuticals approved for reimbursement by the insurer or paid for by the health care system. Such lists are often compiled by expert committees who evaluate the therapeutic value of each drug, largely based on results from clinical trials, but sometimes on results from pharmacoeconomic analyses. The lists are often organization specific, so not made as NMPs, although they can be. The World Health Organization has drawn up a Model List of essential drugs that can be put into a NMP (World Health Organization, 2003). Although their list is primarily intended to meet the principal health needs of a community with very limited resources rather than to support cost-containment, the WHO advocates its use for determining the pharmaceutical needs of a population and therefore providing a basis for a national medicines list (World Health Organization, 2001).

NMPs often seek to manage the prices of medicines, the margins that pharmacies can have, and sometimes even the total profits of the pharmacies nationwide. Strict price controls are often applied to community pharmacies for prescription and even OTC medicines. In some instances this means that there is a fixed price allowed for medicines which leads to no competition on prices. Price setting is mostly done through negotiations at the manufacturer level with large payers (who can be national health insurers or governmental bodies dealing on behalf of the insurance system). The end price of a medicine affects the income of community pharmacies but many other factors in the market impact on pharmacy profits besides those that have to do with the

margins and profit ceilings allowed. Currently prescribed pharmaceuticals are no longer the mainstay of the income of pharmacies and sale of other products (OTCs and other goods) play an even more important role (Almarsdottir and Traulsen, 2005).

Over-the-Counter Medicines and Other Goods Sold in Pharmacies

One issue that affects the practice of pharmacy in the community is OTCs and the decision as to which drugs are OTC is often found in NMPs. OTCs are medicines that are sold directly to a customer and do not require a prescription from another health profession (see Chapter 720 in this Encyclopedia). The policy decision which allows a medicine to be sold as an OTC is based on knowledge about the safety profile of the drug but this is not to say that the drug is without safety issues. Switches from prescription to OTC (also referred to as reclassification of medicines) has been practiced widely in the last two decades. This practice has been seen as serving two purposes: first, to save time and money for the patient who avoids a visit to a physician and at the same time saves the prescription charge at the pharmacy. Second, third party payers save due to a reduction in physician visits and the shift of drug costs to the patient. This practice has had a big effect on pharmacists and pharmacy staff who are important advisers in the choice of self-medication (Almarsdottir and Traulsen, 2005). The switch from prescription to OTC products has in many cases meant that pharmacies play a larger role in advising patients on the use of these medicines.

Another aspect concerning OTCs are whether they are allowed to be sold outside pharmacies in stores (such as drug stores and supermarkets) that do not employ health professionals with special knowledge about medicines. In cases where this is allowed, the practice is often a result of public pressure for more access to the specific widely used medicines such as nicotine replacement products and pain medications. Another important actor who stands to benefit from this type of NMP is retailers of health products.

Whereas retail businesses have been reaching into the realm of community pharmacy, pharmacy has in turn sought to regain lost ground through the sale of other goods, be they health care related (such as vitamins and bandages) or not health related (such as food and beverages). NMPs often deal with this issue by specifying what a community pharmacy can and cannot sell.

Patient Copayment and Insurance for Medicine Costs

What patients pay for their medicines and how they are insured for medicine costs varies greatly according to countries. It can vary from national or regional publicly funded health care systems such as the UK and the Nordic countries, to highly regulated private health insurer markets such as the Netherlands and Germany, to free market for insurance such as the USA. These widely varying systems all have a commonality in that NMPs usually stipulate access to medicines for all citizens. The variation lies in whether NMPs stipulate equal access (often seen in national/regional publically funded systems) or basic access (privately funded systems). In these latter types of systems, there are often special programs available which address the needs for access by vulnerable populations such as the elderly, minorities, and indigent populations.

Clinical Services (Cognitive Services) Provided by Pharmacists or Their Staff

NMPs can to a large or moderate degree govern the prices, profits, and reimbursement for medicines. Moreover, national policymakers can affect pharmacy practice through the extent to which pharmacists are allowed to practice or be remunerated for clinical services (often termed cognitive services). Examples from such national systems are England, Denmark, and Australia. The UK National Health Service (NHS) has been seen by many within pharmacy as a trailblazer for remunerating pharmacist cognitive services and engaging pharmacy practitioners in more clinical work, both in the community and in hospitals. In 1986 a seminal report was published based on the work of the Nuffield Foundation Pharmacy Inquiry Committee (Nuffield, 1986) which had far reaching and (in the 1980s) bold recommendations on how to involve pharmacists in health care and public health. From then on many changes have been made to improve the training of pharmacists and to introduce new pharmacist-led health services in all health care sectors. One of the most notable changes can be seen in the use of community pharmacies in dealing with minor ailments and in how pharmacy is used in public health prevention and promotion (Anderson, 2007). Another change was that pharmacists in the UK started to get involved in supplementary prescribing of medicines through contracts with physicians (Cooper et al., 2008). An example of a country where the development has been slower is Denmark, where only two services have been remunerated through the national health services scheme. One is a service to improve the use of inhaler devices for asthmatics and COPD patients, and the other is a consultation service for newly diagnosed chronically ill patients about their medicines to support adherence (Kaae et al., 2016). Vaccinations at community pharmacies are currently becoming a widespread service offered in many countries, either remunerated by insurers or paid out-of-pocket by the customers. Lastly, Australia started a program of Home Medication Reviews in 2001 which funded community pharmacists and medical practitioners to work collaboratively with the patient, the patient's caregivers and, when appropriate, other health practitioners to address issues concerning the use of medicines (Cipolle et al., 2012). The availability and accessibility of pharmacies has been mentioned and this has contributed to policy makers' interest in utilizing the competencies of the workforce there.

As mentioned above, the view policymakers have of community pharmacy as a shop or a health care center impacts remuneration patterns. This means that if they see it as a shop, they will not be willing to compensate pharmacies for anything other than the sale of medicines. Similarly, policymakers' thrust for cost cutting and cost containment in drug procurement in the secondary sector has

made for a more product-focused work environment for hospital pharmacists which can make it difficult for hospital pharmacists to find the time and space to provide much needed clinical services (Almarsdottir and Granas, 2015).

Division of Labor Between Pharmacists and Other Health Care Professionals in Relation to Medicines

The role of most health care professionals is subordinate in one way or another to that of physicians. Whether someone is a community pharmacist or a hospital pharmacist, their professional role is ultimately controlled, or at least limited, by the authority and dominance of the medical profession, and the relationship is contentious (Turner, 1995). This subordination stems from the historic strong position of physicians in relation to national policymakers where pharmacists have traditionally not had such a strong voice and therefore not been able to affect NMPs to a large extent. It is not impossible though to have a large impact on implementing and instituting clinical pharmacy services as seen in 1980s with the advent and subsequent implementation of the Nuffield report in the UK and the strong advocacy of the American Society of Health-System Pharmacists (ASHP) in USA (Zellmer, 2006).

While on the one hand pharmacists can be seen as infringing on the physicians' traditional task of prescribing, on the other hand pharmacists are encountering the problem of dispensing physicians. By law in most countries, dispensing physicians are allowed to sell drugs to patients in certain remote and thinly populated areas, often places where there are no pharmacies. However, because selling medicine can be a very lucrative business, many developing countries have dispensing physicians in even the most populated areas, including large capital cities (Trap et al., 2002). Policy discussions about who should be allowed to prescribe and who should be allowed to dispense continue, because the inherent conflict of interest in allowing the same profession to prescribe and sell drugs has been and still is an overriding concern.

Shifts in the division of labor in the pharmacy are a direct result of political and economic changes in society as a whole and NMPs have dealt with this issue of using the manpower optimally. The division of labor between pharmacists and pharmacy technicians is a case in point. Traditionally helpers and assistants to pharmacists, pharmacy technicians' jobs and training have been increasingly regulated and upgraded in many countries, and more and more frequently technicians have been taking over tasks previously performed by pharmacists. The upgrading of the skills and knowledge of the pharmacy technicians varies from country to country. In some countries, pharmacy technicians have little if any training, and obviously pose no threat to the pharmacist. In others (i.e., in Denmark and the Netherlands) they are highly trained and have even been taking over tasks previously seen as pharmacists' roles both in community and hospital pharmacies. It was seen in the debates about liberalizing community pharmacy ownership in Sweden that the legal requirements for the composition of pharmacy personnel was a very contentious issue. It seemed that policymakers were quite unsure of the competencies of the various professional categories and which of these were really needed to work in community pharmacies (Statens Offentliga Utredningar, 2008).

Concluding Remarks

NMPs have a great impact on pharmacy practice and there are a number of issues and actors at play. Pharmacists are of course also an important actor defining the role of pharmacists—i.e., as drug product or health care providers. Throughout the ages pharmacists themselves have been instrumental in shaping their profession through their ideas and visions. New and expanding roles for the pharmacy profession were sometimes inspired by external events but were often the result of the pharmacists' own prerogative. One example of a profession mediated idea is the vision and development of pharmaceutical care as a professional role for pharmacists and expanding their role through clinical pharmacy (Hepler and Strand, 1990). Professional organizations of pharmacists throughout the world have not only embraced these expanding roles, they have also contributed by further developing them (American College of Clinical Pharmacy, 2017; European Society of Clinical Pharmacy, 2017). However, there are also reactionary or status quo tendencies seen in the pharmacy profession as they do not see themselves as patient care providers but prefer to continue doing what is known as their field of work—namely dispensing medicines (Rosenthal et al., 2010).

Glossary

Clinical pharmacy Clinical pharmacy is a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices. Clinical pharmacy includes all the services performed by pharmacists practicing in hospitals, community pharmacies, nursing homes, home-based care services, clinics, and any other setting where medicines are prescribed and used.

Cognitive pharmacist services The use of specialized knowledge by the pharmacist for the patient or health professionals for the purpose of promoting effective and safe drug therapy.

National medicines policy or national drug policy (NMP) A common national framework used to address and solve problems associated with pharmaceuticals; it is a commitment to a goal, and provides guidelines for action. NMP involves all the major actors in the pharmaceutical field including actors in both the public and private sectors. Most NMPs prioritize

medium-to long-term goals set by the government for the pharmaceutical sector including all the main actors in the pharmaceutical field. An effective NMP formulates and identifies major strategies for attaining these goals.

Patient copayment The part of the health care cost (i.e., the cost of a medicine) that is paid by the patient. Copayment for services generally is meant to instill cost awareness in the user of health care services, thus reducing unnecessary use.

Pharmaceutical care Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life.

Pharmacoeconomic analyses Evaluation of the economic consequences of the use of a drug. This assessment can be made before placing a drug on the market or afterwards, possibly including a comparison with another drug or another health care intervention.

Positive lists Are also called formularies. They are lists of pharmaceuticals approved for reimbursement by the insurer or the lists of drugs that may be used in a particular organization (hospital) without getting a special permission.

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Pharmaceutical Company Sponsored Medication Assistance Programs

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Growing health expenditures per capita has been an issue for all countries, rich or poor. Health spending growth in the United States between 2015 and 2025 was projected to average 5.8% or 1.3% points higher than growth in the country's gross domestic product. United States health expenditure will account for 20% of the total economy by 2025 (Keehan et al., 2016). Similar situations were seen in upper middle-income countries, lower middle-income countries and even in low-income countries (Jakovljevic and Getzen, 2016).

What is Driving the Increase in Health Expenditures All Over the Globe?

The rise in health expenditure is accelerated by several factors including aging population, changing disease pattern from infectious diseases to chronic diseases, and inefficiencies in the healthcare system. Advances in health technology, especially high costs innovative medicines, has been pointed out by many researches as the principle driver for increasing health expenditures (Sorenson et al., 2013; Kesselheim et al., 2016) around the globe.

To contain costs in healthcare, innovative medicines that are mostly high-priced are the target of cost containment strategies. The prices of innovative medicines differ from country-to-country due to differences in healthcare system and healthcare markets (Kesselheim et al., 2016).

Studies found that in the United States where healthcare are offered mainly through market system, the price of the drug is set by pharmaceutical company solely based upon the market exclusivity of the drug (Rosenthal and Graham, 2016; Kesselheim et al., 2016; Savage et al., 2017). The cost of these drugs, even though reimbursable by major health insurance payers, has many hurdles for patients to access, for example, prior authorization, higher out-of-pocket spending, co-payment or co-insurance (Tefferi et al., 2015). Price of drugs in other healthcare systems where universal coverage is achieved, is also high. As a result, coverage decision by major health insurance payers is mostly delayed (Bae et al., 2016; Kandolf Sekulovic et al., 2017). In this case, patient's out-of-pocket spending becomes the major healthcare financing source.

Literature has shown that higher out-of-pocket expenditure can lead to non-compliance of medicines. Patients were reported skipping their medications or refusing to refill their prescriptions when co-payments for their drugs were high. This actually leads to poor health outcomes for the patients. Olszewski et al. (2018) found that patients receiving financial assistance for medicine have longer overall duration of therapy.

The emergence of pharmaceutical company sponsored medication assistance program has been documented in the literature since 1990s. The program primarily provides medication to patients who do not have prescription drug coverage from either public

or private insurance for free. These patient assistance programs are funded by pharmaceutical companies voluntarily. The offerings of these programs are not required by the governments.

We began this chapter by describing the characteristics of pharmaceutical company sponsored medication assistance programs. We then turned to distinguish between this and patient assistance programs sponsored by the government or other programs between pharmaceutical companies and the health insurance payers. Role of pharmaceutical company sponsored medication assistance programs in the United States is also explained.

What is Pharmaceutical Company Sponsored Medication Assistance Program?

Pharmaceutical company-sponsored medication assistance programs are also known as drug company-sponsored patient assistance programs (Choudhry et al., 2009), patient assistance programs (PAPs) (Felder et al., 2011b) or prescription assistance program (PAP) (Gao et al., 2016), medical assistance program (MAP) (Horswell et al., 2008) or pharmaceutical manufacturer assistance programs (PMAPs) (Sarrafizadeh et al., 2004).

These programs offer brand name medicines by pharmaceutical manufacturer to patients at a lower cost or sometimes at no cost. Most programs are for a certain medication and sometimes for a certain indication (Chu et al., 2011). However, some programs are funded for specific diseases by several pharmaceutical manufacturers mostly through non-profit organizations. The latter programs are not only limited to medication but also include financial assistance to the patients for insurance premiums and co-pays, assistance for diagnostic testing, and travel assistance for clinical trials or consultation with disease specialists. Examples of these programs are National Organization for Rare Diseases (NORD): a patient advocacy organization dedicated to individuals with rare diseases, or American Kidney Fund that provides direct financial assistance to kidney patients.

Pharmaceutical companies use patient assistance program as a price discrimination tool to price its product at the profitable level in the market where there is an ability to pay while offering assistance program in the market where affordability is the major criteria for product selection. In a changing pricing environment in pharmaceutical market, assistance program is a win-win pricing tool to limit the use of international reference pricing.

The terms patient assistance program has also been used elsewhere for government patient assistance program. However, these programs are mainly funded and operated by the government and are different from pharmaceutical company sponsored medication assistance programs. The purpose of the government-funded programs is to help its citizens have better access to medicines. Details of the program vary with the criteria set by the government. In the United States, government patient assistance program are run separately by each state or country. List of government patient assistance programs in the United States can be found on the website of National Resource Center for Prescription Assistance Plan (501(C)(3) organization, 2019).

Examples of government PAPs in the United States include:

- Pennsylvania prescription assistance program for older adults (The Pharmaceutical Assistance Contract for the Elderly or PACE program): The program provides prescription assistance for older adults in the state, and provides low-cost prescription medication to qualified residents aged 65 and older. To be eligible for PACE program, a person must also have an income in the income range determined by the state of Pennsylvania.
- The Madison County Commission SENIOR Rx Program: The program helps low-income Madison County residents, aged 55 years and above who do not have prescription drug coverage for free or at a low-cost. The medicine, however, only includes medication for chronic illness(es) or condition(s).
- AIDS Drug Assistance Program (ADAPs): The program provides HIV/AIDS drug to HIV-infected patients. Funded mainly by the federal government through the HIV/AIDS bureau under the Health Resources and Service Administration, the program, however, differs significantly from one state to another. Each state has an authority to determine drugs to be listed in its ADAP formulary. Variation in drug coverage, both antiretroviral drugs as non-HIV medications, were found in each ADAPs state (Smith and Buchanan, 2001).
- 340B program (340b health, 2018): The program was created in 1992 by the United States federal government requiring pharmaceutical companies to provide Medicaid-covered outpatient drugs at cheaper price to eligible government healthcare facilities or "covered entities". The program aimed to serve the Medicaid as well as uninsured seeking care in those health facilities.

Government Prescription Assistance Programs in Countries Other than United States

Government prescription assistance program have also been found in other countries for example, Philippines government medical assistance program.

Philippines Government Medical Assistance Program

In 2016, Philippines Ministry of Health (MOH) published guidelines on the availability of medicine assistance funded under the President's p1billion fund (Department of Social Welfare and Development, 2016, 2017). The program helps patients who seek medical assistance. Funded by the office of the president, the program provides free medication mainly to indigenous and vulnerable patients.

In some settings, the term patient assistance programs have also been used for risk-sharing programs or managed entry agreement program. The differences are that patients who receive pharmaceutical products from pharmaceutical company sponsored medication assistance programs are patients who could not access pharmaceutical products mainly because it is not reimbursed by their health insurance or the patient themselves do not have insurance coverage. However, risk-sharing programs are between pharmaceutical manufacturers and health insurance payers, and they share the risks and uncertainties that arise in reimbursement decision-making. These programs would not be mentioned here in this chapter but readers can get more information from '*Managed entry agreements for pharmaceuticals: the European experience.* EMiNet, Brussels, Belgium' (Ferrario and Kanavos, 2013).

Role of Patient Assistance Program in United States Healthcare System

Access to medicine in the United States healthcare system mainly depends on patient's health insurance status. Patient assistance programs are used as a safety net for patients who cannot access their medications through their current health insurance status (Felder et al., 2011a). The Pharmaceutical Research and Manufacturers of America (PhRMA) decided to launch "PPA program" to facilitate patients enrolling in patient assistance program offered by the company that are PhRMA members. The PPA program was launched in 2005. In 2018, PhRMA reported on its website that PPA sponsored by pharmaceutical industry has helped more than 10 million US residents (Pharmaceutical Research and Manufacturers of Americas PhRMA, 2018).

Pharmaceutical sponsored patient assistance program is not limited to uninsured patients; it can be accessed by underinsured as well. Underinsured are mostly overlooked since they have health insurance coverage, yet have to pay a large amount of their income on health care. The Commonwealth Fund study has found that even though Affordable Care Act reduced uninsured population by nearly 2 million from 2010 to 2012, the number of underinsured increased from 29.9 million to 31.7 million (Cathy Schoen et al., 2014).

US population who are insured but most at risk of underinsured are, for example, Medicare beneficiaries who have low income but not low enough to be eligible for Medicaid or low-income subsidy for Medicare Part D. Medicare beneficiaries who are qualified for Medicaid except they have a high spend down amount; beneficiaries under private commercial insurance plan have high deductibles or copays or have formulary restrictions.

Although the use of pharmaceutical sponsored patient assistance programs can be helpful for patients who otherwise would not be able to access these medications, the process of acquiring these drugs under PPA can be challenging. The website of the PPA programs shows that in 2018 more than 200 patient assistance programs were offered by 80 pharmaceutical companies. Most programs, however, offered access to only one or two specific drugs [Partnership for Prescription Assistance (PPA), 2019]. It was reported that the structure of PPAs, application process as well as benefits offered varied widely (Zafar et al., 2015).

Each program has different eligibility criteria and documentation requirements. Eligibility criteria include patients' income level, for which some require proof-of-income documents while some do not, patient's insurance status, drug coverage status, and United States residency status.

Medications offered via patient assistance program range from medications for chronic diseases for example, Lipitor (atorvastatin), Advair Diskus (fluticasone propionate and salmeterol) to medications for acute illness, for example, Nexium (esomeprazole) and high cost medicines, for example, anticancer biological drugs. However, programs are generally not appropriate for acute illness where medication should be taken as soon as possible as the application process for patient assistance program takes quite some weeks.

Some companies offer assistance programs for vaccines For instance, Merck has vaccine patient assistance program as well as nutrition support therapy and Abbott offers nutrition patient assistance program. The trend in medication offerings and patient assistance program has changed as medications for controlling chronic conditions were among the most commonly requested for patient assistance program in 2006 (Chauncey et al., 2006). Currently, anticancer drugs are the most frequent group of medication sought under patient assistance program as the price of these medicines are surprisingly high at approximately $10,000 or more per month. Study by Olszewski et al. (2018) has shown that more than one third of patients receiving cancer medication used financial assistance to offset out-of-pocket costs. Examples of patient assistance programs offered in the United States are listed in **Table 1**.

Enrolling in Pharmaceutical Company Sponsored Medication Assistance Programs in the United States

Patient Assistance Program Enrollment Process in United States

The number of patient assistance programs has been increasing with the increasing complexities of the program offered by each company. The enrollment process of all patient assistance programs can be summarized into four steps:

Step 1: Patient locating patient assistance program application form for the medicine he/she would like to enroll in.

Before enrolling in any patient assistance program, a patient needs to determine if the needed medication has patient assistance program offered. Some programs do not require patients to complete an application form at all, while some program require application form to be filled in by the patient. Patient assistance program application form is usually available online from the pharmaceutical company website. Some company, however, would send an application form only to patient or healthcare professional per request especially for specialty medications and high-cost medications.

Table 1 Example of pharmaceutical company sponsored patient assistance program offered in the United States healthcare market

Drug group	*Example of drugs offered patient assistance program*	*Details of the patient assistance program*	*Eligibility criteria*
Non-communicable diseases	• Insulin lispro injection (Humalog) • Dulaglutide (Trulicity)	• A 120-day supply of medicine will be shipped to the doctor's office • Enrollment period is 1 year • Refills are requested by fax refill form by the prescriber	• Have no insurance or have Medicare Part D and have a household annual adjusted gross income ≤400% federal poverty line (FPL) • Healthcare provider has prescribed a medication • A permanent, legal resident of the United States or Puerto Rico • Not enrolled in Medicaid, full low income subsidy (LIS, "Extra Help") or Veterans (VA) Benefits • If patients are a Medicare Part D patient, they have spent $1100 on prescription medication this calendar year.
Infectious disease	Lamivudine	• Refills are sent at no cost for up to 12 months after enrollment • Each refill must be requested at least 3 weeks before existing supply of medicine runs out	• Live in one of the 50 states, District of Columbia or Puerto Rico • Have no prescription drug benefits through anyinsurer/payer/ program • Meet certain income eligibility requirements
Immunosuppressive	Cyclosprorine	• The majority of products are dispensed in a 30 or 90 day supply • All products will be shipped directly to the physician's office	• Have limited or no private or public prescription coverage • Income at or below 600% of FPL • Must reside in the United States, Puerto Rico or the United States Virgin Island
Antipsychotic	Aripiprazole (Abilify)	• The amount of drug supply is various. • The drug will be sent to doctor's office or patient's home • Patient can re-apply yearly	• May have insurance • Eligible Medicare part D patient • Have income at or below 300% of Federal Poverty Level (FPL) • Must reside in United States
Cancer	Denosumab	• Medications are provided through the HealthWell Foundation • Includes assistance on coinsurance or copayment required as well as insurance premium	• Diagnosed with the disease eligible • Income level falls within eligibility criteria • Receiving treatment in the United States.
Oral contraceptive	Levonorgestrel		• Must have no prescription coverage for needed medicine • Not a Medicare part D eligible patient • Must be residing in the United States or Puerto Rico
Vaccines	Hepatitis B vaccine (Engerix-B)	• Prior to enrolling patients, prescribers must register in the program • For patient enrollment, prescribers must fax the completed and signed application • Applicant will be eligible to receive vaccine for up to one year • Patient can receive subsequent doses of vaccine by having the prescriber complete the dose authorization request form	• Have no third party coverage for Vaccines OR be enrolled in a Medicare Part D Prescription Drug Plan and have spent at least $600 on prescription medicines through your Medicare Part D Prescription Drug Plan during this calendar year • Be an adult, age 19 or older • Live in one of the 50 states, District of Columbia or Puerto Rico • Have a household income within program eligibility criteria
Nutrition supplement	• Calcilo XD powder • Cyclinex-1 powder • Ensure • Glucerna	• Providing products at no cost to individuals in need	• Have no healthcare coverage for the requested product and do not have access to alternative sources of coverage or funding. • Review on a case-by-case basis.

All of these factors are time consuming and thus hinder patient assistance programs. Study by Gellad et al. (2011) has found that only 1.3% of seniors who are Medicare beneficiaries reported participating in an industry-sponsored patient assistance program. In response to this problem, many resources are available to help healthcare professionals as well as patients to navigate through the information regarding these programs.

Examples of resources are listed as follows:

- *NeedyMeds*: A non-profit organization aims at helping patients finding the assistance programs they need for medicines as well as health care. The website not only offers database of manufacturer-sponsored and government prescription assistance programs but also database on disease-based assistance programs as well as free- and low-cost healthcare facilities.
- P*artnership for Prescription Assistance (PPA*): PPA is mainly sponsored by America's biopharmaceutical research companies. The website has a list of Pharmaceutical Research and Manufacturers of America (PhRMA) member company programs available for download. Mainly sponsored by industry, PPA's website offers both public and private sponsored patient assistance programs.
- *RxAssist*: This web-based medication assistance resource center also provides searchable database about prescription assistance programs as well as other program related to pharmaceutical access. RxAssist, however, does not operate any medication programs.
- *MEDBANK of Maryland*: It is funded mainly through state and foundation grants, as well as monetary donations from individual sponsors. The organization aims at helping uninsured and underinsured residents of Maryland, who are eligible for patient assistance programs to gain access to brand-name prescription medicines. MEDBANK also offers an in-house pharmacy service to increase the speed at which patients can receive their medications.
- Medicare website: Medicare also provides database of patient assistance program. Patient assistance programs can be searched using drug name. The website provides data on program name, eligibility criteria, benefits offered, contact of the program.

Patient should then check their eligibility criteria for the patient assistance program, sought. The majority of patient assistance programs base their eligibility criteria partially on income level of the patient. Other eligibility criteria used by pharmaceutical companies include patient's insurance status, drug coverage status, and United States residency status. The last factor is crucial for facilities serving recent immigrants or undocumented residents or who are not yet US citizens and who are mostly uninsured or underinsured.

Step 2: Patient completes patient assistance program form and prepares required supporting documentation, for example, proof-of-income documents.

Application Process

The details of the application form and how to complete it vary from program-to-program. Application form provides demographic information on patient, including date of birth, address, financial status as well as disclaimers and disclosures. Patients usually need to submit financial documentation, for example, federal income tax forms, and social security benefit letters. Patient's or guardian's signature is needed to complete the submission. Most applications also need information regarding the prescriber name, office address, contact information and license number of the prescriber. Information pertaining the requested medication including the name, strength and dosage of the medication. Prescriber signature is also required to complete the application process (Needy Meds Organization, 2019; Gilead Sciences Inc., 2019, Nastad Organization, 2019).

Required supporting documentation is needed to test the eligibility of the patients. Thus, proof-of-income documents such as tax returns or social security statement and the prescription and patient's clinical information including International Classification of Diseases (ICD) diagnosis code or confirmation from a physician that the medications are being used for an approved indication of patient assistance program are also usually required by the pharmaceutical company.

To simplify the application process, some health care facilities, for example The University of North Carolina (UNC) Health care system (Mitchell et al., 2018), The University of Texas M.D. Anderson Cancer Center (MDACC) (Felder et al., 2011a) or a smaller private ambulatory care facility like Altamont Internal Medicine and Pediatrics (AIMP) in upstate New York (Sarrafizadeh et al., 2004), have created a systematic approach to deal with a large number of patient assistance programs.

Step 3: Patient submits completed patient assistance program form along with other documents to the pharmaceutical company.

The submission can be done either by fax, e-mail, or an online platform developed by the manufacturers. Some manufacturers require the application with the patient's signature and submission of the original application along with other documents. Pharmaceutical company then reviews the submitted applications. This process normally takes 4–6 weeks.

Step 4: Medicine from Patient assistance program is received by the patient.

To be enrolled in the program requires patient to submit their application directly to a pharmaceutical company's PAP for the medication needed. Once approved, the requested medication will be delivered either directly to the patient or to the physician's office/clinic. Some programs, however, provide voucher for patient to use as a discount at a retail pharmacy.

Empirical Evidence of Impact of Patient Assistance Programs

Involvement of healthcare providers in patient assistance programs process would undoubtedly improve patient access to needed medication as well as better coordination of pharmaceutical care provided. A systematic review of patient assistance programs effectiveness has found that most studies do not consider the use of patient assistance program alone but together with the

enrollment assistance plus some other medication services (e.g., counseling) (Felder et al., 2011b). The study found that patient assistance programs along with enrollment assistance, are significantly associated with an improvement in patient health outcomes for example, patient's glycemic control and lipid control (Felder et al., 2011b).

However, implementing patient assistance programs into the healthcare settings means financial burden to the healthcare facility. Study by Clay and colleagues on costs of patient assistance program implementation showed that clinic need to pay an extra of $81,835 per year or approximately $10.42 for an enrollment in one program. Costs are higher when manufacturers require patient to submit their applications for every single refill (Clay et al., 2007). Mounts and colleagues (2005) have listed costs associated with patient assistance program application process, which includes pharmacy technician time and salary, use of telephone and fax, postal charges and stationeries (paper, ink for printer, copy machine), computer software for patient assistance program management, computer and printer, internet access and usage of area of the facility.

The major costs in patient assistance program are personnel costs. Some organization may decide to use pharmacist while some use pharmacy technician or administrative staff to manage patient assistance program enrollment process. It was estimated by Sarrafizadeh and colleagues that the total pharmacist time needed to process each medication order was approximately one hour per year. Another study found that pharmacists spend an average of 12 h/month while physicians spend 20 h/month on patient assistance program in their healthcare facilities. Other staffs were reported to spend on average 79 h/month on patient assistance program activities (Duke et al., 2005).

Provider-Patient Communication and Patient Assistance Programs Enrollment in United States

Despite its potential to increase patients' access to medication, few people are aware of these programs (Gellad et al., 2011) especially in the vulnerable population, for example, African Americans (Pisu et al., 2010). Given the complexity of patient assistance program enrollment, patients usually acquire this information from their healthcare providers. However, it was seen that provider-patient communication on patients' need for financial assistance is very rare. Study by Wilson and colleagues found that only one-third of elderly who had financial issue in accessing the medication needed discussed the issue with their physician (Wilson et al., 2007). Others have concluded similarly on provider-patient communication in healthcare (Piette et al., 2004; Alexander et al., 2004; Alexander et al., 2003).

Use of Pharmaceutical Company Sponsored Medication Assistance Program in Other Health Care Systems

Report by the Access to Medicine Foundation showed that the use of pharmaceutical company sponsored medication assistance program is not limited to only United States. It was found that 13 multinational pharmaceutical companies have implemented some kind of patient assistance program in at least 45 different countries covering more than 19 cancer medicines (Access to Medicine Foundation, 2017). Example of these initiatives and how each country manage these programs are listedas follows:

Canada

Pharmaceutical manufacturers have also implemented patient assistance programs in Canada to increase access to high cost drug especially cancer drugs. Patient assistance programs mostly are available when the medicines are not reimbursed by government. Some provinces like Ontario have the official guidance on how to procure and dispense unfunded drugs while some provinces like Vancouver does not have any standard consistent approach available (Kletas and de Lemos, 2018).

The situation in Canada is similar to what happen in the United States where the number of these programs has increased over the past few years. The BC Cancer Agency, an organization responsible for setting the cancer care standard in Vancouver has developed an official guidance along with a provincial repository containing information on all programs related to cancer medicines available in the market (Kletas and de Lemos, 2018). The repository is maintained centrally by the Drug Information Services. The drug information pharmacists were employed at the center to identify any new patient assistance programs when it became available. Information on patient assistance programs in the repository includes name of the program, contact information, eligibility criteria, other types of assistance offered (e.g., compassionate use of drug, financial assistance on special laboratory tests and the other financial assistance offered to patient). The funding status of the cancer drugs offering patient assistance programs were classified into four categories (Kletas and de Lemos, 2018):

- Class I: Reimbursed for active cancer or approved treatment or approved indication only
- Class II: Reimbursed for approved indications only. Completion of a special form—Class II Approval Form— is necessary prior for dispensing drugs. In addition, where indicated, approval from Tumor Group Chair or delegate is required for reimbursement
- Restricted funding: Reimbursement for approved indications only. Completion of the Compassionate Access Program application form is necessary to provide the appropriate clinical information for each patient
- Not funded

The BC Care Agency has created a repository to update the patient assistance programs by actively searching for upcoming drug therapy available in the market (Kletas and de Lemos, 2018; BC cancer, 2019). This systematic approach to deal with the changing structure of the patient assistance programs can be applied to other health systems to facilitate better access to information on these programs.

Asia-Pacific

Evidence has shown that even in the healthcare system where patient assistance programs implementation framework is in place, the patient assistance programs are not fully utilized. Given the significant benefits of high-cost innovative medicine, the need to access to these drugs in this region is very high.

Malaysia

Many manufacturer sponsored patient assistance programs are available in Malaysia and they are called patient access schemes (PAS). The numbers of patient access schemes has increased in the past few years. In May 2018, the government issued the guidelines for the implementation of these programs. Patient access scheme in Malaysia is similar to patient assistance program in other countries as it provides medication mostly without costs to patients who have no access to medications.

The unique characteristic of patient access scheme in Malaysia is that the scheme proposed by the industry need to be agreed upon by Malaysian Ministry of Health (MOH). In Malaysia, medications needed to be listed in national formulary so that the government can reimburse them.

The regulation of patient access scheme in Malaysia currently requires pharmaceutical companies to submit information on the drug, the program (program details, start and end date, expected number of patients enrolled in the program, etc.). The committee will then review, assess, and make a decision on approval of the scheme. The scheme that does not get approval by the committee would not operate its program in Malaysia's public hospitals. (Ministry of Health Malaysia, 2018)

The patient access scheme in Malaysia is managed independently by the pharmaceutical company that proposes the program. Several online resources developed by the pharmaceutical companies become available to facilitate the redemption of medication as well as provide healthcare professional to monitor the patients in the program.

Thailand

Thailand achieved its universal health coverage in 2001. Similar to Malaysia, access to medicines in Thailand is mostly through the reimbursement of public health insurance. National list of essential medicines (NLEM) is the reimbursement list used by the three main public health insurance in Thailand. Patient assistance program available in Thailand were mostly for medicines not listed in national list of essential medicine. In this situation, patient out-of-pocket spending becomes the major source of financing these high cost innovative medicines (Tanvejsilp et al., 2019).

Kittirotruchi and colleagues have found variation in the structure of patient assistance programs as well as the application processes and the management of these programs in Thailand (Kittirotruji et al., 2018).

Vietnam

In 2017, the National Assembly of Vietnam adopted a new law on Pharmacy allowing pharmaceutical companies to provide free drugs to healthcare facilities through patient assistance programs (The Union for International Cancer Control's, 2018). The program, however, is sponsored by pharmaceutical company through a special fund. Vietnam Ministry of Health has to approve the patient assistance program before its launch and implementation in the country (Biospectrum Asia, 2018).

International Patient Assistance Programs

The most recognized international patient assistance program is the Glivec International Patient Assistance Program (GIPAP) (Lassarat and Jootar, 2006). The program is an international donation program sponsored by Novartis Pharma AG. The program administrator is The Max Foundation, a nonprofit, nongovernmental organization (NGO). The program aims to facilitate access to imatinib, the innovative treatment for chronic myeloid leukemia (CML) and GI stromal tumor (GIST) for patients in developing countries. It was reported that since program inception in 2001, more than 50,000 patients suffering from CML and GIST in 80 countries have received their imatinib through this program. The program has donated more than 2.3 million monthly doses of imatinib (Garcia-Gonzalez et al., 2015).

Using World Health Organization (WHO) guidance on drug donations(WHO, 2010), GIPAP has developed its own program structure that includes medical and financial eligibility criteria. The eligibility criteria and program structure of GIPAP are quite similar across countries.

The Max Foundation has grown its program to partner with other pharmaceutical companies. The program now includes eight anticancer medications including nilotinib, ponatinib, sunitinib maleate, temsirolimus, crizotinib, dasatinib, and bosutinib. The

program, however, needs participation of volunteer healthcare professional. These healthcare professionals support the application process, documentations, appointment reminders, and requesting and dispensing the medicines.

Future Trends and Challenges

With the advances in health technology and with the new high cost medicines, the number of patient assistance program will keep rising in the future. They are considered as safety net for patients when no other means to provide medicines are available. The concerns include transparency as well as the need for a more systematic approach. This systematic approach should include repository of all patient assistance program, application process, dispensing as well as monitoring process for patients. These programs should also be evaluated objectively, even as more evidence is needed for their impact on patient health outcome, compliance,and financial burden as well as on the health system.

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Pharmaceutical Pricing Policies

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Context

Relevance of Pricing Policies

Ensuring affordable access to essential medicines (i.e. those medicines that satisfy the priority health needs of the population (WHO, 2017a)) is a major policy objective globally (United Nations, 2017). One-third of the world's population; however, is estimated to have limited or no access to essential medicines (WHO, 2011). One of the key barriers is the high price of medicines. In many countries, particularly in low- and middle-countries (LMIC), essential medicines are largely unaffordable for patients who have to pay out-of-pocket (Cameron et al., 2011; Lu et al., 2011; WHO, 2004). Governments have been urged to regulate medicine prices to keep them at a level that is affordable (WHO, 2013). This is done through so-called pharmaceutical pricing policies.

Numerous countries have made progress toward Universal Health Coverage (UHC) which means that all people and communities can use the promotive, preventive, curative, rehabilitative, and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship (WHO, 2018). Many high-income countries have publicly funded, solidarity-based health care systems in place that aim to provide affordable access to needed medicines. With the advance of new medicines (e.g. in the areas of oncology or Hepatitis C) with high price tags in recent years; however, policy makers even in rich countries have been struggling to make these medicines affordable through the solidarity-based health system while not jeopardizing the financial sustainability of that system. High-income countries have implemented a variety of pharmaceutical pricing policies but they are seeking to optimize and develop alternative policies (Expert Panel on effective ways of investing in Health, 2018; Vogler et al., 2017b, 2018b).

Pharmaceutical pricing policies are key because medicines are no normal goods and health care, including pharmaceutical, systems are not normal competitive consumer markets. Patients may be in high need for medicines and health technologies (i.e. they have high price elasticity), medicines can be subject to risks (safety concerns that require responsible handling and use), and there is, sometimes considerable, information asymmetry between the parties involved (e.g. between the prescribing doctor and the patient).

Concepts and Definitions

Prices

A price is defined as "the value component of expenditure" (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016) whereas expenditure combines both volume and value components. The Organisation for Economic Co-operation and Development (OECD) defines expenditure as "the values of the amounts that buyers pay, or agree to pay, to sellers in exchange for goods or services that sellers provide to them or to other institutional units designated by the buyers" (OECD, 2008).

The medicine price is the price related to one or more medicines. It may relate to different market segments (e.g. outpatient or inpatent market, on-patent or off-patent market, prescription-only medicines or nonprescription medicines, orphan medicines, reimbursement segment) and may be defined as different price types.

The price type refers to the stage at which the price is set since the price likely increases as the medicine moves along the supply chain. The MWPP price taxonomy[1] (Vogler et al., 2018c) defines four major price types that are common in the outpatient sector of countries with solidarity-based health systems:

- Ex-factory price (synonyms: manufacturer price, ex-manufacturer price, and manufacturer's selling price): the price at the level of industry, charged by a pharmaceutical manufacturer.
- Wholesale price (synonyms: pharmacy purchase price, pharmacy purchasing price): the price charged by wholesalers to the retailers (usually community pharmacies); it is based on the ex-factory price and additionally includes any remuneration for pharmaceutical wholesale (e.g. in the form of a wholesale markup or a wholesale margin).
- Pharmacy retail price (synonyms: consumer price, public price) net: the price charged by community pharmacies to the general public; it is based on the pharmacy purchasing price and additionally includes any pharmacy remuneration (such as a pharmacy markup, a pharmacy margin, or dispensing fee). If net, it does not include value-added tax (VAT) or other taxes.
- Pharmacy retail price (and synonyms) gross: The pharmacy retail price including VAT and/or other taxes.

Further price types such as Cost Insurance Freight (CIF), the tender or procurement price, the hospital price and the reimbursement price exist (Vogler and Martikainen, 2016). The latter describes the maximum amount paid by a third party payer (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016) since in many publicly funded health care systems the price of medicines eligible for reimbursement is only partially covered by the public payer and patients have to cover the remainder (Vogler and Martikainen, 2015).

While the MWPP price taxonomy relates to high-income countries with price regulation, there might be more stages (and price types) in non-price regulated settings. The World Health Organization/Health Action International (WHO/HAI)

[1] MWPP stands for manufacturer price, wholesale price, pharmacy retail price net, and pharmacy retail price gross. It can also be read as referring to the actors involved: manufacturer, wholesaler, pharmacy, and patient.

methodology to measure medicine prices, availability, affordability and price components (WHO and HAI, 2008) defines five stages:

- First stage: manufacturer's selling price (MSP), which is the price the manufacturer charges for the medicine, and/or the CIF price for imported medicines. The latter reflects the costs of insuring and shipping the medicines to the countries of destination; there are different shipping terms (such as Ex-Works, Free on Board, and Delivered Duty Unpaid) that vary with regard to the split of costs between seller and buyer.
- Second stage: "landed price" that describes the cost of a medicine after it has arrived in a country, has cleared all customs and import requirements and is then supplied to the main distributor (e.g. the importer, the wholesaler or a Central Medical Store). The landed price contains the import tariffs, inspection and port charges (including costs for quality control testing), importer's markup, local transport costs and any national taxes that are levied on the medicines purchased by the importer or supplier as add-ons to the MSP or CIF.
- Third stage: wholesale selling price or Central Medical Stores price. This price component contains any wholesale markups added by the wholesaler (or Central Medical Stores) as well as regional or state taxes levied at this stage and transport costs to move goods from the wholesaler to the retailer.
- Fourth stage: retail price (in the private sector) and dispensary price (in the public sector). A major component adding to the previous stage is the retail markup that pharmacies and other retailers add to cover their costs, including their profit. Additionally, local or town taxes may be levied at this stage.
- Fifth stage: "dispensed price" which contains the sales taxes such as a value-added tax (VAT) or a general sales tax (GST) and fees (e.g. a dispensing fee) that are collected when the medicine is dispensed.

Similarities between the two taxonomies are obvious. The major difference between the MWPP price taxonomy and the WHO/HAI methodology is that the latter specifies the landed price as a separate price component to account for the different intermediaries that may charge tariffs and that it explicitly considers taxes levied at any stage.

Consideration of different price types is key in the design of pharmaceutical pricing policies.

Pharmaceutical Policies

Governments can take different action to achieve defined objectives. These are referred to as policies or regulation. In the area of medicines, the term "regulation" often relates to issues of patient safety, quality, and effectiveness (i.e. regulatory functions such as marketing authorization, inspection and surveillance of market actors, pharmacovigilance, advertisement, and provision of independent information on medicines to professionals and the public (World Health Organization, 2003), whereas policy or policies usually describe government action that aims to ensure or improve affordable and equitable patient access to essential medicines. The term "policy" (or "policies") is frequently used in the context of setting and controlling medicine prices but the notion "price regulation" also exists.

It is important to note that policies (and regulations) are actions by governments and not by private sector representatives. Price sector actors (e.g. pharmaceutical industry) can develop and implement strategies to achieve their objectives. For instance, a pharmaceutical company can design a pricing strategy that aims to maximize profits (e.g. price discrimination by charging different prices to different countries). The approaches of private sector actors; however, are not policies but strategies and plans. In this chapter, pharmaceutical pricing policies that governments can implement will be described.

Pharmaceutical pricing policies are defined as "regulations and processes used by government authorities to set the price of a medicine as part of exercising price control" (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016). A medicine price, that represents the value component of expenditure, is not the sole element that governments might want to address to reduce pharmaceutical expenditure. For instance, pharmaceutical policies that address volume (e.g. prescribing budgets for doctors) may also be implemented.

In countries with advanced UHC, linkage between pricing and reimbursement (i.e. coverage of expenditure by a third party payer such as a social health insurance/national health service) can be strong. In many countries, the scope of price control relates to the reimbursement market, that is to those medicines that are, at least, partially funded by the state (Vogler et al., 2008, 2018a). As a result, pharmaceutical pricing policies also include reimbursement elements, as their description is shown in the following subsections. The presentation and discussion of pricing policies is split into two parts: on policies undertaken when the price is first set (cf. Section Pharmaceutical Pricing Policies at Launch) and on pricing policies along the supply chain (Section Pharmaceutical Pricing Policies in the Supply Chain).

Pharmaceutical Pricing Policies at Launch

This section presents pharmaceutical pricing policies targeted at the price type that is the first one being regulated (or controlled). This section could also have been entitled "pharmaceutical pricing policies at manufacturer price level" because the ex-factory price is the first price type controlled. In some countries, however, medicine prices are set at the level of the wholesale price (see also Section Distribution Remuneration), so the general term "at launch" appears to be more appropriate. The distinction is made between "price at launch" and further price types along the supply chain (e.g. pharmacy retail price) for which specific pricing policies apply.

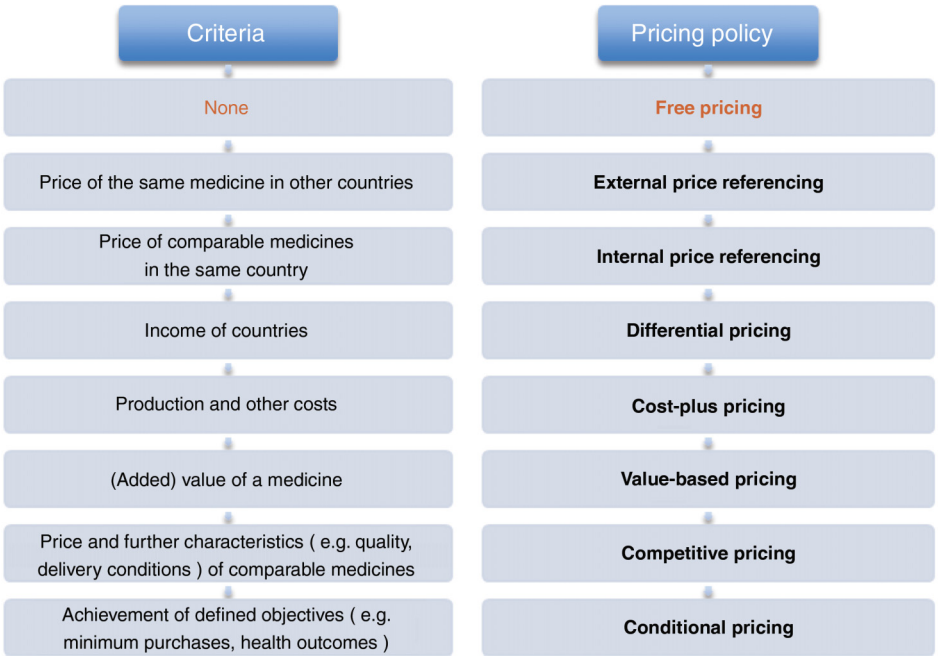

Figure 1 Taxonomy of pharmaceutical pricing policies at launch. Source: The author

Governments may use different criteria to set medicine prices, resulting in different pharmaceutical pricing policies. Criteria include, among others, the prices of the same medicine in other countries or in the same country (policies of external price referencing (EPR) and internal price referencing), production costs (cost-plus pricing) and the (added) therapeutic value of a medicine (value-based pricing). For an overview of key criteria and resulting pricing policies, see Fig. 1.

Each pricing policy has benefits and limitations, and some may be more appropriate for specific medicine groups. The characteristics of major pricing policies at launch will be discussed in the following.

Free Pricing

Free pricing defines a pricing policy in which governments allow pharmaceutical companies to determine the price of the medicine. It could be argued that free pricing is not a pricing policy because it does not relate to any actions taken by a public authority but it is, in fact, government inaction. For completeness, it is, however, described below.

Use

Free pricing is probably the most commonly used pharmaceutical pricing "policy" all over the world. In numerous countries, particularly in LMIC, there is no price regulation in the private sector (Babar, 2015; Cameron et al., 2011). In high-income countries with solidarity-based reimbursement systems (e.g. European countries), medicines that are not reimbursed by a public payer (similarly to the "private sector") tend to be out of scope of government's price control (Vogler and Martikainen, 2015).

Benefits

From a public health perspective, there are no arguments in favor of free pricing since there is evidence that unregulated medicine prices tend to be higher than prices in regulated settings (WHO, 2013). From an industry perspective, there are arguments in favor of free pricing, particularly for nonfunded medicines (private sector, nonreimbursement segment). By leaving medicines to full competition, it was hoped to "help to establish a viable market outside the state sector for some medicines" (European Commission, 2002). It should be remembered, however, that competition is only possible if alternatives exist.

Limitations

Free pricing is linked to the risk of higher prices given the lack of control. Studies have shown that unregulated prices (e.g. in the private sector) were, often considerably, higher than prices achieved through tenders or other pricing policies (Babar, 2015; Babar et al., 2018; Cameron et al., 2009). This is particularly an issue if availability of medicines in the public sector is limited and many essential medicines are only accessible in the private sector against out-of-pocket payments. Unregulated high medicine prices are usually unaffordable for patients and their carers, or they drive them into catastrophic payments (Wagner et al., 2011; Xu et al., 2003). This is why the WHO Guideline on Country Pharmaceutical Pricing Policies recommends that countries "use a

combination of different pharmaceutical pricing policies that should be selected based on the objective, context, and health system" (WHO, 2013).

External Price Referencing

External price referencing, abbreviated EPR and also known under the synonyms of external reference pricing, international price comparison, international price benchmark, and international reference pricing, describes "the practice of using the price(s) of a medicine in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016).

Use

EPR is a commonly used pricing policy. In Europe, for instance, EPR has been implemented in 26 of the 28 Member States of the European Union (all but Sweden and the United Kingdom) and in further countries such as Iceland, Norway, Switzerland, and Turkey (Rémuzat et al., 2015; Vogler et al., 2016a). EPR is also applied in some African countries (e.g. Egypt, South Africa), in some countries in the Asia-Pacific region (e.g. Malaysia, Japan, and South Korea), in some Latin American countries (e.g. Brazil, Colombia, and Mexico) and in Canada (Espin et al., 2014; Schneider and Vogler, 2018). EPR is not a pricing policy solely used in high-income countries, but also in LMIC (Espin et al., 2011, 2014). The number of countries that have introduced EPR has increased over time.

EPR is predominantly used for on-patent medicines that are subsidized by the state and applied in the outpatient sector (Espin et al., 2014; Leopold et al., 2012b; Toumi et al., 2014; Vogler et al., 2016a).

Benefits

There is evidence that EPR has been able to lower medicine prices (Filko and Szilagyiova, 2009; Håkonsen et al., 2009; Leopold et al., 2012a; Merkur and Mossialos, 2007; WHO, 2013; Windmeijer et al., 2006). EPR's effectiveness appears to be strongest immediately after its implementation but it tends to "fade out" after some time (Vogler et al., 2016a).

EPR has been described as "a relatively simple and easy-to-apply system" (Espin et al., 2011). While it does require some effort and capacity (see below), it is fair to note that EPR can be implemented with fewer investments compared to other policies such as value-based pricing. Furthermore, it may be assumed that use of EPR in many countries all over the world has likely contributed to its introduction in other countries since policy makers may consider EPR's popularity as a proxy for its effectiveness. In any case, many countries have gained experience with EPR that they can share with other countries.

In general, pharmaceutical pricing policies can be designed in different formats, and this is also and particularly true for EPR. In practice, countries have opted for different methodological designs (Espin et al., 2014; Leopold et al., 2012b). Simulations have shown that changes in the methodology (e.g. consideration of discounted prices, regular price revisions, and different methods to calculate the benchmark prices) can impact medicine prices achieved through this policy (Toumi et al., 2014; Vogler et al., 2016a).

Limitations

Major limitations concern the availability of medicines on the market and price transparency (and, as a result, limited negotiating power of payers).

Delays in market launches of medicines, often of considerable duration, were observed in countries that have lower price levels or smaller market volumes. To avoid lower benchmark prices calculated through the EPR methodology, pharmaceutical companies are incentivized to launch medicines first in countries with higher prices, and delay, or not launch, in lower-priced countries (Danzon and Epstein, 2008; Danzon and Towse, 2003; Danzon et al., 2005; Espin et al., 2011; Kanavos et al., 2010; Kanavos et al., 2017; Kyle, 2007; Rémuzat et al., 2015; Stargardt and Schreyögg, 2006; Toumi et al., 2014; Vogler et al., 2016a).

EPR's capacity to robustly inform policy makers about the price situation in other countries is strongly distorted by the fact that "real" prices are frequently not known. Confidential discounts granted by industry to public payers are common, particularly for high-priced medicines (Morgan et al., 2017; Vogler et al., 2012). By referencing official list prices instead of real discounted prices, payers risk overpaying (Bouvy and Vogler, 2013). This information asymmetry also limits their negotiating power, for instance in a potential follow-up negotiation, since they are not on an even level playing field with the pharmaceutical industry that has the full picture of the prices in all countries where the medicine is marketed. There is no evidence that payers actually have got "the best deal" as suppliers pretended to offer to them (Vogler and Paterson, 2017).

Finally, it should be acknowledged that EPR, though "simpler" than other policies still requires capacity-building to ensure the performance of high-quality EPR. The methodological design should enable the achievement of the intended policy objectives and should contain solutions for challenges (e.g. missing data because medicines are not yet marketed in some countries, exchange rate volatility) (Kanavos et al., 2010; Vogler et al., 2016a).

Internal Price Referencing

Internal price referencing is defined as the practice of using the price(s) of identical medicines (which corresponds to level 5 of the Anatomical Therapeutic Chemical classification system (ATC) of the WHO) or similar products (ATC 4 level) or even therapeutically equivalent treatment (not necessarily a medicine) in a country to derive a benchmark or reference price for the purposes of setting or

negotiating the price or reimbursement of the product in a given country (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016).

A prerequisite for internal price referencing is availability of comparable medicines. Thus, internal price referencing is usually implemented after patent expiry of a substance when generic or biosimilar medicines enter the market.

One variant of internal price referencing is a so-called generic (or biosimilar) price link. This policy refers to the practice of setting the price of a generic (or biosimilar) medicine in relation to the originator medicine, usually at a certain percentage lower than the originator price. Another internal price referencing policy is a so-called reference price system (RPS). In a RPS, identical medicines (ATC 5 level) or similar medicines (ATC 4 level) are clustered in a reference group. A third party payer funds a maximum amount (=reference price), while the patient must pay the difference between the reference price and the actual pharmacy retail price of the medicine, in addition to any co-payments (e.g. prescription fee, percentage co-payment of the medicine price).

Use

Internal price referencing is in place in many countries with solidarity-based pharmaceutical reimbursement systems, in the form of a price link and/or a RPS. In Europe, for instance, 22 of the 28 European Union (EU) Member States have a RPS (all but Austria, Cyprus, Luxembourg, Malta, Sweden, and the UK) (Gombocz and Zimmermann, 2017). A price link, however, between a biosimilar and its reference product is less common. According to a study relating to 2016 data, 30 out of 42 surveyed countries (40 countries of the WHO European region, Canada, and South Africa) reported having a generic price link in place but only 15 of them also applied this link policy to biosimilar medicines (Vogler and Schneider, 2017).

Benefits

The implementation of internal price referencing is rather easy. It is a policy that ensures, by definition, lower prices of alternative medicines. In addition, an RPS encourages patients to ask for lower-priced medicines because they would otherwise be charged higher co-payments for high-priced medicines. For private sector actors (e.g. industry), internal price referencing increases planning security because, in case of a price link, for instance, they know in advance the price that will be set as the extent of requested price difference is stipulated in law.

Limitations

Internal price referencing is a rather static method that does not fully exploit the efficiency potential of lower-priced medicines. It would, therefore, be important to accompany the pricing policy with further measures that target the volume with a view to increasing generic uptake. Lower prices will only be able to reduce the pharmaceutical bill of public payers if lower-priced medicines are utilized. Demand-side measures such as prescribing by International Non-Proprietary Name and generic substitution can support the effectiveness of internal price referencing (Kaplan et al., 2016). An exploratory study of a few medicines in European countries showed that differences between originator and generic prices were higher in countries that had implemented competitive pricing policies in combination with demand-side measures to enhance generic uptake compared to countries with more static methods such as a generic price link (Vogler, 2012).

Differential Pricing

In differential pricing, the relevant criterion for consideration is the income of countries. Differential pricing, also called tiered pricing, is based on the idea of having different prices for different purchasers (in the case of medicines, they are public purchasers representing countries of different income levels).

Sometimes, differential pricing is also referred to as "price discrimination" or "Ramsey pricing". These terms relate to situations in which pharmaceutical companies achieve optimal pricing (from a business perspective) by differentiating markets according to purchaser demand elasticity. Ramsey pricing is thus a commercial strategy used by marketing authorization holders and not a government policy. As government action, differential pricing describes a cross-country policy of setting the price of a medicine in accordance with the ability-to-pay and/or economic situation of different countries involved, based on coordinated decisions taken by national governments or by international organizations. Alternative names for such differential pricing approaches are equity pricing (Rovira, 2013) and minimum-level pricing (Mossialos and Dukes, 2000).

Use

Differential pricing has mainly been used in LMIC. It tends to be limited to a few therapeutic areas (e.g. HIV/AIDS, malaria, and tuberculosis) or specific products (vaccines). Apart from these medicine groups, differential pricing has not been widely used for other essential medicines. Purchasers are frequently international organizations such as United Nations (UN) agencies (e.g. UNICEF, PAHO, and UNFPA) and programs as well as initiatives such as the Global Alliance for Vaccines and Immunization (GAVI) or the International Drug Purchasing Facility UNITAID. In a few cases, particularly related to middle-income countries, national governments have been involved in differential pricing (Babar and Atif, 2014). More recently, differential pricing has been implemented to increase access to medicines for noncommunicable diseases, mainly as part of public–private partnerships to improve access (Access and Affordability Initiative, 2018).

Benefits

This policy has sometimes been effective in ensuring patient access. For instance, there were indications that for some least-developed countries access improved in situations in which medicines would otherwise have been unaffordable (Babar and Atif, 2014; Moon et al., 2011; Yadav, 2010).

Limitations

Differential pricing is not an appropriate policy to lower medicine prices since its major aim is to improve access. Studies showed that generic competition was more effective in reducing prices than differential pricing (Moon et al., 2011; Waning et al., 2009).

Further limitations of this pricing policy relate to its methodology: differential pricing (if it were applied as a collaborative approach of governments) requires from the involved countries an agreement of principles, mechanisms, and rules. Common understanding of the procedure (e.g. the extent of markdowns or markups to reflect different ability-to-pay levels of countries) has to be reached. In addition, the issue of how to set the starting price needs to be settled.

Given high price tags of some medicines in recent years, it has been discussed whether, or not, high-income countries could also use differential pricing. A study (Vogler et al., 2016a) exploring the feasibility of introducing differential pricing as a collaborative policy of EU Member States concluded that, though commonly mentioned limitations (existence of EPR and parallel trade) could be addressed, differential pricing appears to be an unrealistic option in the EU for political reasons since it would require high political commitment from all 28 Member States to agree on principles.

Cost-Plus Pricing

Cost-plus pricing is a policy that determines a medicine price by taking into account production costs, promotional expenses, investments into research and development (R&D), administration costs, overheads, and profits. Prices are based on information on the costs incurred provided by the marketing authorization holder plus a profit margin considered "reasonable".

Use

Use of cost-plus pricing is known from several countries all over the world. It is predominantly applied in LMIC. Cost-plus pricing is used, for instance, in Vietnam, China, Sri Lanka, Bangladesh, Iran, and Pakistan. The number of countries using cost-plus pricing; however, has been decreasing as some countries (e.g. India, Colombia) have discontinued applying this pricing policy (Nguyen et al., 2014; WHO, 2013). In the European region, some countries (e.g. Cyprus—for locally produced generics, France, Greece, Spain, Slovakia, and Turkey) used cost-plus in their pricing decisions two decades ago (Kanavos, 1999; Vogler et al., 2008; Vural, 2015), but as of today (2018) no EU Member State applies cost-plus pricing.

Benefits

While there is a lack of analytic studies on the impacts of this pricing policy, no evidence has been identified to support use of cost-plus pricing (WHO, 2013).

Limitations

The WHO Guideline on Country Pharmaceutical Pricing Policies advices not to use cost-plus as an overall pharmaceutical pricing policy (WHO, 2013). As a major limitation, public authorities depend on the pharmaceutical company's information about their costs. This could incentivize marketing authorization holders to engage in the "manipulation of costing data" (WHO, 2013) and could lead to higher prices. Obtaining independent information is very difficult and practically impossible for many governments.

Value-Based Pricing

Value-based pricing (VBP) describes an approach in which the "value" that a medicine offers determines the price. But a clear and generally agreed definition of the VBP policy is missing (Garner et al., 2018). In a narrow interpretation (in the context of the English National Health Service/NHS), VBP has been defined as "(the price) that ensures that the expected health benefits [of a new technology] exceed the health predicted to be displaced elsewhere in the NHS, due to their additional cost" (Claxton, 2007). Applying a broader approach of understanding, any policy linking the price of a medicine to its added therapeutic benefit could be considered to fall into the VBP category. The assessment of the value of new medicines can account for different dimensions: improvements in length and quality of life, comfort of use, cost savings in other parts of the health system, and gains in labor productivity for patients and carers. It can be focused on the health care system or be applied to a broader societal approach (Paris and Belloni, 2013).

To assess "value", pharmacoeconomic evaluations and health technology assessments (HTAs) are performed. A key pharmacoeconomic method in this respect is the cost-effectiveness analysis (CEA) in which an incremental cost-effectiveness ratio (ICER) is determined. Usually, the quality-adjusted life years (QALY) approach is applied to assess the benefits of a health care intervention (including medicines). In general, an intervention is considered cost-effective if the ICER (e.g. price per QALY) is below a predetermined threshold.

In the European context, HTA is defined as "a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value" (EUnetHTA, 2018). It has been stressed that HTA is a tool to support pricing and reimbursement policies, but it is not a policy. HTA offers evidence to support prioritization, but it is up to policy makers to appraise the findings from HTA (Patera and Wild, 2014). In contrast to the concise definition of HTA in Europe, a broader understanding of HTA is found in other regions of the world, especially related to LMIC where HTA is understood as "a systematic approach to evaluate the properties, effects, and impacts of health technologies or interventions" (World Health Organization, 2015).

Use

Countries in which pharmacoeconomics play a major role in setting medicine prices are Australia, New Zealand, Canada, Sweden, and the UK. Australia was the first country to require pharmaceutical companies to provide economic data in their application for inclusion of new medicines in the Pharmaceutical Benefits Scheme (PBS); the first set of formal pharmacoeconomic guidelines was published in 1992 (Henry, 1992; Langley, 1993). In 1993, the Pharmaceutical Management Agency (PHARMAC) in New Zealand and the Canadian Agency for Drugs and Technologies in Health (CADTH) published pharmacoeconomic guidelines for their processes (Davis, 1993; Detsky, 1993). Sweden introduced a VBP system (in the narrower sense) in 2002: with pricing and reimbursement processes being completely integrated, eligibility for reimbursement is assessed against three criteria: the human value principle to guard against discrimination of individuals, the need and solidarity principle that gives priority to those in greatest need and the cost-effectiveness principle (Pontén et al., 2017). England has been applying pharmacoeconomic principles for years. It wanted to move to a full-fledged VBP scheme in 2014 (Claxton et al., 2011) but this plan was eventually not implemented (Rafferty, 2014). Still, England continues applying a value-considering approach in pricing and reimbursement (value-based assessments). Many further European countries also consider pharmacoeconomic evaluations and HTA (Paris and Belloni, 2013; WHO Regional Office for Europe, 2015). In some European countries, HTA is applied for all new medicines and in others for medicines with uncertain clinical benefits or expected high budget impacts. At least one HTA institution is in place in many European countries (WHO Regional Office for Europe, 2015).

Benefits

With VBP, the value of new medicines is put into the center. As such, VBP addresses one of the main drawbacks of EPR that has been criticized for not taking into account value considerations.

HTA and pharmacoeconomic evaluations aim to lead to more sound assessments that support policy makers in pricing and reimbursement decisions.

A major element of VBP is the willingness-to-pay (WTP) of public payers. If payers disclose their WTP, this could create an incentive for the development of products that generate increased added value (Bouvy and Vogler, 2013; Godman and Gustafsson, 2013). It has been argued that by signaling their public health priorities (e.g. related to R&D), policy makers and payers could become more active whereas the current pharmaceutical policy framework appeared to be supply-driven (Consultative Expert Working Group on Research and Development, 2016; Franken et al., 2012).

Limitations

Overall, VBP is a resource-intensive pricing policy. To perform HTA and pharmacoeconomic evaluations, extensive capacity-building is required. It has been discussed whether, or not, small countries should establish HTA agencies, or if they could use evidence from other countries and translate it into their settings.

VBP offers opportunities to industry for "gaming", in particular in the choice of the comparators and the threshold (Kanavos et al., 2010). In a VBP system with published cost-effectiveness thresholds, marketing authorization holders are incentivized to price up to the threshold (Hughes, 2011).

In theory, a new medicine with a price above the ICER threshold would not be reimbursed, but in practice policy makers may deviate from the ICER threshold, and have done so in the past, in case of unmet medical need, rarity and severity of the disease treated and public pressure (Paris and Belloni, 2013; Simoens et al., 2013).

This tends to support the position that "a 'value-based' pricing model is not viable in many countries because it does not take into account affordability and total cost" (WHO, 2017b). While the importance of informed decisions based on CEA and HTA has been generally acknowledged, risks of using value-based assessments as the sole basis for pricing have been stressed since this does not take into account need, prevalence and affordability (Garner et al., 2018).

Competitive Pricing (Tendering)

Tendering and tendering-like procedures are mechanisms of competitive pricing which can be applied in settings where competition is possible, with multiple suppliers for same or similar medicines (e.g. therapeutic equivalents). In a tendering procedure, "tenders (offers) are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous." (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016). In many cases, it is the (lowest) price that makes a bid most advantageous but other criteria, such as supply conditions, payment terms, frequency of delivery, or packaging can also play a role (Vogler et al., 2010).

Use

Tendering is the key procurement method in the public sector in many countries, including many LMIC (Seiter, 2010). In high-income countries, tendering mainly occurs in the hospital sector; it is done by individual hospitals and hospital groups or through pooling of regional hospital procurement at national level by procurement agencies (Vogler et al., 2010). Use of tendering, or tendering-like systems, in the outpatient sector is less frequent. It is in place in the outpatient off-patent sector in some European countries (e.g. Denmark, Germany, the Netherlands, Romania Slovenia) (Dylst et al., 2011; Kanavos, 2012).

Benefits

Tendering is able to achieve lower prices due to competition. The price-reducing effect of competition has been shown, for instance for HIV/AIDS medicines. In Brazil, the price of HIV/AIDS medicines confronted with generic competition was reduced by 82% over 5 years while prices of medicines without generic competitors remained rather stable, falling 9% over the same period of time. In LMIC, generic competition resulted in a decrease of the price of the AIDS triple-therapy from US$10,000 per patient and year to US $350 within 1 year (T'Hoen et al., 2001).

Limitations

The key argument against competitive policies such as tendering is that these practices could contribute to shortages and nonavailability of medicines, as suppliers are driven from the market.

A study (Vogler et al., 2017a) investigated the impacts of tendering for outpatient off-patent medicines in three European countries (Belgium, Denmark, and the Netherlands). While the study confirmed high savings for public payers due to competitive pricing, it did not identify a withdrawal of companies from the market in the three surveyed countries.

Overall, to mitigate the risk of availability limitations, it has been advised to do "strategic procurement" and maintain a naturally balanced competitive situation (Ferrario et al., 2016). In this respect, a "divide-the-pie" strategy may be more appropriate to ensure a "healthy market" even though the "winner-takes-it-all" principle will likely drive prices down to lower levels.

Conditional Pricing

Conditional pricing describes a pricing policy that links the price of a medicine to specific criteria (e.g. health outcomes, minimum purchases). Conditional pricing falls under a variety of terms and taxonomies. "Risk-sharing" and "pay-for-performance" are commonly used terms to describe such pricing and reimbursement policies (Carlson et al., 2010; Garrison et al., 2013). In the European Union, the notion "managed-entry agreement(s)" (MEA) has been established as an umbrella term for these conditional pricing policies (Ferrario and Kanavos, 2013). A MEA is defined as "an arrangement between a [pharmaceutical] manufacturer and payer/provider that enables access to (coverage or reimbursement of) a health technology subject to specific conditions" (Klemp et al., 2011).

Typically, MEA are distinguished into two categories: either financial-based (or nonhealth outcomes-based) schemes or performance-based (or health outcomes-based) schemes. Financial-based MEA include (price or dose dependent) discounts, price or utilization capping or price-volume agreements. Performance-based MEA comprise, among others, variants such as outcome guarantees (i.e. an agreement where the manufacturer provides rebates, refunds, or price adjustments if the product fails to meet the agreed outcome target), coverage with evidence development (i.e. reimbursement where additional data gathered in the context of clinical care would further clarify the impact of the medicine), and patient eligibility linked to patient registries to measure post-marketing clinical outcomes (Ferrario and Kanavos, 2013).

Use

Conditional pricing (application of MEA) is typically used for new medicines with high prices that are not affordable for public payers. Financial-based MEA are more common than performance-based MEA that are more complex in design. Nearly all high-income countries have implemented MEA, and use of conditional pricing and reimbursement arrangements have also been reported from upper–middle income countries and emerging markets (Babar, 2015; Carlson et al., 2010; Ferrario and Kanavos, 2013; Ferrario, 2016; Garrison et al., 2013; Morel et al., 2013; Neumann et al., 2011; Pauwels et al., 2017; WHO Regional Office for Europe, 2015).

In many cases, MEA are add-on arrangements taken after an initial price has been determined based on other pricing methods, usually EPR (cf. Section External Price Referencing). To agree on a price that payers can afford, a lower (reimbursement) price is negotiated, taking the EPR benchmark as a starting point. The arrangements about agreed conditions, including the discounted price, are usually kept confidential. Pharmaceutical industry has an interest to keep officially communicated list prices high as other countries will refer to them in their EPR application (Bouvy and Vogler, 2013).

Benefits

A conditional pricing arrangement is considered to be beneficial for patients as it facilitates access to high-priced medicines that would otherwise be unaffordable. MEA provide earlier accessibility of medicines through the publicly funded health care systems, even if added therapeutic value has not yet been proven while providing fail-safes if the medicine does not deliver. Thus, they allow the public payer to manage some uncertainty (Ferrario and Kanavos, 2013). This is particularly the case for performance-based MEA that, in combination with patient registries, help collect real-life clinical data.

Limitations

A major limitation of MEA is linked to the confidentiality of data. While MEA allow for the agreement of lower prices than those published, the exact difference in these amounts is unknown. Confidentiality, however, weakens the negotiating power of payers since they have no alternative but to trust industry's promise that they "got the best deal" (Vogler and Paterson, 2017). Manufacturers may systematically ask for higher departing prices in expectation of a MEA (Gerkens et al., 2017). It has been argued that by agreeing to MEA public payers implicitly accept high (list) prices (Vogler et al., 2016c).

While confidential discounts have been in place for a long time, formal use of MEA, particularly of performance-based agreements, has been increasingly observed more recently. As a new tool, MEA have been developed through experimenting and learning-by-doing. No standard methodology for MEA has been implemented. Since particularly performance-based MEA are challenging, and data collection and monitoring of the progress can be time-intensive, payers can encounter high administrative and transaction costs (Adamski et al., 2010; Carlson et al., 2010; Gerkens et al., 2017). The implementation of MEA needs to be accompanied by a clear disinvestment strategy when updated data support discontinuation of funding a high-priced medicine under a MEA. Such a disinvestment strategy; however, can be difficult to implement in reality if patient expectations have been created (Vogler et al., 2017b).

Pharmaceutical Pricing Policies in the Supply Chain

As mentioned above in Section Prices, the price will be increased along the supply chain: the add-ons are wholesale and pharmacy markups or other forms of distribution remuneration as well as taxes, duties, and fees.

Distribution Remuneration

Commonly applied distribution remuneration includes add-ons for pharmaceutical wholesale and dispensaries, usually community pharmacies (also for dispensing doctors and hospital pharmacies that dispense to outpatients, for instance). Remuneration of distribution actors may be regulated, or not; if so, regulation can be limited to specific medicines (e.g. prescription-only medicines, publicly subsidized medicines). Regulation of distribution remuneration defines how distributors and dispensaries are rewarded for their services, for example through a markup (i.e. a defined linear or percentage amount is added on to the cost of a good to create a profit), a margin (i.e. the percentage of the selling price that is profit) or a fee, or of a combination of fees, for the services rendered.

The WHO Guideline on Country Pharmaceutical Pricing Policies recommends that "as part of an overall pharmaceutical pricing strategy, countries should consider regulating distribution chain markups (distributors/wholesalers)" as well as "regulating retail chain mark-ups and fees (pharmacies, dispensing doctors, dispensaries)" (WHO, 2013).

To support the development of this WHO Guideline, a review of remuneration for pharmaceutical distributors was produced. The review concluded that regulation of distribution remuneration as part of a comprehensive pricing policy will probably lead to reduced medicine prices (Ball, 2011). The review also pointed to a lack of evidence on distribution remuneration in general, even of descriptive data. Information on the size and extent of distribution remuneration is mainly available for high-income countries. This suggests that regulation of these price components also contributes to improved transparency. Evidence from European countries seems to support this assumption: In some European countries (e.g. Cyprus, Denmark, Finland, the Netherlands, Norway, Sweden, and the UK) wholesale remuneration is not regulated, and medicine prices are set at the wholesale price level. Wholesale margins are negotiated between the manufacturer and the wholesaler, usually on a confidential basis (Vogler and Martikainen, 2015). For these countries, average wholesale margins are usually not known, even not by public authorities, whereas such data have been published for other countries (Vogler et al., 2014).

Many high-income countries (e.g. in Europe) implemented regressive wholesale and pharmacy markup or margin schemes, in which the add-ons for higher-priced medicines gradually decrease (Vogler and Martikainen, 2015). The WHO Guideline on Country Pharmaceutical Pricing Policies recommends regressive markups or margin schemes rather than fixed percentage markups and margins since the latter provide an incentive for higher-priced products to receive a higher net margin (WHO, 2013).

Still, even regressive schemes are linked to the price of a medicine at previous stages. Distribution remuneration can also be designed independently from the price of the medicine: in a fee-for-service system, public payers specify fixed fees for defined services (e.g. dispensing, consultancy, generic substitution, and night service) in a tariff catalog. Such fee-for-service distribution remuneration has been in place in the Netherlands, Switzerland, and the UK for many years, and, more recently, some further European countries combined a fee (e.g. per prescription dispensed) and price-dependent funding elements of markups and margins to remunerate community pharmacies (Vogler et al., 2014).

Taxes

Additionally, indirect taxes can form part of the final prices of medicines. As shown in the presentation of the various price types in the WHO/HAI methodology to measure medicine prices, availability, affordability and price components (cf. Section Concepts and Definitions), sales taxes can be added at any stage in the supply chain (WHO and HAI, 2008).

A WHO/HAI review on sales taxes for medicines (Creese, 2011) noted that LMIC have increasingly used VAT as a common revenue-raising strategy since the early 1990s. The review considered indirect taxes on medicines as inequitable because, with the amount paid on a certain medicine being a percentage of the prices for everyone, the medicine tax will result in a larger share of a

poor person's income than a rich person's. The review also found that taxation on medicines varied between countries, ranging between 2.9% and 34% in LMIC and between 0% and 25% in high-income European countries (Creese, 2011). Furthermore, many European countries apply a VAT rate on medicines that is lower than the standard rate. Some countries (e.g. France, Ireland, Sweden, and the UK) have different VAT rates for different groups of medicines (e.g. reimbursable/prescription-only medicines vs. non-reimbursable/nonprescription medicines) (Vogler and Martikainen, 2015).

The WHO/HAI review discussed the issue of "taxing for the poor" and suggested applying the principle that "unhealthy products and behavior should be taxed while health-promoting actions and goods should be tax-exempt or subsidized" (Creese, 2011). In line with this principle, the WHO/HAI Guideline on Country Pharmaceutical Pricing Policies recommends that countries should consider exempting essential medicines from taxation and should ensure that any reductions or exemptions from taxes on medicines have the effect of reducing costs to the patient/purchaser (WHO, 2013).

Taxes that account for a considerable part of the medicine price constitute a barrier to affordable medicines for patients in settings (e.g. LMIC) where they have to pay fully out-of-pocket (Cameron et al., 2009; Levison and Laing, 2003). This might result in patients refraining from purchasing needed medicines (Creese, 2011). In solidarity-based high-income countries with public coverage of prices of essential medicines, this might be less an issue. Still, interestingly, during the global financial crisis that hit some European countries hard, an increase in VAT rates on medicines was one of the most frequently applied cost-containment measures, probably because this policy can be implemented rather swiftly compared to other policies (Vogler et al., 2016b).

Conclusions

Pharmaceutical pricing policies comprise a variety of measures. When developing pricing policies for medicines, policy makers are recommended to consider some overarching principles.

1. **Mix of policies**
   Some policies are only applicable, or meaningful, for specific price types and certain medicine groups (e.g. if generic equivalents are available, competitive pricing policies can constitute a feasible option, and there is no need for resource-intensive value-based pricing). The choice of pricing policies may also depend on national health priorities and practical issues such as available resources. It is, however, disadvised to focus on one sole price type or a single market segment and disregard the other price components and medicines. Regulation of distribution remuneration without regulation of either the manufacturer or retail prices is unlikely to lower medicine prices (Ball, 2011). In this respect, it should be reminded that pricing is only one area of the pharmaceutical policy toolbox. Thus, in developing the most appropriate "policy mix", other policies (e.g. volume-impacting policies, reimbursement policies) have to be taken into account as well. For instance, any pricing policy that lowers the prices of generics still does not bring economic benefit to patients (in the private sector) or to a public payer (in a reimbursement system) if higher-priced originator medicines continue to be prescribed and dispensed. Further measures might be required to enhance the uptake of lower-priced medicines; possible (nonprice related) interventions could be the improvement of the quality of generics (in case of quality issues) and to build trust and acceptance of generics with patients, doctors and pharmacists (Kaplan et al., 2016).
2. **Enforcement**
   As for any policy, pricing mechanisms are required to be enforced, as also stipulated in the WHO Guideline on Country Pharmaceutical Pricing Policies: "If regulation of pharmaceutical prices is introduced, effective implementation will be required to ensure compliance (e.g. incentives, enforcement, price monitoring system, and fines)" (WHO, 2013). This involves, for instance, building staff capacity of the pricing authorities and, if need be, targeted stakeholders. Resources might also be required to ensure access to price databases for surveying data needed for EPR, to literature and other databases for performing HTA, to establish a unit that validates price data submitted by marketing authorization holders and/or to regularly perform price surveys, for example in accordance with the WHO/HAI methodology (WHO and HAI, 2008).
3. **Evaluations and reviews**
   Similarly, to ensure sustainable effectiveness of pricing (and further) policies, it is important to regularly evaluate whether, or not, the mix of policies is able, and continues to be able, to achieve the intended policy objectives. A policy that yielded expected results in the beginning might "fade" out its effectiveness over time because the circumstances might have changed and stakeholders have learned to "game" the system (Rosian et al., 2001).
   The above-described pricing policies are applied to set the prices of medicines at their market entry. Pricing, however, is not a one-point-in-time intervention but has to be understood as continuous government action, as part of an effective enforcement strategy. Thus, regular price reviews are advised, with the possibility of subsequent price changes if need be. Sufficient resources and capacity should be made available in advance. It is recommended stipulating details of price reviews (e.g. frequency, scope such as 50 top-selling medicines and methodology) in pricing regulation.
4. **Transparency**
   Last but not least, price transparency should be a major principle. Distortions due to confidential price negotiations and secret discounted prices and their impacts have been discussed (cf. Sections External Price Referencing and Conditional Pricing). It is not solely an issue of EPR and MEA but there is need for transparency in any pricing policy and for all price types (e.g. lack of transparency due to the unknown rebates and claw-back systems between supply chain actors). Transparency is not only required with regard to the outcomes (i.e. medicine prices), but also related to processes: thus procedures of how decisions on prices are taken, and upon which criteria, must be clear. Policy makers should aim to attain the highest possible level of transparency.

The chapter has shown that each pricing policy can be designed in different formats. The methodology that is considered as most appropriate for achieving intended policy objectives should be chosen, and, if needed, adapted after evaluation, for each of the policies.

List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ATC	Anatomical Therapeutic Chemical (classification system)
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CIF	Cost, Insurance, Freight
EPR	External price referencing
EU	European Union
GAVI	Global Alliance for Vaccines and Immunization
GST	General sales tax
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
LMIC	Low and Middle-Income Countries
MEA	Managed Entry Agreement(s)
MSP	Manufacturer's selling price
MWPP	Manufacturer (price), wholesale (price), pharmacy (retail price net) and pharmacy (retail price gross); alternatively: manufacturer, wholesaler, pharmacy and patient
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan-American Health Association
PBS	Pharmaceutical Benefits Scheme
PHARMAC	Pharmaceutical Management Agency
QALY	Quality-adjusted life year(s)
R&D	Research and development
RPS	Reference price system
UHC	Universal Health Coverage
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations International Children's Emergency Fund
USD	United States Dollar
VAT	Value-added tax
VBP	Value-based pricing
WHO	World Health Organization
WTP	Willingness-to-pay

Glossary

Term and possible synonyms	*Definition*
Price	The value component of expenditure. It may relate to different market segments (e.g. outpatient or inpatient markets, on-patent or off-patent markets, prescription-only medicines or nonprescription medicines) and may be defined for different price types.
Price type	The level (i.e. stage in the supply chain) at which the price of a medicine is set.
Ex-factory price (synonyms: manufacturer price, ex-manufacturer price, manufacturer's selling price)	The price at the level of industry, charged by a pharmaceutical manufacturer.
Wholesale price (synonyms: pharmacy purchase price, pharmacy purchasing price, wholesale selling price)	The price charged by wholesalers to the retailers (usually community pharmacies); it is based on the ex-factory price and additionally includes any remuneration for pharmaceutical wholesale (e.g. in the form of a wholesale mark-up or a wholesale margin).
Pharmacy retail price (synonyms: consumer price, public price)	The price charged by community pharmacies to the general public; it is based on the pharmacy purchasing price and additionally includes any pharmacy remuneration (such as a pharmacy mark-up, a pharmacy margin or dispensing fee). It can be gross (including value-added tax and further sales taxes) or net (excluding taxes).

Reimbursement price	The maximum amount of a medicine price that is covered by a third party payer.
Policies (synonyms: policy options, policy measures)	Instruments, tools and approaches that allow policy makers to achieve defined objectives. Policies are government actions (in contrast to strategies of private sector actors).
Pricing policies	Regulations and processes used by government authorities to set the price of a medicine as part of exercising price control.
Pricing (synonyms: price control, price setting, and price regulation)	Government actions to set, monitor, review and adapt the price of medicines.
Free pricing	Pricing policy where pharmaceutical companies determine the price of the medicine they launch.
External price referencing (synonyms: international price comparison, external reference pricing)	The practice of using the price(s) of a medicine in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country.
Internal price referencing	The practice of using the price(s) of identical medicines (ATC 5 level) or similar products (ATC 4 level) or even with therapeutic equivalent treatment in a country to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement of the product in a given country.
Anatomical, therapeutic, and chemical classification	A classification system of medicines where the active ingredients are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Medicines are classified on 5 specified levels (ATC 1, ATC 2, ATC 3, ATC 4, and ATC 5) of which the first level divides medicines into 14 main groups. ATC 2 specifies the therapeutic subgroups (e.g. medicines used in diabetes). ATC 3 and 4 indicate the pharmacological and chemical subgroup, respectively (e.g. oral blood glucose lowering medicines and biguanides, respectively) and ATC 5 is the chemical active substance (e.g. metformine). The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups.
Differential pricing	Cross-country approach of setting the price of medicine in accordance with the ability-to-pay, and/or the economic situation of the involved countries. The pricing decision would be taken in a collaborative approach by the governments of the involved countries or an international organization. There is a difference to "price discrimination" ("market discrimination", "Ramsey pricing") that describes a business strategy of economic actors to segment the market according to the observed demand-elasticity of consumers.
Cost-plus pricing	Pricing policy that determines a medicine price by taking into account production costs, promotional expenses, research and development, administration costs, overheads, and profit.
Value-based pricing	Through this policy authorities set the prices of a new medicine and/or decide on reimbursement based on the therapeutic value that a medicine offers, usually assessed through health technology assessment (HTA) or economic evaluation. In a full-fledged VBP policy, the pricing and reimbursement systems are integrated, and the price and reimbursement decision is taken jointly based on a value assessment.
Health Technology Assessment	A multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.
Tendering	Any formal and competitive procurement procedure through which tenders (offers) are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous.
Conditional pricing	Pricing policy that links the price of a medicine to specific criteria (e.g. health outcomes, minimum purchases). Conditional pricing falls under a variety of terms and taxonomies (e.g. managed-entry agreements, risk-sharing, pay-for-performance).
Managed-entry agreement	An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms and are usually classified into financial-based and performance-based MEA.
Distribution remuneration	Reward for distribution actors (e.g. wholesalers, community) to pay them for their services. Distribution remuneration can take the form of linear or regressive markups (add-ons) and margins that constitute part of the final pharmacy retail price, and of fee(s) for service not linked to the price.
Markup	A defined (linear or percentage) amount is added on to the cost of a good to create a profit. The wholesale markup is the gross profit of wholesalers, expressed as a fixed or percentage add-on to the ex-factory price. The pharmacy markup is the gross profit of pharmacies expressed as a fixed or percentage add-on to the wholesale price.
Margin	The percentage of the selling price that is profit. The wholesale margin is the gross profit of wholesalers, expressed as a percentage of the wholesale price. The pharmacy margin is the gross profit of pharmacies expressed as a percentage of the pharmacy retail price.
Fee-for-service	Payment to a provider (a pharmacy, for instance) for each act or service rendered.

Source: Definitions based on the Glossary of WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, 2016), Adapted; definition of Health Technology Assessment taken from EUnetHTA (EUnetHTA, 2018)

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Development of the Theoretical Concept of Pharmaceuticalization

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Introduction

The aim in this chapter is to provide a roughly chronological overview of the development of the behavioral sciences concept of pharmaceuticalization, its evolving and expanding definitions, parameters, insights, and potential future directions while at the same time offering the reader a way into the research and literature encompassed by this line of enquiry.

For over 40 years, annual global sales of prescription medicines have increased dramatically to USD1.35 trillion in 2017, making the multinational pharmaceutical industry a powerful global economic force (IQVIA Institute for Human Data Science, 2018). Pharmaceuticals are an important element in the therapeutic toolbox for improving health and relieving human (and animal) suffering; however, their use must not go without critique.

In spite of a decline in the development of new medicines and therapies, consumption of pharmaceuticals continues to grow (Abraham, 2010; Busfield, 2015). Ageing populations with complex health needs in developed countries and growing populations in developing countries might account for some of the growth but that is not the whole story. So, why are people taking more medicines than they were two or three decades ago?

Scholars and researchers from sociology, anthropology, and related disciplines have been studying pharmaceuticals and the pharmaceutical industry since the mid-1980s (Abraham and Sheppard, 1999; Braithwaite, 1984; Gabe and Bury, 1988; Gabe and Bury, 1996; Medawar and Hardon, 2004; Whyte et al., 2002), and this work eventually developed into the field of study known today as pharmaceuticalization.

Pharmaceuticalization is an explanatory, anthropological/sociological concept advanced in recent years to capture and direct our developing understanding of the place of pharmaceuticals in society and individual lives. It is a dynamic and evolving theoretical concept with fields of enquiry and definitions that are, necessarily, changing and expanding in depth and breadth. Early debate (see Conrad, 2007, for example) revolved around whether it was even a necessary concept or just a component of the concept of medicalization that originated in the 1970s. Medicalization is *defining a problem in medical terms, usually as an illness or disorder, or using a medical intervention to treat it* (Conrad, 2007, pg 3). More recent scholars (Abraham, 2010; Bell and Figert, 2012; de Camargo, 2013; Gabe et al., 2015), however, have argued that it is possible to *have pharmaceuticalisation without any significant degree of medicalization* (Gabe et al., 2015, pg 193) and that pharmaceuticals are now used beyond the realm of clinical medicine and medical authority for lifestyle and enhancement purposes. Abraham stated that there is

> *a need for the concept of 'pharmaceuticalization' because the empirical phenomena to which it refers cannot be adequately captured or explained by recent revision to medicalization theory* (Abraham, 2010, pg 605).

The Pharmaceutical Person

The term "the pharmaceutical person" was first used in a 1967 film entitled *Drugs in Our Culture* and then again by Emily Martin in 2006 to investigate contemporary US culture in relation to the consumption of medicines from the individual micro level where they might be taken to maintain order or even enhance capacity ("a pill for every ill" (Busfield, 2010)) to the societal macro level where potent *precision-engineered molecules* are produced for corporate profit (Martin, 2006, pg 280).

Martin's article was inspired by a 2003 exhibition entitled *Cradle to Grave* at the British Museum (http://www.urban75.org/blog/thousands-of-pills-cradle-to-grave-by-pharmacopoeia-at-the-british-museum/) in which Susie Freeman (a textile artist), David Crtichley (a video artist), and Liz Lee (a GP), exhibiting under the name of Pharmacopoeia, displayed a work knitting together

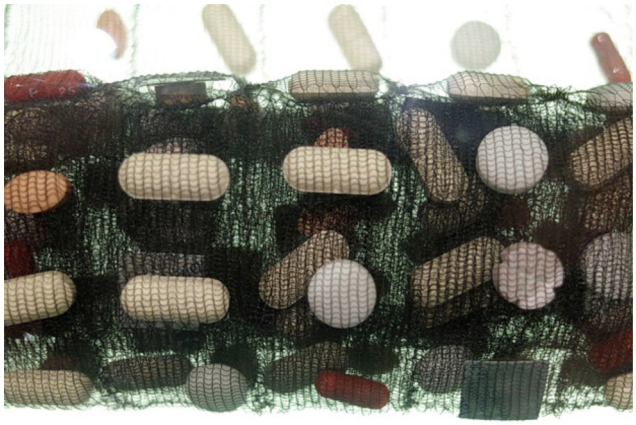

Figure 1 Thousands of pills: Cradle to grave by Pharmacopoeia at the British Museum.

all of the prescribed medicines consumed by a man and a woman in Britain over their lifetimes. Astoundingly, the artists calculated that each person would consume over 14,000 prescribed pills, tablets, and capsules and, if over-the-counter medicines were included, it would be 40,000 (Martin, 2006) (**Fig. 1**).

Martin argued that one way people become pharmaceuticalized (although she did not use that specific term) is when medicines are personified, that is, when individuals use them to produce a new identity, to make them *a better person, an enhanced person or, more precisely, more like the person they really are without the interference* of a particular health condition (Martin, 2006, pg 276). People, she wrote, are now expected to be responsible for reducing their suffering, optimizing their capabilities and maintaining control of their environment. One way they can do this is with the help of doctors, by finding the right combination of medicines to enable that they function in a manner acceptable to society (Rose, 2003).

In addition, Martin argued that companies market medicines in a manner that invests them with personality traits to enhance our connection to them in an attempt to make us better people (*If this drug was a person, what kind of a person would it be?* pg 275). She also suggested that medicines move from being poisons to remedies when their dangers or side effects are minimalized, such as in the use of very fine print or rapid speech of advertisements and the flimsy paper of patient information leaflets. She claimed that the side effects of medicines are *displaced* by being *hidden in plain sight* (pg 283), which enables us to ignore their dangers and make them part of our daily lives (Martin, 2006).

The Pharmaceuticalization of Daily Life

Medicines as part of everyday life, as a concept, was further elaborated upon by Fox and Ward (2008) who picked up on the development and use of "lifestyle" drugs (*profitable medicines for a range of daily activities* pg 856), for, arguably, nonhealth-related complaints such as impotence (e.g., Viagra), hair loss (e.g., Regaine), weight loss (e.g. Xenical), and various other conditions including sleep disturbances, heartburn, and high cholesterol, for example (Fox and Ward, 2008). Pharmaceuticalization of daily life, they suggested, occurs when drugs interact with social and cultural lifestyle factors to normalize daily activities. It involves the domestication of pharmaceutical consumption beyond medical or health professional supervision. Direct to consumer advertising (in the United States and New Zealand) and other marketing activities such as pharmaceutical company detailing and support for patients' groups, access to medicines via the Internet, the ability of pharmaceutical companies to construct knowledge, and the willingness of health systems to fund "lifestyle" drugs are all factors that have driven pharmaceuticalization.

> *Pharmaceuticalisation of daily life is a complex mix of factors that involves the biological effect of a chemical on a human tissue, the legitimacy of a condition as a disease, the willingness of consumers to adopt the technology as a 'solution' to a problem in their lives, and the corporate interests of drug companies* (Fox and Ward, 2008, pg 865).

The Pharmaceuticalization of Society

Moving forward, then, to the end of that decade and John Abraham (2010) wrote about the "pharmaceuticalization of society," a step change metamorphosis from emphasis on the personal to the societal expose of medicines (Abraham, 2010). Drawing on the work of others (Busfield, 2006; Conrad, 2007; Fox and Ward, 2008; Marshall, 2009; Williams et al., 2009) on aspects of disease states and specific medicines, Abraham argued for a theoretical understanding of the concept of pharmaceuticalization, focusing particularly on the prescription drug sector. He defined pharmaceuticalization as

> *the process by which social, behavioural or bodily conditions are treated, or deemed to be in need of treatment, with medical drugs by doctors or patients* (Abraham, 2010, pg 604).

Abraham (2010) proposed five heavily interrelated *biosociological explanatory factors: biomedicalism, medicalization, pharmaceutical industry promotion and marketing, consumerism, and regulatory state ideology or policy* (pg 603). Biomedicalism (the belief that the expansion in drug treatment reflects advances in biomedical science), he stated, partially explains the growth in the use of pharmaceuticals as a consequence of progress in medical science, including research and development within the pharmaceutical industry, increased health needs, and improved diagnostic tools. The relationship between biomedicalism and pharmaceuticalization, however, is not always straightforward because of other interests and drivers. Medicalization [the *process by which nonmedical problems become defined and treated as medical problems* (Conrad, 1992, pg 209, cited by Abraham pg 604)], Abraham argued, is also a big part of the explanation for pharmaceuticalization. Industry activities, such as promotion and advertising of medicines, health professional "expert" endorsement of medicines and the creation of "new" diseases also drive the increased use of pharmaceuticals. Abraham called this the '*medicalization-pharmaceuticalization complex*' (pg 608) and pointed out that until 2010 most sociological debate had revolved around the use of medicines for lifestyle conditions and various social disorders. Consumerism—the transformation of patients into consumers of medicines and their related activities, both adversarial (e.g., citizen and class action related to harm from medicines) and collaborative (e.g., activism around access to medicines, e.g., HIV/AIDS treatments (Epstein, 1996))—explains both growth and (potential) decline in pharmaceuticalization. The final factor to shape pharmaceuticalization, (decreased) state regulation and policy related to medicines as a result of consumer and industry collaboration and lobbying, has made some medicines more quickly available, in spite of doubts about their overall benefits and cost-effectiveness (Abraham, 2010).

Abraham's overall thesis is that pharmaceuticalization has been driven more by medicalization and the activities of the pharmaceutical industry, in collaboration (co-constructed) with consumerism, to expand markets than by improvements in medical science. His summarized his position as follows:

> *. . . pharmaceuticalization in the form of new drugs offering significant therapeutic advance has been* shrinking *in the last 15 years. Expansion in pharmaceuticalization cannot be explained by growth in techno-scientific discoveries of therapeutically significant innovations that meet health needs because no such growth has been forthcoming* (Abraham, 2010, pg 615).

Further to Abraham's realist approach (focus on "real life," facts and scientific methods in the development of knowledge) to the pharmaceuticalization of society, Williams et al expanded the definition of pharmaceuticalization, to cover both the medical and the nonmedical use of drugs, as the

> *translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention* (Williams et al., 2011b, pg 711).

They proposed a framework for analysis of empirical and theoretical work to

> *look at the way that pharmaceutical products are used* outside *the medical domain and explore the broader way in which pharmaceutical* futures *are shaping how we think about innovation, policy and the very meaning of health and illness, therapy and enhancement* (Williams et al., 2011a, pg 730).

Williams et al were the first to coin the phrase *pharmaceutical regime* to capture the complex, evolving, and dynamic nature of the *socio-technical process* of pharmaceuticalization (Williams et al., 2011b, pg 711). They argued for the need to cover all aspects of the process of development, production and consumption of pharmaceuticals, including the networks of people and organizations and their intellectual endeavors, and recent developments in active social resistance to the process from individuals and collectives.

They suggested six areas in which future research might profitably explain why pharmaceuticalization, as a theoretical standpoint, is becoming more and more important:

- *Selling sickness? The redefinition and reconstruction of health problems as having a pharmaceutical solution*
- *Changing forms of governance: globalization and the new role of regulatory agencies in promoting innovation*
- *Mediation: the (re)framing of health problems in the media and popular culture as having a pharmaceutical solution*
- *Patients, consumers, and the life world: the creation of new social identities and the mobilization of patient and consumer groups around drugs*
- *From treatment to enhancement? The use of drugs for nonmedical purposes and the creation on new consumer markets*
- *Pharmaceutical futures in the making: drug innovation and the colonization of health futures* (Williams et al., 2011b, pgs 712–721).

Anthropologists, Bell and Figert, entered the debate around the intersection between medicalization and pharmaceuticalization, seeing them as distinct processes and arguing for a reconceptualization to include *modern and postmodern theories in empirical studies throughout the globe . . .* to address *significant gaps . . . in social science understandings of pharmaceuticalization* (Bell and Figert, 2012, pg 781). In particular, they focused on public health and inequalities in *pharmaceutically mediated health-care delivery* (pg 781) between developed and developing nations. Williams et al responded with a call to develop *a framework that can more fully explain the global complexities and contingencies* of pharmaceuticalization (Williams et al., 2012, pg 2130). They highlighted a number of areas of investigation that are adding to our understanding including resistance to the use of pharmaceuticals by individuals and groups (adversarial consumerism, see the depharmaceuticalization subsection below); the relationship between the medical profession and the pharmaceutical industry; the use of medicines for nonmedical (enhancement) purposes; the economic and innovation challenges facing the pharmaceutical industry; and more equitable global access to medicines and development of drugs for neglected diseases (e.g., pharmaceutical philanthropy as in the work of the Bill and Melinda Gates Foundation).

A one-day symposium entitled *Pharmaceuticals in Society*, at the University of Warwick, UK, in December 2011, enabled leading pharmaceuticalization scholars from a variety of disciplines to *consider the empirical and theoretical questions arising from recent trends in the development, regulation, marketing and use of pharmaceutical products* (Gabe et al., 2015, pg 193), critique previous, and current work and set an agenda for future collaborations. This symposium sparked a series of papers and lively debate culminating in a special edition of the journal *Social Science and Medicine* in 2015.

The special edition contained an eclectic mix of individual studies on specific topics (e.g., drugs, conditions, processes),

> *taking account of both upstream level processes concerning the development, testing and regulation of pharmaceuticals and downstream level processes concerning the meaning and use of pharmaceuticals in medical practice and in everyday life . . . to explore in a sustained way the broad processes of pharmaceuticalization and its consequences for individuals and society* (Gabe et al., 2015, pgs 193-194).

The articles in the special issue (Social Science and Medicine Special Issue Section, 2015) moved pharmaceuticalization theory forward considerably. It is beyond the scope of this chapter to discuss the individual studies (although readers are strongly encouraged to look at them), but the editors provided an overview under five themes (Gabe et al., 2015):

- *Markets for medicines*, for example, over treatment and overuse of medicines (Busfield, 2015) and local and global inequalities in access to medicines (Pollock and Jones, 2015)
- *Regulatory agencies and the state*, for example, globalization and governance on developed world/pharmaceutical industry terms (Sariola et al., 2015), governments as drivers of pharmaceutical innovation, especially in countering bioterrorism and pandemics (Elbe et al., 2015)
- *Patients, consumers, lifestyles*, for example, meanings of medicines in people's lives and identity formation (Dew et al., 2015), consumers as holders of information, consumers as champions and resistors of medicines (Britten et al., 2015)
- *From treatment to enhancement—the use of drugs for nonmedical purposes*, for example, illicit "markets" for prescription medicines (Vrecko, 2015) and the quest for new "diseases" amongst healthy people
- *Pharmaceutical futures in the making*, for example, expectations of pharmaceutical research and development (Brown et al., 2015; Fisher et al., 2015)

This body of work was helpful in enabling us to consider the sociological analyses of the factors contributing to pharmaceuticalization at the societal and individual level, but it hardly dealt with how and why people become pharmaceuticalized or, more recently, possibly depharmaceuticalized.

Living Pharmaceutical Lives

At about the same time that Abraham, Williams, and others were writing about the pharmaceuticalization of society, Ballantyne et al., sticking to the personal, were writing about becoming old as a "pharmaceutical person" in an ethnoculturally diverse community in Toronto, Canada (Ballantyne, 2011). Contrary to the popular perception of the elderly as passive recipients of health care, these researchers showed that older people are active agents who are ambivalent about medicine use, make *thoughtful, reasoned* decisions including nonadherence, and are self-monitoring and responsible for their own health. They suggested that, *the older-person-as-patient needs to be re-conceptualised as a "pharmaceutical person"* (*Ballantyne, 2011, pg 182*).

In a similar vein, research on how medicines are used in the home provided insights into how people see themselves, their personal identities and responsibilities, and their relationships with others including family members and health professionals, all mediated through medicines (Chamberlain et al., 2011; Dew et al., 2014; Hodgetts et al., 2011). The perspective of this team was that:

> *Attitudes change according to why pharmaceuticals are taken and who is taking them, their impacts on social relationships, and different views on the social and natural production of disease, the power of the pharmaceutical industry, and the role of health experts. Pharmaceuticals are tied to our identity, what we want to show of ourselves, and what sort of world we see ourselves living in* (Dew et al., 2015, pg 272).

Dew et al. (2015) concluded that the way people behave around the consumption of medicines could be thought of as a form *pharmaceuticalized governance* (pg 273), with varying responsibilities and moral implications, whether self-imposed or as directed by others.

More recently, Ballantyne et al. (2018) attempted to understand *the formation of the young and middle-aging "pharmaceutical person"* in New Zealand. Investigating medicine use in a prospective, longitudinal birth cohort of children born in 1972/3, they showed that while the proportion of people using medicines did not change from age 26 to 38, the actual quantity of medicines consumed by medicines-users did increase. This led them to speculate about incremental normalization of the use of medicines to mediate life and pose questions about the gradual progression toward polypharmacy in later life. Interpretation of the findings through a pharmaceuticalization lens, they suggested, shows that forces other than therapeutic need and effectiveness are driving increased use of medicines with inherent overtreatment, and even harm, while at the same time blinding users to other means of maintaining health (Ballantyne et al., 2018).

Pharmaceuticalization as a Theorising Concept

Scholars (Ballantyne et al., 2018; Williams et al., 2011b) have argued that one strength of pharmaceuticalization as an *analytical framework for empirical and theoretical research* (Williams et al., 2011b, pg 722) is its value-neutral stance, in contrast to value-laden terms like "disease mongering" (Moynihan, 2002; Moynihan and Mintzes, 2010), which is pejorative, or biomedicalism, which is presumed to be positive and laudable, for example. In actuality, though, these different perspectives simply offer different interpretations of why the consumption of medicines is increasing and the factors that are driving that increase.

Another strength of the pharmaceuticalization thesis is its ability to encompass micro, meso, and macro (downstream, midstream, upstream) level analyses of the places of pharmaceuticals in society (Ballantyne, 2016; Gabe et al., 2015). It enables the development of understandings around which pharmaceuticals are developed, how they are brought to market and promoted, regulated, accessed and consumed and most importantly, why these things happen as they do. It enables investigation of the various actors in a variety of complex networks including asking whose interests are being served. Ultimately, it enables us to explain what is happening, question the status quo, and potentially change what is *disconnected from or even contrary to the well-being of populations* (de Camargo, 2013, pg 845).

Gabe et al. (2015) have pointed out, however, that *the concept does have some limitations* and that *pharmaceuticals are but one part of the contemporary therapeutic landscape* (pg 197). Pharmaceuticals sit alongside and sometimes compete with alternative therapies, traditional healing practices, self-help lifestyle changes, and outright social reform that could relieve human suffering and improve quality of life. Focusing only on pharmaceuticalization dominates scholarship to the detriment of developing understanding in other areas of health and medicine.

Finally, it is worth mentioning Williams et al.'s 2011 plea that scholars not try to *provide some sort of grand theoretical synthesis* but remain open to the multilevel, multidimensional complexities of pharmaceuticalization and maintain *theoretical eclecticism* (Williams et al., 2011b, pg 722). This was more or less reiterated by Gabe et al's 2015 construction of the

> *pharmaceutical regime . . . based on three central features: the close association of medicine with science, the dominance of a science-based pharmaceutical industry with strong links to basic research and the medical profession, and a central role played by government agencies in regulating the process of drug development, production and sale . . . that can be analysed along cognitive, organisation and technological dimensions* (Gabe et al., 2015, pg 197).

Depharmaceuticalization

Depharmaceuticalization can be broadly defined as a decreased use of pharmaceuticals to deal with the problems of living. It might occur at the individual or societal level as a result of resistance to the growth in the use of medicines.

Few if any areas of life once pharmaceuticalized become depharmaceuticalized (Williams et al., 2011a, pg 730), wrote Williams et al. in 2011 but they had already acknowledged that pockets of resistance to pharmaceuticalization, from *the media, government, medicine, patients, and diverse publics*, show that depharmaceuticalization in part might be possible (Williams et al., 2011b, pg 722). They also acknowledged the unevenness in the pharmaceuticalization process that has seen growth and decline over time. Although depharmaceuticalization is rare, it is worth recording here a few possible examples.

Resistance to medicine taking by individuals, framed in biomedical terms as nonadherence, can be thought of in terms of purposeful depharmaceuticalization on an individual level. This includes attempts to minimize intake and cessation of use for various reasons, such as undesirable side effects, social stigma, fears of dependence, and denial of diagnosis (e.g., with antipsychotics and antidepressants) or a general wish to be medicine free (e.g., with many long-term conditions such as asthma and hypertension). These individual depharmaceuticalization decisions are often as a result of complex personal cost/benefit analyses involving experiential knowledge, personal priorities, and social situations (Britten et al., 2010; Pound et al., 2005).

Deprescribing, *the process of tapering, stopping, discontinuing, or withdrawing drugs* (usually in elderly patients), *with the goal of managing polypharmacy and improving outcomes* (Thompson and Farrell, 2013, pg 201), can be thought of as depharmaceuticalization on a professional level.

To balance the power between pharmaceutical industry-sponsored patient support groups, that are able to influence access to medicines and research agendas in line with their own interests (*propharmaceuticalization access-oriented groups*), and the contrasting adversarial consumer activist groups seeking compensation or redress for injury (*depharmaceuticalization injury-oriented groups*), Britten et al. (2015) suggested that the involvement of patients in medicines licensing decisions might address *democratic accountability and citizen-participation in regulatory decision-making* (Britten et al., 2015, pg 295). In a case study, these researchers showed that patients could contribute their own experiential knowledge and critical focus on benefits and risks to the discussion about whether or not to license a medicine. This is a new area for end-user involvement that might add to (de)pharmaceuticalization processes and debates.

Pharmaceuticalized Futures

How pharmaceuticals are used in the future can largely be determined by their use in the past alongside cognizance of current and developing scientific, medical, political, and social trends, so it seems obvious that the technological revolution will play an

important part. Social media, technology-mediated adherence (digital apps and inserted devices to monitor physiological parameters, for example), artificial intelligence, pharmacoprinting (3D manufacture of medicines), (de)regulation, and deprescribing are a few of the influential factors. Pharmacogenetics or personalized medicine is likely to become increasingly important, especially in relation to rare diseases.

One of the main areas to be addressed by scholars and policymakers, however, is the inequality of access to essential medicines and how this might be addressed in the future. As Bell and Figert (2012) noted, pharmaceuticalization *maps onto global patterns of wealth and poverty, and of power and inequality* (Bell and Figert, 2012, pg 779). Will careful theoretical analyses of how this happens provide solutions that aim to alleviate human suffering worldwide not just in wealthy parts of high-income countries?

Another area for attention is the research focus of the pharmaceutical industry and the development of important, as opposed to profitable, medicines to tackle 21st century global problems (Fisher et al., 2015), such as pain, diabetes and communicable diseases including those capable of setting off pandemics, and bioterrorism, for example (Elbe et al., 2015). Governments are playing an increasingly important role in *influencing the development, regulation, sale and consumption of pharmaceuticals designated as "medical countermeasures" to these biological threats* (Gabe et al., 2015, pg 195). Who will set the agenda for the development of new medicines in the future?

Finally, pharmaceuticalization, as a concept, offers a means of understanding people's perspectives on the varied relevance of medicines in their lives. Members of the public will play a more prominent and crucial role in the cessation of the use of ineffective treatments and the development of safer, more efficacious, targeted medicines some of which will be accessed via nonclinical routes. Will social media become a means of reinforcing *existing power relations* (Williams et al., 2011b, pg 716) and further pharmaceuticalization of lives or a channel for increased resistance and public activism or, more likely, both?

> *It is vital . . . to develop a framework that can more fully explain the global complexities and contingencies [by] paying attention to resistance and ambivalence, the ongoing role of the medical-pharmaceutical nexus, the innovation 'crisis' in the industry and the contribution of research in both the global north and south* (Williams et al., 2012, pg 2130).

Conclusion

Pharmaceuticalization is a way of viewing life, health, and our response to illness through medicines. Pharmaceuticals are important in modern therapeutics and human enhancement but their discovery, regulation, production, and use must not go unquestioned. Pharmaceuticalization provides a useful theoretical and analytic framework for the critique of our pharmaceutical futures and how we will choose to live pharmaceuticalized lives.

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Technology and Pharmacy: Theory, Practice, and the Future Vision

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The purpose of this chapter is to examine the importance of technology to pharmacy practice. We do not discuss this relationship using the everyday, reductionist interpretation of "technology" being manufactured objects (such as laptop computers) or technological processes (such as algorithms). Instead, we emphasize its "performative" nature by focusing on the ways in which human performance can be enhanced technologically. To fully understand this issue, we explore how different philosophies of pharmacy practice (for instance, dispensing and pharmaceutical care) discuss, analyze, and treat technology as an issue. From our exploration, we suggest that the existing philosophies fail to fully represent technology and its wide ranging implications for professional activities. In response, we suggest that there is a need for a supporting conceptual framework to help fill the gaps, which we introduce in summary. We also present a cyclical model of planning, action, and fact-finding based upon the principles of action research that may be used to examine pharmacy-related technologies throughout their lifecycle. Finally, we conclude that pharmacy practice is inseparable from technology and now is the time for the profession to rethink its technological worldview.

To meet the primary aim of this chapter, we perform the following tasks in the sections below. First, we provide an introduction to health technology using the World Health Organization (WHO) definition and discuss its implications for pharmacy. Next, we explain how technology may be viewed as "performative" and introduce the concepts of "intrinsic" and "extrinsic" technologies. In third section, we provide a brief history of the use of technology in pharmacy practice. The fourth section introduces the concepts of General Purpose Technologies (GPTs) and Technology-enabled Pharmacy (TEP). Next, we outline the conceptual framework suggested by Baines and Hale (2005) and discuss the importance of its institutional perspective. The sixth section presents a cyclical model of the technological lifecycle based upon the principles of action research. Finally, we conclude that technology is, and will always be, a vital part of pharmacy practice and it is important that further research and development is performed on this topic.

Introduction

The WHO defines "health technology" as the "application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures, and systems developed to solve a health problem and improve quality of lives." This definition is written from a "performative" perspective because the holders of technical knowledge don't just report what they know as education or narratives, but they must be productive and do it efficiently by maximizing input/output ratios (Lyotard, 1986). Therefore, technologies should be viewed as part of dynamic production processes involving both humans and machines, changing in time, evolving within societal institutions, redefining professional roles, shifting technical and economic boundaries. In other words, health technologies are designed to enhance human performance at improving human health and well-being.

The World Health Assembly (WHA) is the decision-making body of the World Health Organization (WHO). In 2007, the WHA recognized that health technologies are indispensable tools for effective and efficient prevention, diagnosis, treatment, and rehabilitation, as well as the attainment of internationally agreed health-related development goals (WHO, 2007). In its report, the WHA specifies that health technologies are both a technical and an economic challenge to health systems worldwide. The WHA adds that investments in health technologies (particularly medical devices) are inappropriate if they: (1) do not meet

high-priority needs, (2) are incompatible with existing infrastructures, (3) are irrationally or incorrectly used, or (4) do not function efficiently. Used wisely, health technologies have their costs and their benefits. Used inappropriately, they are a potentially damaging waste of resources.

The WHA statement suggests that technologies may be viewed from both a technical and an economic point of view (Freeman, 1994). From the former, the successful adoption of new technologies is an engineering problem, which considers the best means of implementing new technical procedures to deliver specified outcomes. In short, what works best to solve specific problems. From the latter, technology adoption is a question of resource use and redistribution. For instance, do the benefits of novel technologies outweigh their costs? This question is addressed by health economists working within the field of Health Technology Assessment (Dawoud and Baines, 2017). Often, economic evaluation studies find that new technologies that are technically feasible are not economically viable. Therefore, all new technologies funded from cash-limited health-care budgets should not only be effective but should be proven to be cost-effective. In other words, they should also be performative. However, recent evidence on the effectiveness and cost-effectiveness of health technologies used in a pharmacy setting has been relatively poor (Baines et al., 2018b).

Pharmacy Practice and Technology

All pharmacy practice relies on some form of technology or another. Both old and new technologies contribute significantly to the technical operation of pharmacy systems. For instance, computerized ordering systems are often employed to maintain medicines inventories (Awaya et al., 2005). Similarly, pharmaceutical care services frequently use software that records patient details and interventions provided (Rossing et al., 2019). As these examples suggest, most pharmacy practice is "technology-enabled" in the sense that the capabilities and the performance of pharmacy practitioners is enhanced by its use. Sometimes, the technologies utilized are mature and long established (they are "vintage"). Other times, they are novel and previously untried (they are "novel"). In this respect, pharmacy is no different to other professions, industries or retail sectors that rely on old and new technologies to supply goods and services for an identifiable gain.

Given that pharmacy is similar to many other economic sectors in its experience of using technology, should pharmacy technology be a separate topic? We suggest that the answer to this question should be "yes" because three fundamental features combine to make the profession a special case. First, the practice of pharmacy is a "craft" (i.e., performed with human hands). Next, the business of pharmacy is a "trade" (i.e., profits are made from providing goods and services). Finally, the practice and the business of pharmacy are based upon identifiable and replicable "routines" (i.e., fixed working patterns and procedures) not employed elsewhere in health systems (Pavitt, 2002).

Combining these features, we can make three foundational statements about pharmacy and technology. First, pharmacy has a "boundary" in the sense that some technical activities are performed by the profession and others are not. Activities that do not involve pharmacists are usually considered to be outside of current pharmacy practice. For instance, pharmaceuticals supplied by dispensing doctors. Next, the practice of pharmacy is "technology-enabled" in the sense that the routines employed for dispensing, pharmaceutical care, counter sales and other professional activities all involve technology. There are very few working practices that do not involve technology somewhere in their procedures or processes. For instance, face-to-face pharmaceutical consultations are usually supported by Information and Communications Technologies (ICTs) that book appointments, record patient details, claim reimbursement, update medical records, order and cancel drugs (Jawla and Rai, 2018). Finally, the routines that define pharmacy as a separate profession must, to be successful, generate resources and reimbursement from health systems commissioners and payers or patients and members of the public. As an example, pharmacists worldwide could support medication switches to newly emerging smart inhaler technologies (Mohammadi, 2018). As yet, there are no examples of health systems or patients paying pharmacists for this type of input. As this example suggests, technological advance not only depends upon invention and innovation but also on appropriate and timely resourcing for the pharmacy profession.

Exploration of the Foundational Statements, Technology, and Pharmacy Practice

An exploration of the foundational statements outlined above may help illuminate the nature of the relationship between technology and pharmacy practice in three ways. First, changes in technology (such as the adoption of novel technologies and the retirement of vintage technologies) will shift the boundaries of pharmacy practice. For instance, advances in robotics could eventually remove, or radically diminish, pharmacist involvement in the dispensing process (Barrett et al., 2012). Consequently, the boundaries of pharmacy practice may shift inwards like they did when industrial drug manufacturing killed compounding as a professional routine (Baines, 2014). Next, changes in technology will also alter what pharmacists do as a profession. For instance, the Internet of Things (IoT) could revolutionize medicines adherence, creating demand for a new specialism, "medicines adherence pharmacy"(Alex et al., 2016). As a result, new methods, technologies, and procedures could combine to create new working routines within pharmacy's shifting boundaries (Strickland-Hodge et al., 2018). Finally, what is technically feasible may not be affordable. As an example, smaller pharmacies serving deprived areas may be unable to afford large-scale robotic dispensaries. Therefore, pharmacy is likely to evolve in a "second best" technological world where funding arrangements and routines mismatch new technical opportunities and the shifting boundary of the profession. Given this situation, a concern with pharmacy technology should, therefore, be a concern with finding the optimal funding and organizational arrangements for

pharmacy practice. However, policies related to pharmacy profession and practice often lag behind the opportunities available to the profession (Kay and Baines, 2017).

What is Technology?

The term "technology" is commonly used to refer to manufactured objects (such as mobile phones) or technological procedures (such as Artificial Intelligence) used by human beings either for their own personal ends or for the production of goods and services for sale (Feenberg, 1991; Vyas et al., 2018). However, this definition reduces the meaning of the concept to the objects and the procedures themselves, while excluding the wider dynamic surrounding their application. For instance, a novel phone app designed to remind patients to take their medicines may be described as a new technology (Car et al., 2017). In practice, the successful use of this innovation by patients may require pharmacist input into associated working processes (such as setting up, regular communications, reviewing, safety checking, and the like). In its truest sense, technology is not just manufactured objects and technological procedures, but also incorporates human inputs and clearly defined operational processes.

An exploration of the etymology of the term "technology" is helpful in clarifying how the word should be applied in a pharmacy context. Technology derives from the Greek word "techne," which means "art, skill, cunning of hand," but also has the implication of "craftpersonship, craft or art." This definition implies that technology is employed by practitioners who develop niche skills in applying specific working practices (Puech, 2016). For instance, pharmacists are experts in the processes surrounding the use of pharmaceutical objects and procedures. Over time, the acquisition and application of practical competencies and technical knowledge creates identifiable groups of practitioners who organize into "crafts" (i.e., occupations or trades requiring skill with the hands). For instance, the widespread consumption of pharmaceuticals by millions of patients worldwide is handled by the profession (craft) of pharmacy, with its specially educated and trained workforce of medicines technologists commonly referred to as "pharmacists." Using this line of reasoning, it is clearly the case that the practice of pharmacy is a craft-based skill, and the profession is defined by the technologies it employs.

As the history of pharmacy demonstrates, technology is not just manufactured objects or technological procedures, but encompasses the dynamics of human performance within identifiable working processes. Following this logic, Baines et al. (2018a) defines "technology' as the "dynamic clustering of techniques, methods, skills, and processes used in the production of goods or services or in the achievement of outcomes that deliver desired benefits for consumers." This dynamic clustering suggests that the relationship between human behavior and technology is "performative," which implies that the human use of technologies evolves over time and is not fixed, *a priori*, but is ceaselessly shaped in social performances that are not routine or matter of fact. Applying this logic, pharmacists may be seen as working within an evolving dynamic of operational methods that shapes the nature of their professional performance. If technological practices alter, the performance of pharmacy practice changes. As our third fundamental feature suggests, the practice and the business of pharmacy are based upon identifiable and replicable "routines" that will evolve as technology changes. For this reason, understanding the nature of technology is a vital prerequisite to generating insights into the possibilities and opportunities that technological advances can offer the profession.

To help understand how technology could create new possibilities and opportunities for pharmacy practice, the following two concepts are useful:

1. "Intrinsic technologies" are innovations that improve current production processes, without changing the range of outputs produced.
2. "Extrinsic technologies" are innovations that expand the range of outputs that are producible, but do not necessarily improve the efficiency of existing or new production processes.

Throughout their history, pharmacists have adopted both intrinsic and extrinsic technologies. As an example of the former, barcode technologies are designed to improve the productivity of dispensing, which improves performance without changing what most pharmacies do. In relation to the latter, recent technological advances could make medical screening possible in a pharmacy setting, thus expanding the range of services available to patients (Lowres et al., 2015). As these examples suggest, technological advances can enable pharmacists to do what they currently do better, as well as creating new production opportunities for the profession. In the hands of pharmacists, new technologies can be performative, both enhancing efficiencies and shifting professional boundaries.

Technology in the History of Pharmacy

Throughout their recent history, pharmacists have undertaken three key roles: compounders, dispensers, and (in the last two decades) providers of pharmaceutical care services. Within the emergence of the modern pharmaceutical industry, pharmacists lost their role as the compounders and the preparers of medicines. In the post-war era, dispensing became the main activity for the majority of pharmacists, with "counter-sales" being a supplementary task in community pharmacy (Baines, 2014). With the

publication of Hepler and Strand (1990), pharmaceutical care became a new vision for professional practice, which shifted the emphasis of pharmacy practice away from dispensing toward the provision of patient services.

During their early history, the evolutionary predecessors of modern-day pharmacists (apothecaries, then chemists and druggists) were "technologists" in the sense of "being experts in a particular field of technology." From the medieval era onwards, apothecaries were specialists in using transformative techniques for turning herbal and other ingredients into potions, poisons and medicaments (Anderson, 2018). This expertise was based upon the technique of "compounding," which involves combining or processing appropriate ingredients using specific tools or processes to meet the personal needs of patients or customers (Anderson, 2005). Through this method of combining, the earliest makers of medicines were able to produce a wide range of diverse products. Vela Aulesa (2015, p. 132) discusses their working practices:

> What linked the diversity of their products that, in many cases, the apothecaries themselves made in their workshops? The answer is that they all shared the same production techniques: decoction, infusion, distillation, sublimation, maceration, pulverization, dissolution and conservation in sugar or honey. The apparent diversity of uses concealed great technical uniformity: most compounds were obtained from formulae that involved similar techniques to obtain products made in exactly the same way but varied in their uses.

The quote suggests that apothecaries were directly involved in the manufacturing process, shaping the products with their own hands. Also, the class of practitioners referred to as apothecaries were definable as a group because they shared the same production techniques (Hunting, 1998). Finally, a diversity of products was achieved using highly uniform technical processes or techniques, which we refer to as "routines."

During the 19th century, chemists and druggists in countries such as the United Kingdom, America, and Germany were at the forefront in experimenting with innovations in the emerging field of modern chemistry (Marland, 1987). Their work not only created new medicines but also led to major developments in manufacturing processes outside pharmacy (such as new methods in the production of dyes). In other words, chemists and druggists developed intrinsic as well as extrinsic technologies. These practitioners also responded with fervour to the opportunities offered by the introduction of mass-produced glass (Silverman, 1953). For instance, they filled their shops with mirrors, glass-fronted cabinets, bottles, and carboys, as well as investing in expensive plate-glass windows to attract customers inside (Chemist and Druggist, 1915).

During this time, chemists often had a workshop at the rear of their retail premises, but would also compound or mix preparations in front of customers. In the medicines marketplace, more successful producers would sell their concoctions to other retailers and an industry of branded medicines flourished until the introduction of institutional controls on the sales of such goods. This trade was enabled by the development of railway networks connecting important commercial centers. To further serve their trade, chemists and druggists led the way in innovating new means of formulating final products, including inventing machines for making tablets, creating capsules, and packaging powders. During the early-20th century, they were among the first retailers to experiment with moving shop displays that used electric motors to create moving parts to attract the attention of passers-by.

As the involvement of the profession in chemistry diminished, during the 20th century pharmacists positioned themselves at the forefront of the revolution in mass-produced medicines by stocking their shops with a rapidly growing range of branded drugs. Accompanying this revolution was a rejection of glass as the defining feature of the pharmacy premises. Instead, technological advances in paper and plastics led to boxes and blister-packs becoming the key methods of medicines storage and display. Pharmacists evolved by responding rapidly to the opportunities offered by new waves of pharmaceutical and retail technologies. Today, this process can be seen again with the increasing adoption of robotic and barcodes dispensing, as well as digital Dossett boxes and pill dispensers (Furmedge et al., 2018).

Throughout history, the dual focus on technological advancement and successful retailing has been a defining feature of the pharmacy profession (Scott and Walker, 2018). The rapid introduction of a new wave of digital technologies in coming years will again make apparent the importance of the technology–retailer relationship in pharmacy practice. Innovations such as robotic dispensing, adherence monitoring devices, the Internet of things, and the like will revolutionize dispensing and pharmaceutical care (Baines et al., 2018b). Emerging technologies will create novel opportunities for the profession, which may be a catalyst for a renaissance in pharmacy practice and a redefinition of the primary purpose of community pharmacy premises.

Renaissance of Community Pharmacies Based Upon Emerging Health Technologies

As pharmaceutical care focuses on the development of professional knowledge and skills for individual pharmacists, since 2000 pharmacy premises have largely been ignored as an area of professional concern. In response, Baines (2015a) proposes a renaissance of community pharmacies based upon emerging health technologies. He argues that community pharmacies should become the health-care technology hubs of the future. To make his vision of Technology Enabled Pharmacy a reality, Baines suggests five steps:

1. Refit the "front of house" as a technology hub that allows patients to connect with the pharmacy, local doctors, the health-care system, pharmaceutical companies, charities, other patients and the like;
2. Exploit the time that patients wait for their prescriptions by connecting them to a technology-enabled task, such as reporting on their medicines use, watching an interactive educational program, completing a questionnaire, or being expert patients in research studies;

3. Network the pharmacy hub into the wider health-care community, including providers, patient groups, and private companies (by doing so become the port of first call for patients), and coordinate their care through the pharmacy's technology-enabled network;
4. Retrain pharmacists in health-care technology not just medicines optimization;
5. Educate and enable the public to become technology-enabled pharmacy users.

These steps are important because they suggest that (1) pharmacies could become the focus of technology enablement not just pharmacists, (2) extrinsic technologies may be important to the future development of the profession, and (3) dispensing may become a poorly reimbursed task completed solely to attract footfall so that other technology-enabled services may be provided. As these developments suggest, the opportunities and threats created by the digital age may encourage the pharmacy profession to evolve yet again.

GPTs and TEP

With the ongoing advance of digital, it is vital that pharmacists fully understand the nature of innovative technologies and their potential impact on the profession (Karampatakis et al., 2018). Following the lead of economists and other social analysts, pharmacists could classify technologies into two basic classes. On the one hand, "general purpose technologies" (GPTs) are those that affect an entire economy and have the potential to disrupt the economic life of whole societies (Helpman, 1998). Lipsey et al. (2005) report that there have only been 24 GPTs in history, including the steam engine, trains, electricity, computing, the Internet, artificial intelligent, and block chain. In contrast, "enabling technologies" are innovations that are directly designed to improve the capabilities or the performance of specific users not society as a whole. For instance, telehealth technologies are designed to enable long-distance communications between health practitioners and patients. Such advances can revolutionize care provision, particularly in rural areas, but will not have spill over effects elsewhere.

Normally, GPTs will eventually affect all industries in an economy. For instance, it is hard to imagine any industrial sector not using electricity or information technology (IT), which are considered to be the two most important GPTs (Jovanovic and Rousseau, 2005). In a pharmacy context, this implies that professional working practices will eventually be affected by all new GPTs (for instance, block chain). As major innovations sweep through the economy, the question is not whether novel technologies should be adopted, but when and how diffusion will occur? (Rogers, 2010). In response to emerging GPTs, there is an argument for profession-wide action because the widespread adoption of whole economy technologies may achieve better outcomes if all production units are involved. For instance, most pharmacy bodies support the use of the Internet as a means of individual pharmacies or chains communicating with patients. For example, via social media (Benetoli et al., 2015). The regular use of such technologies ensures that the profession does not lag behind technical developments commonly adopted in other industries. In sum, GPTs can be seen as a special case, especially due to their rare occurrence and disruptive effects.

The Concept of "Technology-Enabled Pharmacy"

Baines (2015a) coined the term "technology-enabled pharmacy" (TEP) to describe the use of intrinsic and extrinsic technologies within a pharmacy setting. The concept of TEP is based upon the notion that technology can improve the capabilities of pharmacists to deliver patient services. As a concept, it is based upon "extension theory," which Lawson (2010) reports conceives of technical objects as "some kind of extension of the human organism by way of replicating, amplifying, or supplementing bodily or mental faculties or capabilities." For instance, enabling technologies could enhance the physical and the mental capacities of working pharmacists, which could increase their incomes and benefit patients. Linking this implication to the notion of intrinsic and extrinsic technologies, TEP has the power to innovate current production processes and to expand the range of outputs pharmacists currently produce.

The above discussion suggests that the impact of GPTs and TEP may be either evolutionary or revolutionary. This may be illustrated using Fig. 1, which shows the relationship between production outputs and costs. Within economics, the operational dynamics that transform the physical inputs of capital, labor, and consumables (i.e., the costs of production) into planned outputs are called "production functions." Production functions for dispensing and pharmaceutical care are outlined by Baines et al. (2018a). Production processes consume inputs in the forms of: (1) labor from pharmacists, technicians, and auxiliary staff; (2) capital investment in premises and production technologies such as automated dispensing; and (3) consumables in the forms of the items used during supply (such as medicines packaging) and pharmaceutical care consultations (such as computing support).

In Fig. 1, the vertical axis shows the outputs derived from pharmacy practice activities such as dispensing and pharmaceutical care. On the horizontal axis, the costs of production are shown. As the model assumes diminishing returns, the relationship between costs and outputs is shown by the curved lines that represent various production functions (PFs). Each PF represents a different package of technology and maps a different relationship between costs and outputs. As the Fig. 1 shows, PF2 is an incremental improvement over PF1. For instance, a new software package for stock control may yield only marginal improvements in dispensing efficiency. In contrast, PF3 is a "technology shock" and represents a major improvement in the outputs that can be produced with existing resources. For instance, pharmaceutical care technologies (such as "smart pill" systems) may greatly enhance productivity. In

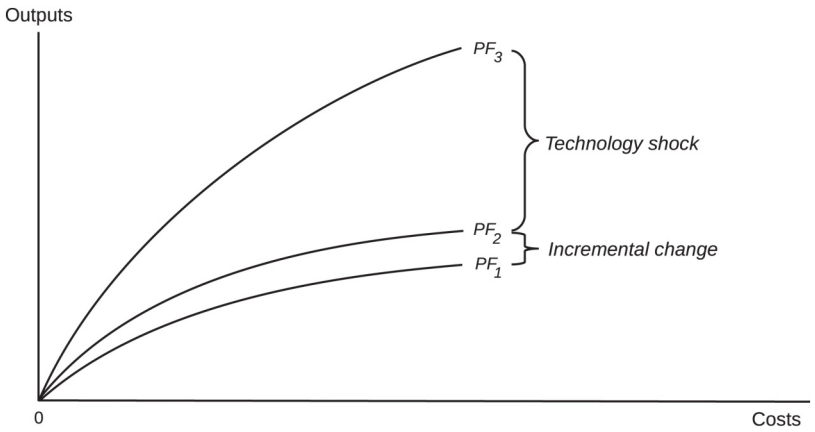

Figure 1 Technology shock verses incremental change.

sum, improvements in productivity are often variable. To secure improvements in performance, pharmacists should pursue small gains that accumulate slowly over time, as well as sudden technology shocks.

Conceptual Framework: Relationship Between Technology and Pharmacy Practice

How the relationship between technology and pharmacy practice is analyzed will often depend upon the conceptual framework adopted. Conceptual frameworks allow researchers to organize ideas about empirical topics. For instance, how should we categorize what we currently know about the monitoring technologies useable in a pharmacy setting? There are several prominent philosophies for analyzing pharmacy practice, notably those for dispensing and pharmaceutical care. Despite their widespread employment, both have limitations in the current context. For instance, the practice philosophy for dispensing focuses primarily on drug supply, while pharmaceutical care was developed in 2000 before the emergence of many new technologies such as the Internet, mobile devices, block chain, and many others. Therefore, pharmacy needs a robust conceptual framework that can truly organize the profession's thinking and knowledge about the ways that technology can and will affect its working practices.

Baines and Hale (2005) outlines a conceptual framework for analyzing how environment, institutions, organizations, and philosophy all influence the ways that pharmacy services are provided. At its core, the framework is based upon a paradigm of thinking developed within economics referred to as "new institutionalism." This approach claims that "history matters" in the sense that current economic opportunities are shaped by the evolutionary paths that economic entities follow. Borrowing a quote from Greif (1998, p.82), the institutional approach suggests that today's pharmacy practice is a product of an "historical process in which past institutional, economic, political, social, and cultural features interact in shaping the nature of contemporary institutions and their evolution." For instance, pharmacists in the United Kingdom became dispensers of medicines (rather than general practitioners) due to a series of unintended events and historical accidents. Because history matters, today's professional arrangements are not based solely upon logical design (Baines, 2015b).

The model in **Fig. 2** represents the conceptual framework suggested by Baines and Hale (2005). Starting at the bottom of the pyramid, environmental factors (such as public funding for pharmacy services and general economic conditions) are the first influence on pharmacy practice. For instance, if governments support technologies that enable pharmacists working in nursing homes, then new roles may be created for the profession. Next, the diagram suggests that pharmacy is governed by a range of "institutions," including laws, regulations, rules, conventions, ethics, and norms governing behavior (Baines and Hale, 2005). Institutions like these limit the innovations deemed suitable for professional use. For instance, the Food & Drug Administration (FDA) regulates the use of novel health technologies, including medicines (Molteni, 2017). Its rules are the

Figure 2 Hierarchy of influences on pharmacy practice.

main institution governing the adoption of digital technologies by pharmacists and other health-care professionals in the United States.

Institutions are important because, as Douglas North (1991) states, they are "the humanly devised constraints that shape human interaction" or, put differently, "the rules of the game in a society." In other words, they are social limits imposed upon technology-enabled individuals. Above institutions in the hierarchy are organizations, which North (1991) defines as "groups of individuals bound by some common purpose to achieve objectives." In order to realize their aims, organizations of individuals must become players of the institutional games governing their activities. For instance, independent and multiple pharmacies may be seen as separate groups of players organized to work for the objective of generating revenue by dispensing drugs within the institutions governing medicines supply. Like most games, technology may be employed to enable players to compete more effectively. For instance, pharmacies could offer coordinated home deliveries using app technologies, which will help them generate more revenue by reaching customers over wider areas than other local pharmacy shops. As rules can be broken, professional and other bodies often police the behavior of players in institutional games. For instance, data protection legislation in many countries imposes penalties on pharmacists who break the rules governing the use of confidential patient information (Gostin et al., 2018).

Although most companies strive to be competitive, they also place limits upon themselves by adopting philosophies that guide their tactics for survival. For instance, most companies now have environmental policies that stop them pursuing profits at any cost. During the 20th century, many pharmacists in the United Kingdom adopted the philosophy of education, professionalism, and fraternity originated by the founder of the Pharmaceutical Society, Jacob Bell. As a result, pharmacy was viewed as a profession not just a trade, which motivated how many pharmacists played the pharmacy game (Holloway, 1991). As time passed, Jacob Bell's practice model evolved, but became less important after the philosophy of pharmaceutical care was launched by Hepler and Strand in 2000. With this change in dominant philosophy came a shift away from dispensing toward patient services as the major concern of pharmacy practice philosophers. In Scotland, this shift led to the emergence of government policy promoting robotic dispensing as a means of freeing community pharmacist time to work with patients (van der Meer et al., 2015). As this example suggests, philosophy of practice is one among a number of key influences that affects pharmacy and its use of technology.

Finally, in the hierarchy, is the practice of pharmacy. This is not the philosophy of practice, but the actions and behaviors of pharmacy practitioners. Because pharmacy is a craft, pharmacists learn by doing, as well as through education and training. In other words, pharmacy practice is a form of "action research." The founder of the approach, Kurt Lewin, describes action research as "comparative research on the conditions and effects of various forms of social action and research leading to social action." In his original paper, he wrote that the method of inquiry follows a "spiral of steps, each of which is composed of a circle of planning, action and fact-finding about the result of the action" (Lewin, 1946). Torbert and William (1981) adds:

> Knowledge is always gained through action and for action. From this starting point, to question the validity of social knowledge is to question, not how to develop a reflective science about action, but how to develop genuinely well-informed action – how to conduct an action science.

As this quote suggests, understanding gained directly from experience may equal or surpass the importance of knowledge learnt from academic education and training. For instance, what practitioners learn from implementing telehealth technologies may be more important than knowledge they can read or be taught (Hebert et al., 2006). In response to this insight, pharmacy practitioners should be guided by a circle of planning, action and fact-finding that illuminates the process of technology adoption, use and decommissioning in their working practices.

Pharmacy Action Research Cycle

As the process of adopting, using, and rejecting specific technologies is dynamic, the pharmacy profession requires a cyclical approach to technological planning, action, and fact-finding. Fig. 3 meets this need by presenting an action research cycle for pharmacy, which embodies the following seven tasks:

1. Scope—The process of technology adoption (or modification) begins with the task of looking for technological advances that could improve or expand production opportunities.
2. Formulate—Next, identified possibilities are expressed as operational blueprints or formulae that include details of how novel technologies may be incorporated into existing (and possibly new) production processes.
3. Experiment—The third task is to test new technological processes under experimental conditions as a means of exploring their performance and safety before widespread dissemination.
4. Reify—Innovations that prove to be promising in controlled experiments may be developed into an actual, concrete procedures useable in practice. These technological processes should have definite forms and functions and be part of identifiable production processes.
5. Implement—Next, reified technological processes are introduced into existing, or innovated, production processes. The ways in which existing production processes are performed may be temporarily modified until new technologies are fully embedded.

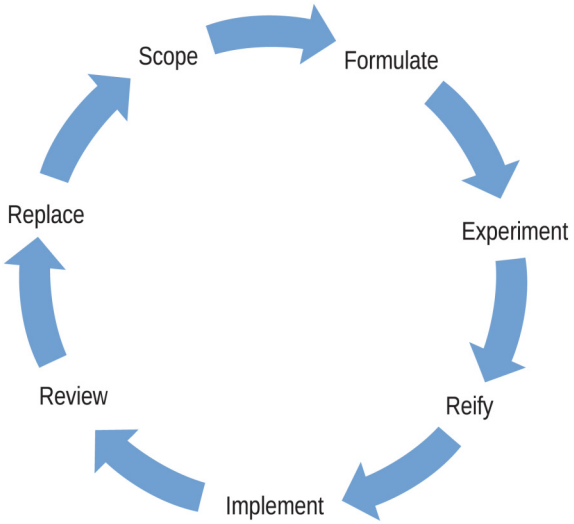

Figure 3 Pharmacy action research cycle.

6. Review—Introduced technologies should be critically evaluated at key stages in their implementation and use. At the beginning, the green light may be given for widespread adoption. At maturity, evidence may suggest that an incumbent technology should be retired.
7. Replace—Finally, technologies that may be replaced with more efficient or superior procedures should be removed from production. However, the need for large-scale capital investment may delay the replacement of some suboptimal technologies.

Together, the above tasks suggest the following: (1) technologies are performative processes that experience complex lifecycles, (2) one-off evaluations like HTA will not capture their true nature, and (3) the use of novel and vintage technologies can be optimized using an action research approach to supporting practitioner learning, evaluation, and choice.

Conclusions

Throughout their history, pharmacists have always been technologists. Their work has led to the development of an untold number of innovations that have benefited the trade of pharmacy and the lives of patients. As well as being inventors, pharmacists have adopted innumerable GPT and TEP technologies developed elsewhere for both general and pharmacy use. With the evolution of the digital age, a new wave of innovations is emerging at a time when the profession is looking for new roles and health systems are seeking to better manage costs. In response, we presented a performative perspective on pharmacy practice and highlighted the importance of taking an institutional approach to analyzing the development of pharmacy-related technologies. After discussing the pertinent issues, we suggested that pharmacists should take an action research approach to understanding the lifecycle of the technologies harnessed by the profession. In sum, we conclude that pharmacy practice is inseparable from technology and now is the time for the profession to rethink its technological worldview.

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Public and Patient Engagement

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Introduction

This chapter describes public and patient engagement and involvement in health and social care and summarizes its progress over the last couple of decades. Definitions of terms that are commonly used to describe public and patient engagement are provided and explanations of the processes for engagement and involvement across various areas of health and social care are described. This chapter focuses on public and patient engagement and involvement in the area of healthcare and acknowledges that there is a large body of work around engagement and involvement in social care. Some reference is made to public involvement in social care, usually referred to as service user involvement. Public and patient engagement and involvement are found in healthcare planning, delivery, evaluation, commissioning, teaching and research, as well as in the wider social context. The achievements and milestones for public and patient engagement and involvement are highlighted and the implications for pharmacy practice and research are discussed. Engagement and involvement of the public and patients in health and social care are part of routine practice across the health and social care landscape and this includes pharmacy practice and research.

The Origin of Public Involvement

Early accounts of the origins of public involvement in healthcare describe the development of a social movement (Morrow et al., 2012; Barnes and Cotterell, 2012; Greenhalgh et al., 2011). Williamson (2010) describes the simultaneous occurrences of: shifting social values, some poor quality healthcare, and a movement in critical sociological research as the start of the patient movement some fifty years ago.

From the health service management perspective it was the introduction of clinical governance in the 1990s in the United Kingdom that placed patient and public involvement (PPI) as a core element of quality in healthcare. Clinical governance offered a strategic framework that ensured systems and processes were in place to support high quality care. Clinical governance was structured in seven pillars including clinical audit, risk management, clinical effectiveness, and PPI (Scally and Donaldson, 1998). Healthcare organizations developed strategies for delivering PPI and healthcare staff were encouraged to involve patients in planning, delivering, and evaluating healthcare (Department of Health, 1999, 2002). The commitment to involving patients and the public across the health sector to effect change was needed because "change will only happen if services are shaped by the people who rely on them" (Glynn et al., 2008, p. 7).

The increase in promoting public involvement sits alongside the drive for professional accountability. Health and social care providers, academic institutions, and research funders have routinely involved public members in service delivery, planning and evaluation, and in policy development and priority setting for well over a decade (Nilsen et al., 2006; Smith et al., 2006; Oliver et al., 2004; Crawford et al., 2002; Boote et al., 2002). Social attitudes have changed and there is not just acceptance but expectation for public involvement in health services.

Parallel activities have taken place in social care and in higher education institutions in the planning and delivery of education and research and in research funding organizations and charities.

The concept of consumerism in health and general welfare was probably the consequence of a political shift with policy makers showing more interest in consumer choice (Beresford and Wallcraft, 1997). As public services developed their consumerist approach, it became usual practice to engage people in the development of services as well as in the delivery and evaluation of these services. This occurred in social care and healthcare delivery but also in education and research organizations and there is now a large body of work demonstrating the growth and potential impact of public involvement in the work programs of health, education, and research organizations. The Evidence Bibliography produced by INVOLVE, an on-line library, contains all the reports and articles about the nature and extent, the impact and reflections on public involvement in research (INVOLVE, 2014).

Over subsequent years the importance and significance of PPI has grown to alter the way in which we work in healthcare. Reflecting the changes in the prominence and value placed upon PPI following a public inquiry, Berwick (2013) stated, "Involvement means having the patient voice heard at every level of the service, even when that voice is a whisper."

Healthcare organizations receive support in their attempts to involve the public through the publication of national guidelines (National Institute for Health and Clinical Excellence, 2008) and through local government Healthwatch organizations (see list of relevant web pages). There is also a moral argument that service users should have a voice in research that may have an impact on their health status (Staniszewska et al., 2011; Smith et al., 2008).

In relation to health research the Department of Health for England's five-year strategy (2006) was for a health research system focused on the needs of the patients and the public and followed earlier strategies that claimed to place user involvement center stage (Ong and Hooper, 2003). It was known that engaging with patients and the public would make research more relevant to peoples' needs and make it more likely for the research recommendations to be put into practice (Frankham, 2009).

There is now an international journal, Research Involvement and Engagement, launched in 2015 that is coproduced by an involved and engaged patient and carer and a researcher (Stephens and Staniszewska, 2017). A reflective paper in 2017 after two years of publication contemplated the impact of their publication as having stimulated wider interest in research about public involvement and shared decision-making, on a global scale. Recent published research has explored the extent of public involvement in systematic reviews (Pollock et al., 2017), in ethics committee reviews (Staley and Szmukler, 2016), in reducing health and care research waste (Minogue et al., 2018) and in mapping health literacy interventions (Howard Wilsher et al., 2017). There are also emerging developments involving young people in research such as research around children and young people with neurodisability (Allard et al., 2014; McAnuff et al., 2016).

Legal Requirements for Public Involvement

In the UK, the requirement to involve patients and the public in the planning, development, and delivery of health services became enshrined in law in 2012 in Section 14Z2 of the NHS Act 2006, as amended by the Health and Social Care Act 2012—public involvement and consultation by clinical commissioning groups (NHS England, 2017).

Key regulations set out the essential standards of quality and safety that people who use health and adult social care services have a right to expect and the regulator provides guidance for providers of services about how to meet the regulations (Care Quality Commission, 2015). Public and patient experience and engagement policies complement the delivery of the essential quality and safety standards (Ocloo et al., 2017).

Definitions for Public Involvement

There are many different terms used in different ways by people from different sectors to describe PPI that can lead to confusion unless definitions are made clear.

Whatever term is used, the principles remain similar and are about trying to ensure that the patient perspective is included in discussions and decisions about healthcare. This might be at an individual level where patients are involved in shared decision-making with healthcare professionals about the care they wish to receive. Or it might be where patients, or patient representatives are involved in corporate decision-making about delivery of care or services from an organizational perspective.

Some of the terms used to describe patient involvement are: public and patient involvement, public and patient engagement, public and patient participation, patient experience, service user involvement and engagement, stakeholder engagement, and several others. In pharmacy practice the term Public and Patient Involvement Engagement and Participation (PPIEP) is often used. We will use the term "public involvement" in this chapter as a broad term to encompass all types of involvement and engagement.

In addition to the activities of involvement and engagement it is also helpful to try to understand the area of practice, discipline, sector, or domain in which the involvement is being undertaken. The area of public involvement that might be of interest to a specific individual or group or organization might include: healthcare planning, healthcare delivery, healthcare evaluation, healthcare commissioning, public health, health research, or health education. Any of these areas could relate to primary or secondary care or other service areas including pharmacy practice.

Drawing on the definitions used by INVOLVE (see list of relevant web pages) below are a few examples of the ways in which members of the public and patients might be involved in the work of health researchers and which can readily transfer to the health service setting including pharmacy practice.

Involvement

The activity referred to as public involvement is where patients or members of the public contribute to the development, delivery, or dissemination of a research study or in fact any activity throughout the research cycle. This might include:

- Joining advisory groups such as those making decisions about prioritization of research, funding research, or those providing oversight to a research study.
- Providing advice about structure and content for material to be used by participants of research such as leaflets, posters, and participant information sheets.
- Assisting in a researcher role (user or carer researcher) with data collection such as interviews or data analysis.
- Supporting the research team in the role as coapplicant on a research funding application.

Engagement

The activity described as engagement in research is when researchers, or others such as patient representatives, communicate their research findings or information about the impact of their research. This activity aims to spread information to the wider research community and beyond and might be specifically targeted at certain groups. It can take a number of different approaches such as: presentations, articles in newsletters, websites, social media, blogs, television, and radio to promote the research and raise awareness, open days at higher education institutions and in hospital settings, science festivals, and research clubs.

Participation

In relation to research, participation refers to the role of people in research as participants where the research team collects data from or about the participants to contribute to the research data collection and therefore influences the research findings. Participation is when people are recruited into a trial or when people provide research data through interviews or questionnaires.

When It Isn't Clear

There are sometimes scenarios where an activity called public involvement can be challenged by others who think it is a research activity, therefore illustrating that there might be overlap in the definitions of involvement and participation. For example, if patients are involved in a focus group as part of a research study the research team might call this public involvement. Some might call this participation because the members of the public are involved in the research itself. There is usually one straightforward way to clarify this. If research data are collected, for future analysis, from the members of the public, then they are participating in research. If the data that are collected are not research data then it is likely they are involved members of the public rather than participants in a research project. Taking the example of a focus group, if members of the public are being asked for their opinions on an intervention from the patient perspective this is probably a research study that is collecting research data from the members of the public as participants in the research. If a research study runs a focus group of patients with asthma to ask their opinions in designing a patient information sheet for a forthcoming trial, this is patient involvement, not participation.

Support for Public Involvement

INVOLVE (see list of relevant websites) describes its purpose as supporting "active public involvement in UK National Health Service (NHS), public health and social care research." INVOLVE uses the term "public involvement" to describe involvement of patients, potential patients, carers, and people who use health and social care services as well as people from organizations that represent people who use services.

While INVOLVE's remit is around health research, the principles and approach are broadly similar to those used for public involvement in healthcare. The INVOLVE website (see list of relevant websites) contains useful definitions about what is meant by public involvement and also what is not. In summary, INVOLVE describes public involvement in research as, "research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them." (© NIHR INVOLVE).

Examples of involvement in research might see members of the public working with research funding bodies to assist in prioritizing research, public members on a research project steering group in an advisory capacity, or helping to design research tools such as questionnaires and participant information leaflets.

People in Research

There are occasions when researchers might find it difficult trying to find suitable members of the public to support them in their research. People in Research is a website (see list of relevant websites) which advertises involvement opportunities in UK NHS research and also uses Twitter to promote their research and help researchers find members of the public to get actively involved in their work by enabling them to advertise their opportunities. The website also allows patients and members of the public to find research they might like to become involved with through searching the database.

What Is Required for Public Involvement to Work?

Being prepared to embrace public involvement requires a shift in thinking and in ways of working. Practitioners no longer view the patient as a recipient of services but as someone with whom they can work in partnership. This resembles a shift in power and therefore requires a different kind of relationship, in which healthcare professionals work in partnership with patients and the public (Parston and Kippin, 2010). Public involvement therefore brings about a shift in power from professionals to a more equal partnership (General Social Care Council, 2012). Power sharing can contribute to the achievement of the goals of a research project and can influence attitudinal change (Boote et al., 2011; Renedo and Marston, 2011; Lindenmeyer et al., 2007; Tritter and McCallum, 2006; Coulter, 2006).

This cultural change helps to drive quality improvement and such changes were seen when healthcare providers included a focus on the measures of patient experience as well as those of clinical care in their monitoring and regulation activities. A significant development in this area has been the introduction of patient reported outcome measures, known as PROMs where data about patient experience are included in measuring success in clinical outcomes. Patients were involved in the development of the patient reported outcomes to determine the appropriate methods and processes for reporting such outcomes in cancer research (Wilson, 2018).

There are now changed beliefs and attitudes toward public involvement as a result of working with patients and the public in research and service development (Mockford et al., 2012). Other changes that have occurred are seen in the NHS Constitution in relation to patient involvement in research (Purvis, 2012), changes to the standards of training in the Health and Care Professions Council (2012), and the recruitment of Patient Research Ambassadors (National Institute for Health Research, 2012).

Each patient or public member brings their individual beliefs, values, and everyday experiences (Fotaki, 2011) and their experiential knowledge is a source of advice that cannot be substituted by professional knowledge, which makes their contribution relevant (Lehoux et al., 2012).

Research involving the public makes the research more relevant to the people for whom it is designed (INVOLVE, 2013; Staniszewska et al., 2011; Research Council UK, 2010). As public involvement is becoming more embedded in the culture of health services and health research members of the public are becoming more experienced and more interested in how they can shape services in the future.

A movement that started in the voluntary sector, promoting patients as leaders, has been gaining momentum in healthcare. It describes the qualities of a patient leader as being similar to a strategic leader with a capacity for self-leadership, the ability to focus on solutions and having a willingness to value and work with others (Doughty and Gilbert, 2012). We now see patient leaders working alongside healthcare leaders to create service improvement through coproduction (King's Fund, 2013).

Standards for Public Involvement

The UK national standards for PPI in research were launched in March 2018 across a small number of test bed organizations. From April 2018 to April 2019, the next stage in developing the standards is to make sure that they work in practice as part of a pilot scheme. The aim of the standards is to improve the quality and consistency of public involvement in research. There are six national

standards, each with supporting indicators, resources, and downloadable documents in different formats. The standards were developed following consultation carried out in 2017 across the devolved administrations in the UK.

Each standard is a statement of good practice that describes one of six core elements in public involvement in research. For each standard there is an indicator, which is a statement of good practice that describes what is needed to demonstrate meeting the standard. Examples are provided on the website for NIHR PPI standards.

Standards for Public Involvement in Pharmacy Practice

Research is being undertaken at the University of Aberdeen about PPI in developing quality improvement standards, indicators and measures for the community pharmacy-based management of acute consultations. The aim of this research is to define, measure, and improve existing practice. There is further information on the Health Services Research Unit at the University of Aberdeen on their website.

Methods for Public Involvement

Public involvement is possible at almost every stage and every level of health service planning, commissioning, delivery, and evaluation and in health education and health research. It is recommended that we consider what is appropriate, when, and how, in terms of public involvement in what we do. For example, we might decide to seek feedback from patients on their experience of accessing a new service by means of a survey and then use a focus group of patient volunteers to contribute to discussions about how to use the survey results to improve the services. Below is a list of some of the methods used for involving the public and patients in healthcare.

- Surveys, questionnaires, focus groups
- Advocacy, facilitation
- Events, open days, science cafés
- Community meetings, consultation, collaboration, listening events
- Newsletters, feedback, social media
- Partnerships, networks
- Social movements, communities of interest, citizen's panels, patient representatives, patient groups, patient ambassadors
- Action research, participatory research
- Power sharing, coproduction
- Campaigns, lobbying
  NHS England guidance for commissioners (2017)

The academic literature holds numerous examples of different methods and approaches for public involvement: participatory research (Cook et al., 2017), community engaged research (Lowrie and Tyrrell-Smith, 2017), participatory learning and action research (De Brun et al., 2017), and participatory theme elicitation (Best et al., 2017) which involved young people in data analysis and other recruitment strategies for public involvement (Vat et al., 2017).

An important consideration is about the support that is going to be provided for the public members who are to be involved and to make sure that carefully tailored training and support for public involvement is available (Caldon et al., 2010; Morrow et al., 2012).

The process of recruiting patients or members of the public has been shown to reflect significantly upon their subsequent involvement experience. Providing the right information and support is part of a well-managed recruitment approach. Early negotiation about roles gives way for mutual respect and an active relationship, and establishes the process of two-way communication (Caldon et al., 2010; Boote et al., 2002). An example about how to recruit patients and the public to work collaboratively on a public panel for a microbiology research study is described by Grier et al. (2018).

With regard to the inclusion of information about public involvement when studies are published there has been much criticism of authors for failing to provide sufficient detail about the public involvement component of a study. This is important, as it is necessary to know of the detail about public involvement, especially when claims are being made about the impact of public involvement. The development of guidelines for reporting public involvement in research has addressed this issue. The GRIPP2 reporting checklists provide authors with a step-by-step approach to including all the details that are required about public involvement in a study and this has the wider impact of adding to the evidence base of public involvement in research.

The GRIPP2 reporting checklist has been developed as evidence-based consensus guidance on reporting PPI in research. It reiterates the importance of providing information on context, process, and impact of public involvement. Staniszewska et al. (2017) introduced the idea of a short form and long form for reporting PPI. GRIPP2 is the first international, evidence-based community consensus informed guidelines for reporting of PPI in research.

One of the approaches used for public involvement is experience-based codesign. The principle of engaging service users in the design of services using the model of experience-based codesign (Bate and Robert, 2006) brings a deeper more rewarding experience and results which are more sustainable (King's Fund, 2013). Another approach is coproduction.

Coproduction

Public involvement can break down barriers, lead to shared experiences, build understanding and seek diversity of knowledge from a range of settings, individuals and organizations and this has the potential to create the setting for coproduction to occur (Boyle and Harris, 2010). Coproduction is the process where members of the public work alongside professionals as partners in the delivery of services (Boyle et al., 2006). Coproduction draws upon the diversity of what public members and health professionals or researchers can bring and they become coproducers of knowledge that can influence health policy and practice (Gillard et al., 2012). Coproduction is seen as a goal of public involvement because it is where knowledge is produced across disciplines.

Good practice in quality improvement in clinical communities to establish shared norms of conduct occurs where members of the community become united by a common purpose to learn or share knowledge and take responsibility for achieving their aims (Aveling et al., 2012; Dawda et al., 2010; Baxter et al., 2001; Lave and Wenger, 1998).

Engaging service users in partnership with professionals creates one of the essential components of reform (Boyle and Harris, 2010). In the context of coproduction, instead of just being consulted, service users become equal partners and cocreators of service change (Social Care Institute for Excellence, 2012). An example of coproduction in creating, delivering, and evaluating a lay assessor training program has been described by Horobin et al. (2017).

The Coalition for Collaborative Care, NHS England describes coproduction as "a way of working that involves people who use health and care services, carers and communities in equal partnership; and which engages groups of people at the earliest stages of service design, development and evaluation" (see diagram below). Coproduction acknowledges that people with lived experience of a particular condition are often best placed to advise on what support and services will make a positive difference to their lives. Done well, coproduction helps to ground discussions in reality, and to maintain a person-centered perspective. Coproduction is part of a range of approaches that includes citizen involvement, participation, engagement, and consultation.

Values and behaviors that are exhibited by those working in a coproductive manner are described by the Coalition for Collaborative Care Action for Long Term Conditions in their coproduction model. See **Figs. 1 and 2**.

http://coalitionforcollaborativecare.org.uk/a-co-production-model/

Guidance on Coproducing a Research Project

INVOLVE has an ongoing work theme around coproduction and in February 2018 produced a guidance document for coproducing a research project (see list of relevant websites). It describes the key principles and key features of coproduction.

Key principles of coproduction are: sharing of power, including all perspectives and skills, respecting and valuing the knowledge of all those working together on the research, reciprocity, and building and maintaining relationships.

Key features of coproduction are: establishing ground rules, ongoing dialogue, joint ownership of key decisions, a commitment to relationship building, opportunities for personal growth and development, flexibility, continuous reflection, and valuing and evaluating the impact of coproducing research.

Organizational Perspectives on Public Involvement

NHS England

The commissioning body for healthcare in England explains the important role of public involvement,

> "Patient and public participation is important because it helps us to improve all aspects of health care, including patient safety, patient experience and health outcomes – giving people the power to live healthier lives."
>
> NHS England website March 2018

Figure 1 Five values and behaviors of coproduction. *Reproduced with kind permission from the Coalition for Collaborative Care.*

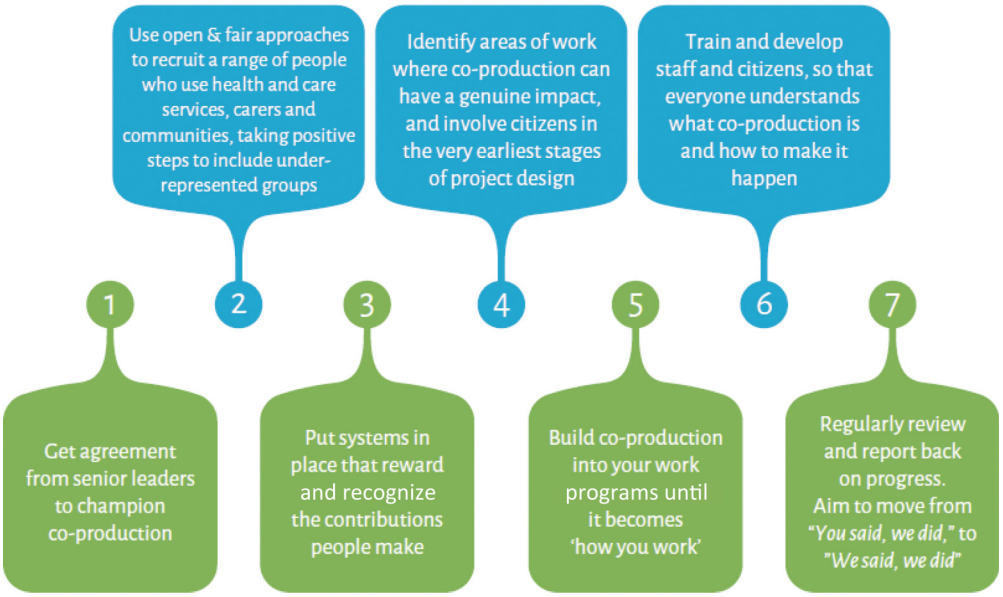

Figure 2 Seven steps to make coproduction happen. *Reproduced with kind permission from the Coalition for Collaborative Care.*

Healthwatch England

Healthwatch England is the independent consumer champion for health and social care and aims to, "have a society in which people's health and social care needs are heard, understood and met." They aim to make sure that people shape and influence health and social care delivery and the services they receive.

NHS England and Healthwatch England have an agreement to work together "to support a shared purpose of improving health and wellbeing outcomes for consumers, including patients, carers, families and communities" (NHS England and Healthwatch England, 2015).

Clinical Commissioning

Public involvement in commissioning is about enabling people to voice their views, needs and wishes, and to contribute to plans, proposals, and decisions about services. Health service commissioners aim to involve anyone who uses services or may do so in the future, including carers and families. The term "involvement" is used interchangeably with "engagement," "participation," "consultation," and "patient or public voice." Different approaches will be appropriate, depending on the nature of the commissioning activity and the needs of different groups of people.

Primary care commissioning managers and those working on national policy and programs affecting how primary care is commissioned consider involvement and participation as an integral part of commissioning, i.e., at all stages of the commissioning cycle. In planning policy, programs, and services, commissioners have to show they are aware of their legal duty to involve the public in this area of work, and take action as appropriate. Commissioners work to a set of key principles aimed at changing the way they embed public involvement in their work. These key principles, outlined in the Framework for patient and public participation in primary care commissioning (NHS England, 2016) are:

1. Reach out to people rather than expecting them to come to you and ask them how they want to be involved, avoiding assumptions.
2. Promote equality and diversity and encourage and respect different beliefs and opinions.
3. Proactively seek participation from people who experience health inequalities and poor health outcomes.
4. Value people's lived experience and use all the strengths and talents that people bring to the table, working toward shared goals and aiming for constructive and productive conversations.
5. Provide clear and easy to understand information and seek to facilitate involvement by all, recognizing that everyone has different needs. This includes working with advocacy services and other partners where necessary.
6. Take time to plan and budget for participation and start involving people as early as possible.
7. Be open, honest, and transparent in the way you work; tell people about the evidence base for decisions, and be clear about resource limitations and other relevant constraints. Where information has to be kept confidential, explain why.
8. Invest in partnerships, have an on-going dialogue and avoid tokenism; provide information, support, training, and the right kind of leadership so everyone can work, learn, and improve together.
9. Review experience (positive and negative) and learn from it to continuously improve how people are involved.

10. Recognize, record, and celebrate people's contributions and give feedback on the results of involvement; show people how they are valued.
(NHS England, 2017)

Public Involvement in Research—A Broader Perspective

This section introduces some broader views and approaches to public involvement and shows how the movement has progressed across continents.

The United Kingdom is said to be a leader in its approach to formalization of public involvement at an organizational level (Spencer et al., 2011) and its progress in spreading public involvement, especially across the public sector cannot be disputed.

In the United Kingdom a blog in the British Medical Journal was used to promote the involvement of patients and the public in research and turn this into a global "social movement" (http://blogs.bmj.com/bmj/2017/11/30/tessa-richards-patient-and-public-involvement-in-research-goes-global/).

In the United States, this work is being led by the Patient-Centered Outcomes Research Institute (PCORI) whose mission is to help people "make informed healthcare decisions, and improve healthcare delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community" (PCORI website March 2018).

In Canada, where the term patient engagement in research is used, the work is led by Canada's Strategy for Patient-Oriented Research (SPOR) and their review of the literature found only two studies that engaged patients in the research process (Adesanoye and Guirguis, 2017).

The Consumer and Community Research Network at the University of Western Australia describes their public involvement in research as, "the active involvement of consumers, community members and researchers working together to make decisions about health research priorities, policy and practice" (Consumer and Community Research Network September 2018).

They have developed an Involving People in Research website:
http://www.involvingpeopleinresearch.org.au/

Patients Included

Patients Included is an initiative that endorses public involvement practice. Patients Included charters are provided to organizations, courses, journals, and any function associated with healthcare that is shown be committed to, "incorporating the experience and insight of patients into their organizations by ensuring that they are neither excluded nor exploited." Charters have been provided for conferences, journals, and patient information resources with many other initiatives awaiting endorsement such as; clinical trials, continuing professional development courses, funding bodies, pharmaceutical companies, and healthcare organizations. See list of relevant websites.

Public Involvement in Higher Education

Professional bodies and government policy in the UK have made it a requirement for higher education institutions to demonstrate involvement of service users and carers in education and training for social workers and for health professionals (Department of Health, 2002).

In 2003 when the educational requirements for a social work qualification changed from a diploma to a three-year degree course there was also a requirement for higher education institutions offering the degree to involve service users and carers in the design and delivery of the program. This is illustrated by their involvement in recruitment and selection of students for the social work degree program, involvement in teaching programs and in the assessment of learning. It is now usual practice for service users and carers to be involved by helping to design the interview process and they might also be involved in undertaking the interviews for social work degree placements (Department of Health, 2002; General Social Care Council, 2005).

Methods for the involvement of service users and carers in social work teaching might take place through sharing their personal stories as case studies or they might be presented in the form of video recordings.

Drivers for service user involvement in social work education programs are similar to those in the health sector—that is, demands from service user-led organizations and regulatory requirements (Robinson and Webber, 2013). The increase in service user involvement in research in higher education institutions over the last two decades has been driven largely by service users themselves, the professional bodies and government policy (Chambers and Hickey, 2012). The Department of Health Education Commissioning for Quality document (2009) includes guidance on user involvement in the design and delivery of education and the Nursing and Midwifery Council requires evidence of involvement in program development and delivery (Nursing and Midwifery Council, 2015; Rhodes and Nyawata, 2010). The Health and Care Professions Council (2012) has developed Standards of Education and Training (SETs) for service user involvement in the design and delivery of their regulated education and training programs. Methods of involving service users in the education of health professionals includes their involvement in course design, student assessment, and teaching in the classroom (Cooper and Spencer-Dawe, 2006; Repper and Breeze, 2007; Haeney et al., 2007; Thomson and Hilton, 2011).

Public Involvement in Pharmacy Teaching

There are examples in the public domain, on websites giving examples of public involvement in pharmacy teaching.
http://www.uclan.ac.uk/about_us/case_studies/pharmacy_patient_public_involvement.php

A lecturer and a teacher practitioner at the University of Central Lancashire invited patients to an event scheduled for fourth year pharmacy students in the cancer module. They hosted chat show style interviews with patients who talked about how pharmacists had helped them with their conditions. Both students and teaching staff had found the session very positive (Becket et al., 2014).

National Coordinating Centre for Public Engagement (NCCPE)

https://www.publicengagement.ac.uk/

The UK NCCPE supports higher education institutions in their public engagement in research. They define public engagement as:

- the myriad of ways in which the activity and benefits of higher education and research can be shared with the public;
- a two-way process, involving interaction and listening, with the goal of generating mutual benefit.

The NCCPE provides training, resources, and holds an annual conference for engagement professionals across the higher education sector.

Resources for Public Involvement

See Table 1.

Conclusion

This chapter has aimed to give a broad overview of where, why, and how public involvement is occurring across the health landscape and offer examples of good practice and resources for others to replicate.

We are moving toward health services, research, and education, which are enhanced through public involvement and where the benefits improve peoples' health encounters, experiences, and outcomes.

Table 1 Resources for public involvement

Name	*Description*	*Weblink*
University of Central Lancashire	Chat show style interviews with patients who talked about how pharmacists had helped them with their conditions	http://www.uclan.ac.uk/about_us/case_studies/pharmacy_patient_public_involvement.php
Grimes et al. (2013)	Paper describing the advantages and the challenges of involving patients and the public in pharmacy education and giving several options for undertaking public involvement	https://www.pharmaceutical-journal.com/research/perspective-article/involving-patients-and-the-public-in-the-delivery-of-pharmacy-education/11138731.article
Going the Extra Mile	The National Institute for Health Research strategy for patient and public involvement in research	https://www.nihr.ac.uk/patients-and-public/documents/Going-the-Extra-Mile.pdf
James Lind Alliance (JLA)	Research Priority Setting Partnerships	http://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm
National Institute for Health Research Newsroom	Health researchers and patients working together to improve stroke research	https://www.nihr.ac.uk/news/exploring-frontiers-of-stroke-research-together/8093
Shaping our Lives National Service User Involvement Network	A national network of service users and disabled people	https://www.shapingourlives.org.uk/
Healthcare Quality Improvement Partnership (HQIP)	Developing a Patient and Public Involvement panel for quality improvement	https://www.hqip.org.uk/resources/developing-a-patient-and-public-involvement-panel-for-quality-improvement/
Parkinson's UK	Patient and Public Involvement—a resource for researchers	https://www.parkinsons.org.uk/sites/default/files/rd2030_ppi_resource_for_researchers_new_boiler_web.pdf
NIHR School for Primary Care Research	Patient and Public Involvement Case Studies in Primary Care Research 2015	https://www.spcr.nihr.ac.uk/files/ppi-3/case-studies-final-march-website.pdf
Administrative data research network	Public engagement methods, activities, panels, large engagement events, voluntary and community sector engagement	https://adrn.ac.uk/public-engagement/activities-and-events/

Involving the public in planning of healthcare can lead to more accessible and acceptable health services whereas involving the public in research can lead to research that is of better quality, more relevant to patients, and of benefit to the end users.

Because the general public knows more and understands more about healthcare, and because reliable information is now so much easier to access, members of the public are even better placed than before to take up their positions as leaders. The leadership potential for patients and the public in influencing healthcare has gained momentum. The roles of healthcare professionals and patients as leaders are being redefined. As healthcare professionals are starting to think differently about the way they practice and the way they communicate, patients too are shifting in their thinking about their partnership role in the transformation that is happening in healthcare.

Pharmacy practice and pharmacy practice research are part of the transformation that is occurring through public involvement. This chapter has brought together some of the many examples of PPI, Engagement and Participation from the research literature and across the health community which provide the evidence base for this exciting transformation.

Relevant Web Pages

INVOLVE

www.involve.nihr.ac.uk

The INVOLVE website is one of the most comprehensive websites for supporting researchers and practitioners in their public involvement in NHS, public health and social care research activity. Although focused on research, much of the guidance provided by INVOLVE is transferable to the practice setting. Key guidance documents are:

- Briefing notes for researchers
  http://www.invo.org.uk/resource-centre/resource-for-researchers/
- Guidance on payment for and recognition for public involvement
  http://www.invo.org.uk/resource-centre/payment-and-recognition-for-public-involvement/
- Budgeting for Involvement including an Involvement Cost Calculator
  http://www.invo.org.uk/wp-content/uploads/2014/11/10002-INVOLVE-Budgeting-Tool-Publication-WEB.pdf
- PPI Standards
  http://www.invo.org.uk/current-work/standards/

People in Research

www.peopleinresearch.org

This website helps researchers find suitable members of the public with an interest in getting involved in research. Likewise it helps members of the public find research that they might be interested in helping with. There is a link to this website from the INVOLVE website in the Resources section.

GRIPP2 Reporting Checklists for PPI

GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539518/

University of Central Lancashire

http://www.uclan.ac.uk/about_us/case_studies/pharmacy_patient_public_involvement.php

The Pharmaceutical Journal

https://www.pharmaceutical-journal.com/research/perspective-article/involving-patients-and-the-public-in-the-delivery-of-pharmacy-education/11138731.article

Grimes et al. (2013) describe the advantages and the challenges of involving patients and the public in pharmacy education and give several practical examples for public involvement.

Healthwatch

https://www.healthwatch.co.uk

There are local Healthwatch organizations across England and their role is to champion things that matter to patients and lobby for improvements to services. A national Healthwatch body has oversight of national issues and reports to government on its activity.

The Royal Pharmaceutical Society in Great Britain

The Royal Pharmaceutical Society in Great Britain provides a Patient Engagement Hub on the resources section of its website: https://www.rpharms.com/resources/ultimate-guides-and-hubs/patient-engagement-hub. It contains a list of useful resources including leaflets, posters, and videos for patients to help them understand how pharmacy can help them with their condition.

Patients Included

https://patientsincluded.org/

NIHR PPI Annual Reports

https://www.nihr.ac.uk/about-us/how-we-are-managed/managing-centres/nihr-central-commissioning-facility/ccf-ppi/ppie-annual-reports.htm

NIHR infrastructure organizations such as Biomedical Research Centres, Collaborations for Leadership in Applied Health Research and Care, and Clinical Research Facilities have their annual patient and public involvement reports published on the NIHR website. These contain many examples of good practice in public involvement and most of them contain links to the organizations' websites and project pages.

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Sociology for Pharmacists

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Historical Development

Traditionally, pharmacy education has been based on knowledge of pharmacology, biochemistry, chemistry, physics, and physiology. This knowledge served pharmacists well when they were considered artisans and craftsmen who could know and utilize all the available knowledge. In the post-antibiotic era with its pursuit of the "magic bullet" and the subsequent growth of the pharmaceutical industry, more and more medicines came to market and the increased specialization in the health-care sector created an increasingly fragmented and complex system. The time had come for pharmacy practice to become reflective and forward thinking, which required taking stock, that is, to control, intervene, and implement change in the delivery of services and pharmacy management.

Organization and research skills were needed if pharmacies and pharmacists were to develop and maintain a key position in health care. This created a need for input from the organizational, behavioral, and social sciences. Sociology was one of the first social sciences to contribute to the field of pharmacy practice research (PPR). As far back as the 1960s, the role of the pharmacist was a much studied topic, and sociological theories of the professions provided a framework for this research (Lau and Traulsen, 2017). Since the 1980s, sociologists and other social and behavioral scientists began to play an important role in the education and research of and for pharmacy.

In 1994, one of the founding academic centers of pharmacy practice research in the United Kingdom asked Nick Mays (a social scientist working in health services research) to conduct a critical review of the existing PPR literature. He concluded that PPR had reached a point where it needed to work with and include other disciplines. He argued for greater utilization of sociological theory as one way to enhance the explanatory capacity and sophistication of pharmacy practice research (Mays, 1994). Through their theories and methods, sociologists provided conceptual and research tools to identify, analyze, and explain the social context of pharmacy and patients and health-care professionals use of pharmaceuticals. This included organizational systems and patient behavior—essential elements in the practice of pharmacy and the extended role of the pharmacist.

In general, sociology accentuates society rather than the individual by viewing individuals within the context of their environment and larger social processes. In this way, sociology differs from psychology, which emphasizes individual behavior often divorced from the social context. Medical sociology studies how people manage issues of health and illness, disease and disorders, how work effects health, how families deal with illness, the socio-economic determinants on health and health care, as well as the care and services for the sick as well as the healthy.

Sociology has enriched PPR by introducing concepts and theories such as social capital (the collective value of all social networks), social inequality (differences in health status), social status (the relative rank of an individual in society), and the organization of health-care organizations, to name but a few (Harding et al., 1990).

Sociology has not always been the preferred collaborator in PPR. Health professionals have often seen sociology as overly critical in its approach, given that it is usually challenging the status quo. For this reason, it has been seen by many in PPR as confrontational, i.e., concerned more with identifying, analyzing, and understanding problems rather than seeking solutions. One reason could be because sociological-oriented research is explicitly concerned with power; however, one might like to define power. A PPR example could be to ask what impact the power and authority exercised by health-care professionals has on patient compliance. In relation to medicine, a sociologist would look at the consequences of expecting patients to comply with a therapeutic regimen that has been shown to be unpleasant, complex, and difficult to live with (Bissell and Traulsen, 2005).

Another example would be to study the power of the powerless, that is, how patients from various social groups challenge, circumvent, and adopt therapeutic regimens.

One of the earliest contributions to medical sociology was made by the American sociologist Talcott Parsons (1951). Parsons theorized and coined the concept of the "sick role"—an approach to understanding the responsibilities and rights of patients in their interaction with doctors. According to Parsons, the sick role maintains order and to this end he attributed the following four components:

1. Ill people are exempt from their normal social responsibilities such as work or domestic labor.
2. Ill people are not held responsible for their condition and cannot be expected to recover by an act of will.
3. Ill people must want to try to get well or they can be accused of malingering.
4. Ill people are obliged to seek and cooperate with medical practitioners to help make themselves well again (Bissell and Traulsen, 2005).

Concepts and topics of particular interest to the field of PPR include adherence, compliance, concordance, the patient perspective, pharmaceutical policy, organization, and evaluation studies.

Whereas sociology was contributing to and becoming visible in PPR, clinical pharmacy research allied itself with health services research and the broad spectrum of methods in that subdiscipline, with relatively little crossover to sociology. Clinical pharmacy research is interested in real-world settings, that is, how well medications work on specific human patients once they have been approved. It is concerned with evidence-based outcomes research and draws on the knowledge of medicine and disease as taught within the framework of basic science and then relates this knowledge directly to the clinical requirements of patients (Harding et al., 1990).

Sociological Contributions to PPR

Sociology has provided PPR with a "toolbox" of study designs, theories, and research methods, including arguing for different approaches to how to design a project, a questionnaire, and concepts used (understood). One especially useful contribution has been the introduction of qualitative methods (Kaae and Traulsen, 2015), such as interviews, focus group interviews, various types of observation, document analysis, and more recently netnography (Kaae and Traulsen, 2015).

Beliefs About Health and Illness

Beliefs about health, illness, and medicines have been one area of PPR. Sociology has contributed a theoretical understanding of the causes of disease and illness, as well as the reasons for seeking various types of medical care (Conrad, 2008). Sociology has also contributed methods and theory for researching patient compliance and noncompliance with medical regimens and adherence issues—the extent to which a person's medicine-taking behavior corresponds to the advice from health-care providers. A further development in the attempt to understand the extent to which a patient's behavior aligns with medical advice has been the introduction of the concept of concordance. Concordance refers to the nature of the interaction between clinician and patient on medication taking, about whether, how, and when medical treatment will be used (Gabe et al., 2004). Whereas Parsons' depiction of patient–professional relationships referred to the "institutionalized superiority of the professional's role," the concordance model describes treatment choices as the "negotiation between equals" (Bissell and Traulsen, 2005).

Sociological studies have contributed to the service user's perspective, providing pharmacists with insight into and vital information about their patients in order to understand where they are coming from and what informs their views on health and medicine. This knowledge is essential for understanding and developing communication skills—a must for pharmacy practice.

Researching Risks

Whereas prior to the scientific revolution, issues of life, death, health, and illness were discussed in terms of fate, chance, personal destiny, and the will of God, today research on risk has become a major approach to assessing public health risks (Gabe et al., 2004). Theories of risk, methods to measure risk, and regulating risk have become ubiquitous features in research concerning the effects and side effects of medicine treatment. Since the late 1970s and early 1980s, the discourse about risk and research on risk has exploded in the clinical and social sciences. Whereas psychologists have been concerned with questions of "how risk is perceived," sociologists have been concerned with "how risks are negotiated" (Bissell and Traulsen, 2005). German sociologist Ulrich Beck and British sociologist Anthony Giddens were two of the most influential proponents in developing the theories of risk and society that laid the foundation for many studies of health services and medicine treatment. A major theme in this literature has been the discrepancy between lay and expert perspectives of risk, which some have explained as the result of competing or alternative rationalities (Bissell and Traulsen, 2005). There is research evidence that experts and patients sometimes conceptualize and perceive risks differently. This complicates the need to manage risks, distancing the expert from the patient and creating a need for "intermediary links"—a common ground where they can work together on risk management. In the world of medicine, the pharmacy has been identified as

this "intermediary link." The risk discourse and the resulting theories of risk have contributed much to health services research as well as PPR; for example, studies of the perceived risk of future drugs; clinical studies that have developed measurement tools; and research on risk communication (especially between pharmacist and patient). As long as pharmaceuticals continue to have side effects, be they physical, social, psychological, economic, or ethical, there is a basis for researching the risk perceptions of patients and various approaches to risk communication and risk management (Bissell and Traulsen, 2005).

The contribution of risk research to the realization that there is a gap between experts and patients in terms of treatment options brings us to one of the major contributions of sociology to PPR—theories and methods for researching the patient perspective. The patient perspective refers to the ideas, perspectives, and sources of knowledge people use to interpret the experiences of health and illness in their everyday lives.

PPR has contributed to and expanded this approach by introducing the patient perspective in a societal context, for example, by emphasizing the role of contextual factors in health beliefs and practices. Sociologically informed research has studied social inequalities and health, effects of gender and ethnicity on health, and use of health services. Most significant has been the wealth of research done on social class and health and the evidence of how social class inequalities correlate with inequalities in health status (Harding et al., 1990).

Pharmaceutical Policy

In the new century, a major area of interest has been patient perspectives and involvement in pharmaceutical policy. Almost every national and supranational health policy document accords high importance to the need to listen to and "empower" patients. This field of research includes studies that look at lay attitudes toward pharmaceutical policy, lay experiences of drug therapy and how it affects their daily lives, patient and public involvement (PPI), the problem of identifying lay representatives, the relationship between industry and consumers, and the effect of the media on medicine users and pharmaceutical policy itself (Traulsen and Almardóttir, 2005a). Topics of concern for PPR have been pharmaceutical policy in relation to the rational use of drugs (Almarsdóttir and Traulsen, 2005a), cost-containment (Almarsdóttir and Traulsen, 2005b), the role of the lay public (Traulsen and Almardóttir, 2005a); and the role of the pharmacy profession (Traulsen and Almarsdóttir, 2005b).

Theories of the Professions

Research accounts of the struggle of professions to attain and maintain a monopoly, strategies of exclusion and usurpation, have formed an interesting and fruitful area of sociological research. Theories of the professions have been a useful framework for studies concerning the future of the pharmacy profession including professional identity, and for decades have been a popular and recurring theme in professional journals and at international pharmacy conferences (Traulsen and Druedahl, 2018).

The work tasks of pharmacists, the environment they work in and the overall status of the pharmacy profession have been fruitful areas of research in sociology (Traulsen and Almarsdóttir, 1999; Traulsen and Bissell, 2004; Traulsen and Druedahl, 2018). For example, sociological studies on the labor market for pharmacists have addressed issues such as gender, wages, and salaries; part-time versus full-time work (Carvajal and Popovici, 2016); labor supply functions; and the consequences of pharmacist shortages (Carvajal et al., 2012). Studies on the working conditions and work environment have addressed concerns among community pharmacists that patient safety is being compromised due to high-pressure working conditions in combination with long working hours without breaks (Gidman et al., 2007). Theories of power and labor market analysis found in sociology can be useful when exploring labor market trends and what they mean for pharmacists. For example, cases where pharmacists report that they are being pressured to focus on providing services that generate extra sales and fees that are reimbursed by third-party payers.

Another field of sociologically informed research deals with demographic shifts in the composition of the pharmacy work force. These include gender, cultural diversity, and ethnicity (Carvajal et al., 2014).

Rising social and economic pressures on health-care systems have made understanding the role of organizational structures and processes in health-care facilities, including pharmacies, an immediate concern in ensuring quality of care. Generally speaking, organizations are stable elements of social life, the basic structures within which the state establishes regulatory policy, business is conducted, and people work. They intersect and interact with political, economics, and labor institutions. Organizations have been and still are a central component of sociology. The increasing complexity of health-care organizations has presented challenges for policymakers, health-care workers, and decision makers, making research into the organization of care delivery a top priority. One goal of these endeavors has been to identify ways of improving care by improving the organizations that provide this care. Sociology has numerous theories and methods that address research in this field.

Of particular concern for pharmacy practice are the challenges of transitional care. Transitional care is the term used to refer to the coordination and continuity of health-care services between health-care practitioners when patients are moved from one health-care facility to another or, in many cases, home. Community and hospital pharmacies are key actors and important service providers in ensuring the quality of this service, and sociology has a history of conceptualizing and theorizing questions and problems pertaining to organizations and management in this field and in health care in particular. More recently, attempts have been made to develop theories of care transition (Bury and Taylor, 2008) in the hopes of contributing to a solution to this problem.

Evaluation Research

Evaluation research aims at providing useful feedback on the impact of social and medical interventions. There is broad consensus that the major goal of evaluation is to influence decision making or policy formulation through the provision of empirically driven feedback. Sociology has contributed much to the field of program evaluation, conceptualizing various forms of evaluation research and developing useful methods for conducting various types of evaluation studies, including need assessments and monitoring studies. Sociological treatment of qualitative research and evaluation methods has influenced many studies of health-care services (Patton, 2002).

Pharmaceuticalization

Pharmaceuticalization, the process by which lives are mediated through pharmaceuticals, is a theoretical concept developed to guide research and understanding of the discovery, production, regulation, distribution, and consumption of medicines at both societal and individual levels. It has evolved from many disciplines, including sociology and anthropology, and it is presented in a separate chapter. It is a fruitful area of enquiry for PPR focusing as it does on all aspects of the development and use of pharmaceuticals.

A Bit of Crystal Ball Gazing

Futurology is a field of research to which sociology has contributed theories and methods. Future studies (as they are sometimes called) provide fertile ground for PPR for those interested in long-term planning and providing visions for the future of pharmacy. Futurology is the study of postulating potential, probable, and preferable futures. Futures studies design can be descriptive as well as prescriptive. The former, also known as the exploratory method, attempts to objectively describe how the future can or could be. The so-called prescriptive method attempts to help people clarify their values and preferences so that they can develop visions of desirable futures.

Futures research is useful in helping people to better understand future possibilities and provide policymakers (including professional groups) with various scenarios from which to make decisions and plan for the future. When successful, it provides critical thinking concerning long-term developments. Gazing into the future is always a risky and uncertain endeavor, but we can extrapolate based on current knowledge about the role of pharmacists and pharmacy practice, as well as predictions for new and revolutionary therapies. Although we will never be able to predict the future, we can identify some of the major trends and challenges known to us today. Realistic and viable visions for the future of the pharmacy and the pharmacy profession require an ongoing analysis of the outside world—especially societal, economic, and workforce trends. Sociology can contribute to insights into the current labor market and world of pharmaceuticals using labor market and work organization theories (Traulsen and Druedahl, 2018). There is general consensus that multiple methods are needed to design these studies, such as the Delphi method, trend assessment, and future scenarios.

The following is a list of some of the most pressing issues that will be affecting the pharmacy sector:

New Technology. Globally the labor market (including pharmacies) is faced with the unprecedented rapid increase in technology and automation often referred to as the "Fourth Revolution." According to a recent report by the World Economic Forum (2016), more than one-third (35%) of the skills considered important in today's workforce will change. By the year 2020, the Fourth Revolution will have introduced more robots, advanced artificial intelligence, biotechnology and genomics, all of which will transform the pharmaceutical industry as well as the work and careers of pharmacists (Traulsen and Druedahl, 2018).

New methods of organizing work. The skills that are foreseen to be important in the future include complex problem solving, critical thinking, people management, and the ability to coordinate others. A World Economic Forum report points out that negotiation skills and flexibility, which were skills high on the list in 2015, will be taken over by machines able to process masses of data (World Economic Forum 2016).

Evolving therapies. Many of the evolving therapies will not only affect but in some cases replace pharmaceuticals as we know them today. These therapies include gene therapy—the therapeutic delivery of nucleic acid into a patient's cells to treat disease; cell therapy—injecting intact, living cells into a patient; and regeneration therapy—the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal functions. Some of the research questions for PPR include: will this therapy replace existing medicine therapy? Will there be a need for coexisting or supplementary pharmaceuticals? What role will the pharmacy and the pharmacist play in this therapy?

Parallel to the search for new therapies is the activity of repurposing medicines, or teaching old medicines new tricks, as it is sometimes called. This endeavor involves finding uses for drugs in the freezers of the pharmaceutical industry, which were tested on humans (safe), but not useful for the purpose originally designed. The job of repurposing medicines, an evolving development, will most certainly require the input of pharmacists and potentially a new role for pharmacies. This development poses a unique opportunity for PPR to be proactive by studying the pros and cons of this development and providing valuable information on which to develop strategies and recommendations that include pharmacy practice expertise.

Sociology and PPR—Looking Forward

Sociologists' working together with pharmacists have been a fruitful collaboration, even if sociology is not the first social science discipline pharmacists reach out to when starting a research project. Sociology is not an exact science and is criticized for being diffuse, jargon-ridden, and lacking a specific coherent subject. In addition, sociology's emphasis on initiating a critical approach to any and all research topics is seen by many as subversive. Being trained as natural scientists and often taking a problem-solving approach to their research, pharmacists tend to shy away from sociology, which is heavy on theory and critical in its approach. However, pharmacy needs to know more about—and more importantly be able to track changes—in society, and here sociology has much to offer PPR.

Essential for communication with patients, pharmacy needs to understand where their patients are coming from and what and how their views are informed. A sociological approach can help pharmacy practice focus their attention on the practical and policy-making implications of the changes currently transforming the field. For example, new therapies, changes in medicine production, and new methods of marketing are already radically changing how pharmaceuticals will look in the future and are destined to change the role of pharmacies and pharmacists. Sociological theories that help explain the scope and breadth of these societal changes, methods that can generate empirical studies of the workplace, the products and the patient can contribute to PPR and help prepare pharmacy practice for this uncertain future.

On the microlevel, sociology can reveal perceptions of health risks and their management as well as risk acceptability of medical interventions. On the macrolevel, sociology can contribute to the study and understanding of social movements, patient organizations, public health risks, and the policy process, as well as the social construction of health risks and their regulation.

The question is always—can sociologists orient themselves better than anyone else with common sense? The answer is yes. Sociology as a discipline is characterized by its rigorous search for interconnections among different societal spheres and its systematic use of comparisons. It is anti-utopian in its claims and anti-fatalistic in its orientation and distinguishes "generalized" knowledge from localized common sense knowledge. Sociology goes further than common sense: sociologists are better at orienting themselves, because they are constantly developing and refining concepts, theories, and research methods. Developing concepts is an ongoing endeavor in sociology—which can help PPR to track, identify, and understand current pharmacy practice problems as well as help plan for the long-term future.

PPR often tries to align itself with mainstream service/practice issues, thus marginalizing sociology. This direction has been fuelled by the fact that the focus of pharmacy practice has become more commercial over the years, with the result that PPR has bonded with social sciences that promise practitioners the reward of being able to change patients' behavior and/or initiate new money-saving organizational changes. This explains the increase in the number of pharmacy practice studies driven by health services research and applied psychology, and positivist policy-oriented sciences moving into health economics, service improvement, and patient safety. This approach has been useful for studying and changing internal and day-to-day pharmacy practices. However, if pharmacy practice and research trained pharmacists are to thrive and maintain a key role in health care and services, it is necessary to plan for the immediate and long-term future. This means to momentarily look away from the micro-world of the pharmacy and the systemization of daily work and consider the implications of global mega trends that are affecting the entire field of pharmaceuticals. From R&D to patient care, sociology has the theories and methods necessary for PPR to do just that.

Glossary

Sociology Sociology is the "science" of society. It is difficult to define its boundaries as a discipline, because sociology overlaps with many other social science disciplines—economics, political science, anthropology, psychology, cultural studies, and human geography. Sociology deals with real-world issues (i.e., research on and with people), and these issues are forever in transition and change. As an academic discipline, sociology takes into account the related disciplines mentioned above. Sociological discourses are ongoing and contemporary, constantly being influenced by lay society, policy, and popular culture. On one hand, sociology seeks to understand how the thoughts, actions, and behavior of individuals are influenced by broader society. On the other hand, sociology seeks to understand how individuals actively create that society through individual and collective actions.

Pharmacy practice research (PPR) Pharmacy practice research (PPR) is a specialty field within the wider area of health services research, focusing on studies of how and why people access pharmacy services, the cost of care and services, and what happens to patients as a result of this care. PPR is often regarded as an applied field of research, in that a large part seeks to intervene, control, and implement changes in the delivery of services and pharmacy management.

Transitional care Transitional care is the term used to refer to the coordination and continuity of health-care services between health-care practitioners when patients are moved from one health-care facility to another or, in many cases, home. Community and hospital pharmacies are key actors.

Future Studies Future studies provide a knowledge base for exercises in long-term planning and developing visions for the future. Futures studies is the study of postulating potential, probable, and preferable futures, these studies can be designed as descriptive as well as prescriptive. The former, also known as the exploratory method, attempts to objectively describe how the future can or could be. The so-called prescriptive method attempts to help people clarify their values and preferences so that they can develop visions of desirable futures.

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Essential Medicine List, Policies, and the World Health Organization

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Overview

- Essential medicines have public health relevance as they satisfy the priority healthcare needs of the population and have evidence on efficacy, safety, and comparative cost-effectiveness.
- In 1963, Cuba was the first country to launch a list of basic medicines. This was followed by the introduction of national lists in Tanzania (1970) and Peru (1972). In 1977, World Health Organization (WHO) published the first WHO Model List of 212 essential medicines.
- A WHO Expert Committee on the Selection and Use of Essential Medicines is responsible for the development and the revision of Essential Medicines List (EML) every 2 years.
- The Nairobi Conference on the Rational Use of Drugs, held in 1985, was the first international conference on essential medicines policies. The development and implementation of Essential Medicines Policies (EMPs) evolved in three periods, that is, 1st era from 1970s to 1990s, 2nd era from 1990s to 2010s and 3rd era from 2010 to present.
- Standard elements of an EMP are procurement, supply, prescribing and dispensing of medicines, financing, and rational use of medicine.
- WHO has devised a framework to guide policy makers for collective action on improved access to essential medicines for Universal Health Coverage (UHC) by 2030. The framework is in line with the Sustainable Development Goals (SGDs) and includes elements such as rational selection and use of essential medicines, their affordability and availability, sustainable financing, and reliable health and supply of quality products.
- Over the years, WHO has widely supported most low- and middle-income countries (LMICs) in the development and subsequent implementation of national EMP. By 2013, most of the LMICs (>90%) had a list of essential medicines.
- The latest (20th) WHO model EML (containing 433 drugs) was published in 2017.
- Implementation of the EMP has resulted in easy availability, better affordability, and improved quality use of essential medicines in LMICs.
- Hospitals and healthcare organizations in high-income countries also use essential medicines concept to allocate funding resources.

Introduction

History and Development of Essential Medicines Policies

What are Essential Medicines?

Essential medicines have been defined by WHO as "those that satisfy the priority healthcare needs of the population. They are selected because of their public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information and at a price which the individual and the community can afford" (World Health Organization, 2003).

Evolution of essential medicine concept

The concept of "essential medicines" was evolved from military tradition in which medicaments (such as antibiotics) were very important to be carried by soldiers into the battle zones (Greene, 2011). Before the involvement of WHO in the essential medicine concept, governments were worried about the circumstances for years, and a few had started to take measures to satisfy the therapeutic needs of their residents by providing them with the essential medicines (Mirza, 2008). In 1963, Cuba was possibly the first country to launch a list of basic medicines (Wirtz et al., 2017). First international checklist of basic medicines was given in Maurice King's revolutionary book in 1966 (King, 1966). This was pursued by the introduction of national lists in Tanzania (1970) (Wirtz et al., 2017) and Peru (1972) (Wirtz et al., 2017). In 1977, WHO published the first WHO Model List of essential medicines, including 212 medicines (World Health Organization, 1977). In 1978, The Declaration of Alma Ata (1978) incorporated the provision of essential medicines as an element of primary healthcare (World Health Organization, 1978), and essential medicines were considered fundamental for preventing and treating diseases, which affect millions of individuals throughout the globe (Pillon, 2016).

Rationale for Essential Medicines

Both demand and supply perspectives are linked to the concept of essential medicines. From the demand side, medicine needs of people from low socio-economic strata are fulfilled marginally by the public healthcare facilities. From the supply point of view, a medicine innovation involving discovery, manufacturing, and delivery is mainly market driven (Pammolli et al., 2006). Influenced by return-on-investment, the pharmaceutical manufactures and private pharmacies stock these medicines so that they could can bring extra profit and concentrate on those consumers who can purchase costly medicines. In this context, essential medicines are not the part of supply and demand cycle and remain unavailable (Hardman and Limbird, 2001; Mirza, 2008).

The rationale behind the essential medicines is that while there are numerous medicinal products registered and accessible in the market, it is vital to be selective considering the medical needs of the majority of the citizens and also to guarantee the safety, efficacy, and cost-effectiveness. Essential medicines approach is reasonable, well organized, and based on sound ethics and economics (Mirza, 2008). It also supports national policies concerning the use and availability of medicines, and encourages the goals of primary healthcare (Hutchings et al., 2010; Management Sciences for Health, 2012).

Steps for the Development of EML

While developing an EML, the WHO expert committee on the Selection and Use of Essential Medicines meets and decides which medicines should be included in the list (Laing et al., 2003). The committee members (generally 8–12 in number) are from appropriate background and have experience in procurement, supply, and/or use of medicines (Foster et al., 2006; World Health Organization, 2011). The WHO has suggested inclusion of the following healthcare professionals in the Expert Committee on the Selection and Use of Essential Medicines (**Box 1**) (World Health Organization, 2011).

Applications for addition, deletion, or change of a medicine in the list are submitted (through concerned departments in WHO) to the secretary of the WHO Expert Committee at least 4 months before the meeting (Murray, 2015).

Box 1 Representatives of the Expert Committee on the Selection and Use of Essential Medicines.

- Representative of the Ministry of Health including employees from the medicines procurement department
- Professional organizations
- National and local health facilities
- ≥ 1 clinical pharmacologists
- Physicians and surgeons
- Child specialist
- ≥ 1 hospital and district pharmacist
- Director of hospital
- Additional specialists as required
- Members of disease control programs, for example, tuberculosis, malaria, and AIDs programs can be designated to attend meetings

Source: World Health Organization, Agenda item for the 18th Expert Committee on the Selection and Use of Essential Medicines: Draft for consultation, 2011.

The steps involved in the selection of essential medicines include efficacy, quality, and safety of medicines followed by their relevance with the current standard treatment guidelines (STGs) (World Health Organization, 2002). A transparent scientific and evidence based process for creating and updating the EML is followed by the Expert Committee. Selection of essential medicines is done on the basis of relevance to the disease pattern, proven efficacy and safety, adequate quality, desirable pharmacokinetic properties, cost-effectiveness, local pharmaceutical manufacturing, and the availability of medicine as a single compound.

These medicines are recognized by the International Non-proprietary Names (INN), or generic name (World Health Organization, 2002; Management Sciences for Health, 2012; World Health Organization, 2011). Resulting essential medicines list is made widely accessible to all healthcare providers and in all healthcare facilities in both electronic and printed form (World Health Organization, 2002). In the WHO, medicines in the model EML are classified into two categories: (1) core medicines that are defined as "efficacious, safe, and cost-effective medicines for priority conditions" and (2) complementary medicines that are defined as "medicines for priority diseases that are efficacious, safe, and cost-effective but not necessarily affordable, or for which specialized health care facilities or services may be needed" (World Health Organization, 2003). A nationally adapted EML based on STGs can help countries spend their scarce resources on the essential and affordable medicines (Van den Ham et al., 2011).

Essential Medicines Policies

The Nairobi Conference on the Rational Use of Drugs, held in 1985, was the first international conference on EMPs. Three decades after Nairobi Conference, essential medicines became a widely acknowledged public health policy concept (Greene, 2011; Wirtz et al., 2017). According to the Lancet Commission on Essential Medicines Policies, the development and subsequent implementation of EMPs can be classified into three time eras (Wirtz et al., 2017) (**Fig. 1**).

Standard elements of an EMP are procurement, supply, prescribing and dispensing of medicines, financing and incentive policies, and rational use of medicine (World Health Organization, 2001; Seiter, 2010; Greene, 2011). WHO has devised a framework to help policy makers improve access to essential medicines for Universal Health Coverage (UHC) by 2030. This is in line with the Sustainable Development Goals (SGDs) and includes the following four elements (World Health Organization, 2017a):

- **Rational selection and use of essential medicines**: It is linked to the development of national standard treatment guidelines and national EML.
- **Affordability and availability**: It is an inevitable factor in access to essential medicines that must be persuaded through multiple mechanisms including use of unbiased available price information, allowing price competition, supporting bulk procurement, implementing generics policies, negotiating fair pricing or abolition of duties, tariffs and taxes, and promoting local production of quality medicines.
- **Sustainable financing**: It can be guaranteed through various mechanisms including reduction in out-of-pocket expenditures, increased public funding, expansion of health insurance schemes, and exploration of external funding and financing mechanisms.

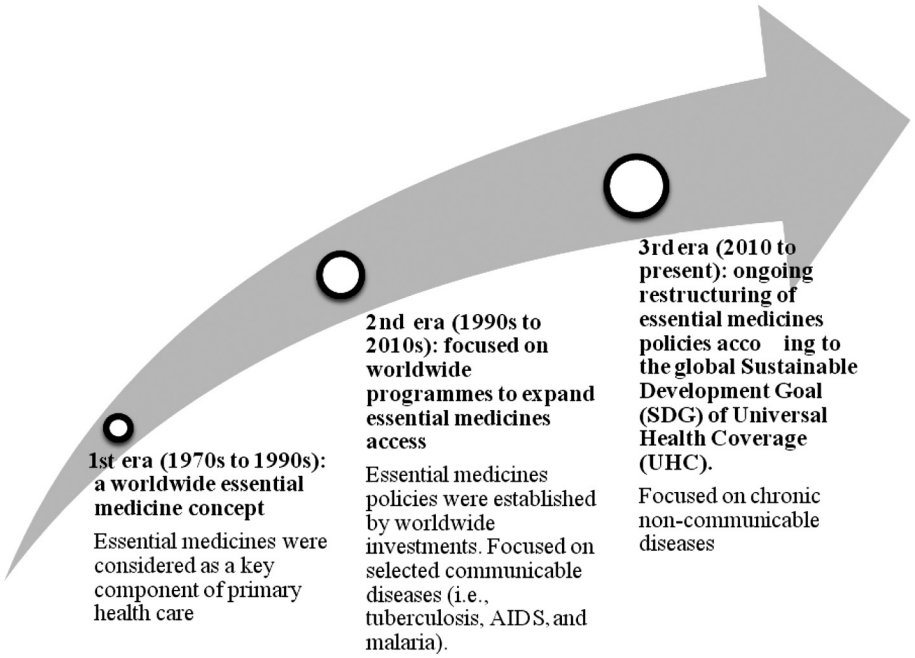

Figure 1 Evolution of essential medicines policies.

Table 1 History and development of EMLs and essential drug policies in few LMICs

Low and middle income country	*History and development of EML and essential drug policy (EDP)*
Bangladesh	• The Ministry of Health of the Government of Bangladesh in 1982 created an eight-member professional taskforce to develop National Drug Policy draft (Islam, 1984). • In 2011, the Government of Bangladesh adopted a new national health policy for the provision of essential medicines for non-communicable diseases (Das and Horton, 2013). • Current EML was published in 2016 (World Health Organization, 2016a).
Nigeria	• Nigeria embraces WHO-promoted essential drugs initiative in 1987 (Adikwu and Osondu, 1991). • Nigeria adopted the Bamako Initiative (BI) program in 1988 to confirm a stable supply chain for essential medicines (Uzochukwu et al., 2002, Chukwuani et al., 2006). • The Nigerian government started two plans to improve access to essential medicines that is the Essential Medicines Scale-up Plan in 2011 and the Save One Million Lives (SOML) in 2012. • Most recent edition of EML was published in 2016 (World Health Organization, 2016b).
India	• The first ever Indian National Essential Medicine List was developed in 1996 (Sharma et al., 2010, 2011). • Government of India in 2011 has announced a policy designed to increase the availability of EMs (Bandameedi et al., 2016). • Current NEML of India was published in 2015 and comprised of 376 medicines (World Health Organization, 2015).
Brazil	• The concept of essential medicines is a focus of the Brazilian National Medicines Policy since 1964. Brazil has had an EML, and from the year 2000 to 2010, the list has been periodically updated 5 times, working as a guide to quality medicine use (Osorio-de-Castro et al., 2018).
Mexico	• Health reform in 2000 introduced the people's health insurance (SPS) in Mexico and the government has implemented policies and reformed to guarantee equitable access to health care (Knaul et al., 2015). • In 2005, the MOH created the background document to serve as a basis for a national pharmaceutical policy (Moïse and Docteur, 2007; Gasman, 2008; Wirtz et al., 2008). • The current Mexican Formulary List (MEX-LIST) was published in 2014 (Roth et al., 2018).
Ethiopia	• The EML was first introduced in 1980 and revised regularly in 1989, 1996, 2002, 2007, and 2010. The sixth edition addressed three levels of health care (Food, 2010, Food, 2014).
Malaysia	• The Minister of Health announced on February 17, 1995 to implement a NEML (Haque, 2017). But it was first established in 2006 (Ministry of Health, 2013). • Last EML was published in 2014 and contained 321 medicines (World Health Organization, 2014a).
South Africa	• The EM initiative of South Africa was built as the National Drug Policy, which was instigated in 1996 since the instatement of the country's new democratic government in 1994 (Department of Health, in press, South African National Department of Health, 1996). • Since 1996, STG/EML has been revised 13 times. Latest edition EML was published in 2018 (Perumal-Pillay and Suleman, 2017, Health Department: Health Republic of South Africa, 2018).
Pakistan	• A National Medicines Policy (NMP) exists in official documentation form and was last modified in 1997 (World Health Organization, 2014b). • The NEML of Pakistan was first published in 1994. The list was revised in 1995, 2000, 2003, 2007, and 2013 by the MOH. The current NEML published in 2018 encompasses 428 molecules (30 categories and 78 sub-categories) (Government of Pakistan, 2018).

- **Reliable health and supply of quality products**: It is vital in sustaining access to essential medicines. Factors that support effective health and supply system include health sector development, efficient public-private-NGO mix, regulatory control, efficient procurement system, and the inclusion of traditional and complementary medicines.

The term "essential" has different interpretations and understanding in different nations, depending on the disease patterns, resources, medical traditions, and the result of pharmacoeconomic evaluation to select medicines. History and development of EML and essential drug policy in LMICs are summarized in **Table 1**.

Challenges Related to Essential Medicines

Over the years, the global health community has attempted to tackle the challenges related to essential medicines policies. The challenges include inadequate financing, improving affordability, quality and safety, improving medicines use, and developing new essential medicines. These challenges for the policies on essential medicines are not new (Wirtz et al., 2017) (**Fig. 2**). The Lancet Commission on EMPs has presented a comprehensive summary of the interventions shown to improve quality use of medicines. Collaborative efforts of the governments, policy makers, healthcare providers, the pharmaceutical industry, donors as well as civil society organizations and international agencies must address these challenges (Wirtz et al., 2017).

Figure 2 Core challenges for essential medicines policies.

Box 2 Highlights of 20th WHO Essential Medicine List

- Antibiotics categorized as access, watch and reserve along with recommendations to promote rational use.
- New drugs added to treat HIV, hepatitis C, tuberculosis and leukemia, including two oral cancer medicines (dasatinib and nilotinib) and first combination therapy added (sofosbuvir and velpatasvir) to treat all six types of hepatitis.
- Addition of two new fixed-dose combinations for malaria (dihydroartemisinin + piperaquine and artesunate + pyronaridine).
- Deletion of streptomycin as a first-line tuberculosis treatment from the core EML list.
- Expert committee strongly emphasized development of essential diagnostic list (EDL) for evidence-based clinical guidance.

The Role of World Health Organization

In May 1975, WHO strongly emphasized the formulation of national pharmaceutical policies based on quality, affordability and availability of medicines (World Health Organization, 1975). A resolution was tabled, and global public health vocabulary was introduced with the concepts of "essential drugs" and "national drug policy" (World Health Assembly, 1975; Quick et al., 2002). The first meeting of the Expert Committee on Selection and Use of Essential Drugs was held in 1976 (Helling-Borda, 2003); in 1977, WHO adopted the first Model List of Essential Drugs (World Health Organization, 1977). In 2007, the World Health Assembly Resolution (WHA60.20) on Better Medicines for Children emphasized the need to formulate child-specific dosage forms of many essential medicines (World Health Organization, 2007a).

As a result, first Model List of Essential Medicines for Children was published in 2007 (World Health Organization, 2007b). Over the years, the WHO has widely supported most LMICs in the development and subsequent implementation of national EMPs. By 2013, most of (>90%) LMICs had a list of essential medicines, and it was published in their national medicines policy document (Kanji et al., 1992).

The WHO Model List of Essential Medicines is updated and revised in every 2 years by the WHO Expert Committee on Selection and the Use of Medicines. The latest (20th) EML was published in June 2017; it contains 433 drugs (30 new medicines for adults and 25 new medicines for children) that meet priority health needs globally. Highlights of the 20th WHO Essential Medicine List are shown in **Box 2** (World Health Organization, 2017b).

Core Functions of WHO Essential Medicines Policies

Core functions of EMP include articulating and advocating policy options, working in partnership with the United Nation (UN) agencies, helping policy-makers through guidelines and tools for executing the elements of a national drug policy, developing norms and standards as a base for effective control, regulation, manufacture, and sale of drugs. The agenda also includes stimulating strategic and operational research; develop human resources and collection, and dissemination of information on medicines issues (World Health Organization, 2000).

Multiple Stakeholders Involvement in Formulating Essential Medicines Policies

Essential medicines strategies are developed and finalized in consultation and coordination with the range of stakeholders including governments, legislative bodies of the member states, WHO collaborating centers, WHO Expert Committees, the broader UN family, NGOs, and other global organizations (Shao et al., 2015). According to researchers, the present essential medicine system requires collaboration of stakeholders, and it would have positive impact if majority of its stakeholders contribute toward essential medicines operating system (Hui, 2011).

Stakeholders concerned with the essential medicine operating system are categorized on the basis of three key traits: power, legitimacy, and urgency. The "power" is the aptitude to instigate societal and political forces. The "legitimacy" is assembled by both normative legitimacy (having a fairness based on moral responsibility) and derivative legitimacy (stakeholders whose actions could influence normatively legitimate stakeholders) (Philips, 2003). The "urgency" is comprised of sensitivity (extent to which administrative delay is objectionable when dealing with the claims) and criticality (the significance of the claims to the

Figure 3 Classification of stakeholders involved in essential medicines policy.

stakeholder). On the basis of these three key traits, stakeholders could be categorized as dominant stakeholder, definitive stakeholders, dependent stakeholders, dormant stakeholders, dangerous stakeholders, or discretionary stakeholders (Mitchell et al., 1997; Shao et al., 2015) (**Fig. 3**).

Pharmaceutical Industry and Distribution Enterprises

Pharmaceutical manufacturers and distributors are dangerous stakeholders in the system, and are possible threats not only for the reason that they lack legitimacy but also because the medicine policies reduce their profits. It is also considered that the benefits of EMP are uncertain for them; however, they can earn profits by supplying medicines. However, industry can negatively impact EMP, if it started working against it (Management Sciences for Health, 2012; Shao et al., 2015).

The Role of Government

According to the Lancet Commission, government can take actions to ensure access, affordability, quality and safety, improved use, and availability of essential medicines. Access to medicines can be ensured through provision of adequate finance and addition of

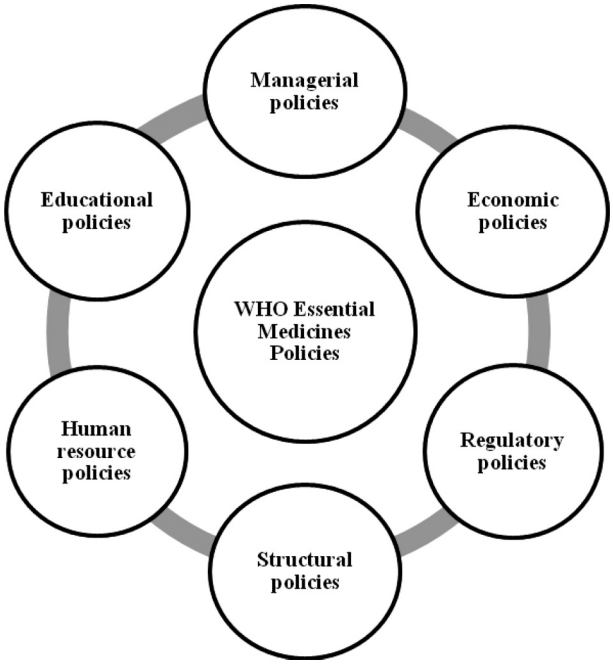

Figure 4 WHO essential medicines policies.

essential medicines in health insurance schemes. The quality and safety is ensured by adopting good procurement practices. The government can develop self-governing pharmaceutical analytics units that work in collaboration with other stakeholders to encourage quality use of medicines. Government also needs to give priority to policy framework for global research and development (R&D) of missing essential medicines, including its financing mechanisms (Wirtz et al., 2017).

Impact in a Globalized World

Access to basic medicines is the fundamental human right (Haque, 2017). However, there are millions of people who cannot access medicines (Lozano et al., 2012; Murray et al., 2012). Almost 10 million deaths globally [4 million in Southeast Asia and Africa alone (Zarocostas, 2007)] can be avoided every year, if access to essential medicines is improved (Guan et al., 2018); however, ensuring access to essential medicines is challenging in LMICs (Kaplan and Mathers, 2011). The HAI and WHO consider 80% availability of medicines as satisfactory in any given country (Kotwani, 2013).

Currently, four out of five countries globally have their own national EML (World Health Organization, 2016). Implementation of EMPs is known to save lives, promote rationale use of medicine as well as improve prescribing (Chao et al., 2018). It also improves detection of adverse drug reactions (ADRs), treatment compliance and reduction in antimicrobial resistance, and lowers prices through effective procurement policies (World Health Organization, 2000; Management Sciences for Health, 2012; Bandameedi et al., 2016).

In 2014, a 54-developing and transitional country analysis revealed overall six domains (**Fig. 4**) of EMPs associated with the better quality use of medicines. These include educational policies (initiation of undergraduate training and continual medical education of doctors and other health care professionals), managerial policies (revision of national EML and STGs, and implementation of generic prescribing and substitution), and economic policies (public health insurance, free supply of essential medicines to patients at all levels of healthcare).

This also includes regulatory policies (restriction on the availability of over-the-counter antibiotics and injections, active ADRs monitoring, and regulation of pharmaceutical marketing), structural policies (drug and therapeutics committees, and presence of national drug information center) as well as human resource policies (no prescribing by untrained staff). These policies were associated with the better use of medicines (Holloway and Henry, 2014). Among these, undergraduate training of doctors and nurses in STGs, unrestricted supply of free medicines to patients, and promotion of rational use of medicines through the MOH based regulatory unit were linked to the quality use of medicines (QUM). (Holloway and Henry, 2014).

Impact of Essential Medicines Policies in Low- and Middle-Income Countries

After the successful implementation of EML in LMICs, availability of essential medicines is a priority. According to a global report, EMPs have been successfully implemented in many low- and lower-middle income countries (Bazargani et al., 2014).

Implementation of the EMPs has resulted in easy availability, better affordability, and quality use of essential medicines in LMICs, but still, there are gaps in regulating medicines prices and improving their affordability.

Among Asian LIMCs, Bangladesh was very successful in launching and implementing an essential drug list in 1980s; however, it slowly deteriorated (Government of Bangladesh and United Nations Country Team, 2005; Islam, 2008; Ahmed and Islam, 2012; Akter et al., 2012; Islam et al., 2017).

A recent Indian study highlighted the need for revision of pricing policies to improve availability (Sarangi et al., 2018). Implementation of national EML also improved prescribing patterns and use of medicines in Malaysia (Saleh and Ibrahim, 2006). However, it was observed that effective price control is needed to control the high drug prices in the country (Babar et al., 2007; Ahmad and Islahudin, 2018).

Before 1993, medicine supply chain system in Pakistan was non uniform (Atif et al., 2017). Introduction of EML concept in the country made an impact and as a result the availability of essential medicines in public healthcare centers improved (Atif et al., 2016a,b). Though there are challenges related to high prices, affordability, and use of medicines (Saleem et al., 2016; Atif et al., 2016a, Saqib et al., 2018) as well as prioritization of research, including in-depth surveillance, promotion of rational prescribing practices, and a rationale pricing policy to promote access and use of medicine in the country (Zaidi et al., 2013; Atif et al., 2017).

In Nigeria, the overall prescribing pattern, utilization, and availability of essential medicines have improved after the introduction of essential medicine concept (Adebayo and Hussain, 2010; Oyeyemi and Ogunleye, 2013; Bazargani et al., 2014; Abdu-Aguye et al., 2016). According to recent reports, access to essential medicines was high in healthcare facilities and the prescribers had satisfactory awareness. However, prescribing practices were poor indicating gaps in the policy implementation (Hassan et al., 2018; Oghuvwu et al., 2018).

In Ethiopia, introduction of EML led to increased medicine availability and improved prescribing practices; however, medicines affordability did not improve (Lindtjorn, 1987; Carasso et al., 2009; Sado and Sufa, 2016). A recent Ethiopian study revealed lower availability and affordability, and high price for essential medicines (Abrha et al., 2018). In South Africa, cautious selection of a limited number of essential medicines and better medicine management resulted in improving quality of healthcare (Perumal-Pillay and Suleman, 2016).

In Mexico, EML is no longer evidence based; there are no uniform guidelines on the selection of essential medicines. Instead, economic and political interests influence the policy (Rivas, 2011; Lopez, 2018).

In Brazil, compromised quality, high prices, and inadequate availability of essential medicines represent flaws and inefficiencies of the national medicine policy (Naves Jde and Silver, 2005; Nogueira et al., 2011; Magarinos-Torres et al., 2017; Osorio-de-Castro et al., 2018).

The Use in High-Income Countries

Healthcare systems in high-income countries (HICs) also utilize selective medicines (from WHO's essential drugs) for effective allocation of resources (Gustafsson et al., 2011), though this is a concept intended essentially for resource-limited nations (Wirtz et al., 2017).

Managing EML is quite easy in high-income countries owing to their better healthcare systems and health insurance schemes (Cameron et al., 2009; Wagner et al., 2011). High-income countries implement health technology assessment (HTA) to evaluate cost-effectiveness of medicines. This is in turn useful for reimbursement and funding decisions in regard to medicines (Lexchin and Mintzes, 2008; Clement et al., 2009). Examples of these organizations are Pharmaceutical Management Agency of New Zealand (Pharmac), the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the Scottish Intercollegiate Guidelines Network (SIGN) in Scotland, and the National Institute for Health and Care Excellence (NICE) in the United Kingdom (Duong et al., 2015).

In 2000, the National Medicines Policy was introduced in Australia with emphasis on the "quality use of medicines." The NMP has been successful in improving the healthcare needs of the population (Yoongthong et al., 2012).

The introduction of essential medicine concept in Saudi Arabia has reduced the cost of medicines and improved prescribing practices (Al-Mazrou et al., 1990; Almalki et al., 2011). A Canadian study has estimated 28% reduction ($4.27 billion savings per year) in expenditure from universal public coverage of essential medicines (Morgan et al., 2017). In Europe, implementation of EMP resulted in rational use of antibiotics (Mölstad et al., 2008; Huttner et al., 2010).

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Implementation of Change in Pharmacy Practice

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Change Management

Change management is the process that guides how we prepare, equip, and support individuals to successfully adopt change to drive organizational success and outcomes. It is the systematic approach and application of knowledge, tools, and resources to deal with change effectively and in accordance with the desired timeline (Society for Human Resource Management, 2018).

Change is defined as a modification to a previous situation (Grand dictionnaire terminologique), and it could occur on an individual, organizational, institutional, national, regional, or global level in different aspects of pharmacy practice, regulation, and education.

Change management is extensively described in the literature and in various publications. In PubMed, change management is mentioned in more than 100,000 publications (Pubmed, 2018), but fewer than 3000 publications are related to the pharmacy profession, including changes mostly in industry, technology design, protocols in collaborative practice, chronic disease management, clinical services, and education. One recent publication presented 16 authors as a source of reference in the field of change management. This review provided a brief theory statement, description of models, and possible methodology of changes that could be adopted (Guérin et al., 2015).

In all publications, key elements described are communication processes, strategy, goal setting, organizational culture, leadership, conflict resolution, as well as barriers and facilitators of the change process in general. It is evident that change is influenced by the vision of the leaders and stakeholders as well as human resource management. As a dynamic entity, change management is seen as a tool to be used to achieve the goal set in the vision of an individual, organization, or nation.

When change is attempted in any organization or system, there are four distinct possibilities in terms of the outcome: it never gets off the ground; it occurs but undershoots the level originally planned for (suboptimal); it achieves focused "pockets of excellence" but no more; and it achieves pervasive and sustained change at the desired level (Vlasses, 2012). Another way to consider the typology of change is the depth and pervasiveness of change achieved. This is depicted in **Fig. 1** (adapted from Eckel et al., 2001).

In this chapter, some of the aspects of change management will be described in a format that is intended to be useful in implementing change in the pharmacy profession.

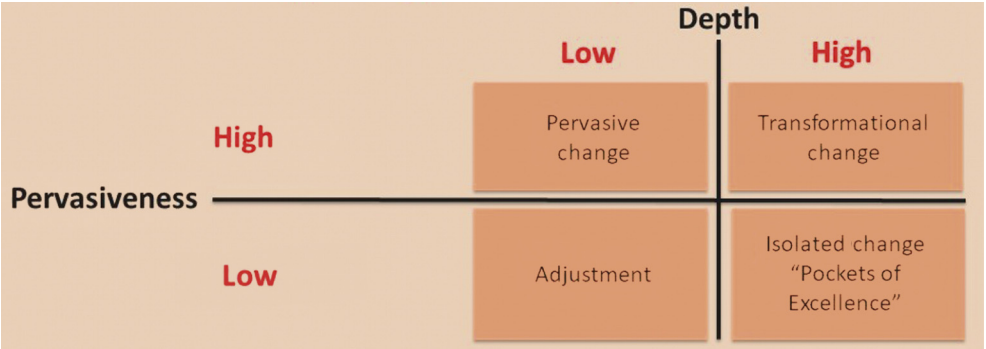

Figure 1 Typology of change.

Perception of Change Management in Pharmacy Practice

The change process in the pharmacy profession is usually observed and perceived as a slow, long, and complex process, involving different barriers and challenges. (Tsuyuki and Schindel, 2008) Different factors influence change in pharmacy practice, such as environmental, contextual, and personal/psychological aspects of change. Strong traditions in the profession, as well as strict regulatory frameworks, influence the dynamics of change, frequently resulting in long discussions and procrastination in the change process.

Many pharmacists will declare the need and desire for change to happen, but not so many are ready to change their habits in learning, practising, and approaching the issues in the pharmacy profession (Bellanger and Shank, 2010). Even if new opportunities, such as new services and roles, are occurring, resistance will often come from within the profession, as well as outside it. More complexity is added considering the fact that many different stakeholders are interested and involved in the change process in pharmacy, advocating for their own perspectives and goals. There are strategies and methods to lead the process of stakeholder involvement and influence the change process (Roberts et al., 2003). Providing support for practice change in a structured and organized way will endorse the process of change and assure the success of the desired vision (Gregory et al., 2017). Leading the change process requires a sensitive approach, strategic planning, leadership skills and dedication, commitment to change, and social intelligence. By knowing and applying some theory behind change management and following some of the available concepts, change in the pharmacy profession should be possible and realistic.

What is Changing in Pharmacy Practice?

Many aspects of pharmacy practice are changing. Products are no longer in the center of pharmacists' attention; they are now seen more as a part of the solution, responding to patients' needs. Cognitive services are developing and emerging as a new way to achieve patient goals and improve the safety and outcomes of medication use, adding value to the pharmacist's role and responsibilities in health-care systems.

Technology advancements are reflecting on pharmacy practice in many ways, from robotic procedures to IT tools and applications for patient use and safety. Data collection, documentation, and interpretation are now part of everyday practice, resulting in growing research and publications in the pharmacy practice field. The communication culture is changing, e-health is available in many regions, providing new opportunities to share and use health-related information in fast and effective ways.

Screening tests, point-of care services, various risk assessment methods, prevention programs, and public health campaigns are changing the face of pharmacy practice, in hospital and community pharmacy, and other practice settings. New services, such as seasonal immunization, pharmacogenomics, home and annual medication review, visits to pharmacies are requiring new knowledge, skills, and attitudes, as well as new approaches to education and training of pharmacy practitioners, including pharmacists and pharmacy support personnel.

Changes in pharmacy education are emerging in many different countries, led by professional organizations, academic institutions, and innovative leaders. New strategies and goals have been set on a global level to build capacity and foster and promote changes in educational activities and methods to achieve the desired competencies of pharmacy practitioners (FIP, 2017).

The pharmacoeconomic aspect of practice is playing a bigger part in health politics and strategies, with great impact on financial savings in health care. Collaboration with other health-care professionals is growing, including joint services with medical doctors, nurses, nutritionists, physiotherapists, and others. Often, changes in regulation are slower than changes in practice, which causes procedural gaps and lack of unity in the profession (Bader et al., 2017).

Who is Involved Into the Process of Change?

Stakeholders are people or organizations with a direct or indirect interest in the process and outcomes of the exercise or project, whether positive or negative. A stakeholder should also be thought of as any individual or group who can affect or is affected by the actions, decisions, policies, practices, or goals of the project. Stakeholders involved in pharmacy practice are many. While varying in the degree of influence on and support of change, they have an interest to be involved, either to facilitate change and make it successful or to block it. Depending on the nature of the change, sometimes the same stakeholder group might have different roles and levels of support, including opposition. For each stage of the change, it is essential that all key stakeholders are identified and, as appropriate, consulted and given the opportunity to participate (e.g., in discussions, planning and decision-making, in a pilot project, in data collection and interpretation) or, at a minimum, kept fully informed.

Stakeholders will differ in a number of important characteristics: their mission and goals, motives, needs, interests, expertise, resources, and focus can be different. It is important to understand these issues before starting to develop engagement strategies to include them in the change process. Additionally, it is necessary to prioritize efforts to ensure that energy is directed at the most appropriate stakeholders.

Stakeholders' Support

Stakeholders' support of the proposed change can be high, low, unknown, mixed, or even outright oppositional in certain cases. One example of an important stakeholder when considering changes—especially expansion—in pharmacy practice would be medical doctors as a group. If the change is focused, for example, on pharmacists' services to improve patients' adherence, they would probably be supportive and influential in helping to achieve that change. On the other hand, if the change relates to immunization as a new role for pharmacists, they might be less supportive or even actively engaged against the change to happen. What can also be the case is that under one stakeholder group, the level of support may differ on an individual-by-individual basis; for example, some medical doctors might support measuring blood pressure in the pharmacy, some might be against that change, some might be undecided. In this case, different engagement strategies would be needed with each subgroup.

Stakeholders' Power and Influence

Before initiating change, it is very important to recognize who the stakeholders might be, to understand their motives and goals, and try to predict how influential (powerful) they are to facilitate or block/impede the proposed change. It is helpful to be well informed about the scope of their responsibilities, as well as their defined mission, so as not to be surprised during the ongoing process of change, if they need to react, give permission, or postpone the decisions and processes of change. It is also important to understand the hierarchy between them and to identify the paths of the change process in order to be successful and complete the change within the desired timeframe. Additionally, it is essential to be aware of the organizational structure of the institutions, channels, and protocols for communication and the time needed to secure required permissions, documents, etc. This might depend on the frequency of important meetings and/or deadlines and procedures in the institution; recognizing that any request will likely compete with other priorities and urgent situations.

It should not be assumed that all stakeholders who offer to be involved in the change management process are supportive. Some stakeholders will want to maintain the status quo, and they will participate primarily to resist change and ensure that their point of view is heard. This group can come from so-called "opinion leaders," who can be very slow in accepting and embracing the changes in their field, especially if they did not come up with the idea or initiate the change.

In the pharmacy profession and practice, we can identify the following stakeholders who might be involved in the change process (**Table 1**) (Mendelow, 1991; Savage et al., 1991): .

Stakeholder Matrix and Engagement Strategies

Once it is known who the stakeholders are, the next step in the change management process is to map them into a stakeholder matrix, according to their level of support and ability to influence (facilitate or block) the desired change (**Fig. 1**). When those two criteria are combined, it is possible to assign stakeholders into typically one—but sometimes two—of the following four boxes (**Fig. 2**):

The statements allocated under each group of stakeholders indicate the essence of the engagement strategies and action plans to involve stakeholders in the most appropriate way. In more detail, those strategies could include, but are not limited to:

1. *Partnering with stakeholders of high influence and high support* because the connection is natural, goals will be aligned and collaboration should realistically lead to successful change and a win/win outcome. When the stakeholder shows high support, the platform for collaboration is open for inclusive participation, shared responsibilities and resources, and combined expertise as there are no threats in the process. Creative ideas and solutions might be presented and accepted within these partnerships.

Table 1 Stakeholders who might be involved in the change process

Governmental (national/state/provincial) institutions:
- Ministry of Health
- Ministry of Higher Education
- Medicines Agency and other regulatory bodies
- Institutes of public health
- Health insurance organizations
- Accreditation agencies/councils

Professional bodies
- Pharmaceutical Chambers (mandatory membership)
- Pharmaceutical Societies (voluntary membership)
- Institutes for quality improvement

International organizations
- International Pharmaceutical Federation (FIP)
- World Health Organization (WHO)
- Regional professional and educational organizations
- Regional pharmaceutical advocacy/trade groups

Pharmacy practitioners
- Hospital pharmacists
- Community pharmacists
- Clinical pharmacists
- Pharmacy assistants
- Pharmacy technicians
- Preceptors
- Pre-registered practitioners

Other health-care professionals (and their professional organizations)
- Medical doctors in general practice
- Medical doctors in specialty practice
- Nurses
- Engineers of medical biochemistry
- Laboratory practitioners
- Nutritionists
- Physiotherapists
- Other health-care professionals
- Interprofessional organizations

Academia and other providers of education, training and credentialing
- National, regional, or international associations of colleges/faculties of pharmacy
- Professors and faculty members
- Researchers
- College/faculty of pharmacy administration
- Students and students' organizations
- Teacher practitioners/preceptors
- Providers of continuing education/continuing professional development
- Credentialing bodies, for example, specialty certification bodies
- Trainers and coaches in pharmacy practice

Patient organizations
- Organizations for the patients' rights/advocacy
- Organizations of special interest groups of patients

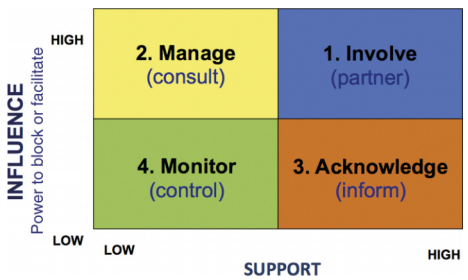

Figure 2 A stakeholder engagement matrix.

High influence will open the opportunities to achieve the results earlier than expected, and efficacy could be high. Also, when leaders of change cooperate with highly influential and highly supportive partners, motivation is high, and engagement is more intensive. That leads to good results to be presented and followed by new actions and procedures. Showing publicly the influential partners' support will change other stakeholders' perceptions of the change. The engagement strategy of active involvement aims to ensure that the support of the stakeholder remains high. Regular meetings with partners must be held to establish implementation project parameters and strategies, define success criteria, identify potential constraints or barriers, review and agree on key issues, and establish a mechanism for early "flagging" of problems.

2. *Managing the stakeholders of high influence, but low support* will take lots of energy and strategic thinking by the leaders of change. The reason for this is that highly influential stakeholders will have power to block the change, delay its realization, or limit its scope. If the stakeholders in this category have low or unknown support, it is essential to include them in the process in a way that they can openly express their concerns, suggest possible solutions, and choose between possible options to maintain their authority and interest. The strategy has to be designed to increase their support and ultimately involve them as partners in the change. These stakeholders need to see that change managers are following their instructions, asking them for guidance and contribution, and creating opportunities for a true partnership. For this stakeholder group, it is important to demonstrate the value of change, either for them directly or for those they represent to achieve more support and engagement. Change might have political implications, such as election results; therefore, it could be part of strategic thinking on a higher level. Once a few influential stakeholders with initial low or unknown support are convinced, other important stakeholders might follow in showing more support.
3. *Acknowledging the stakeholders with high support and low influence*. A high level of support for change is always welcome, but it will not necessarily lead to realization and sustainability in practice. Many stakeholders who can contribute to the success of change could come from this group (e.g., students, practitioners, patients, and educators), but if the change process is too slow and not promising, the stakeholders might lose interest and slow down their engagement activities and support. Change leaders must clearly communicate to these stakeholders the nature of and rationale for the change and regularly inform them of progress and results.
   It is very important to acknowledge the support and contribution of these stakeholders, not just at the time of their engagement, but also in later stages, when first results are starting to be visible. Once the change is achieved, it is appropriate to keep this group engaged, visible and recognized, as their influence might be crucial in other projects and changes in the future. The essence of the engagement strategy is to ensure that their support remains high. If the level of support drops, there is a risk that the "influence" of this group can increase indirectly through their advocacy efforts with those who hold real power to block or limit change.
4. *Monitor the stakeholders with low support and low influence.* The contribution to the change process of this group of stakeholders might be underestimated, as they might not have the power to stop or block change, but they could slow down the process of change and bring confusion to the active partners on the process of change. If not "controlled" this group of stakeholders can become a distraction and consume valuable time and effort. It is, therefore, good to monitor their activities carefully to ensure that they do not become a distraction for the change management team. The engagement strategy is to find ways to increase their level of support and involvement if possible because, as with Group 3, there is a risk that their "influence" can increase indirectly through their advocacy efforts with those who hold real power to block or limit change.

Some authors have suggested a more detailed approach to stakeholder engagement, implying that change initiatives can be evaluated using six factors (Peltokorpi et al., 2008):

- the effect of the planned intervention on stakeholders' actions and position;
- stakeholders' capability to influence the project's implementation;
- motivation to participate;
- capability to change;
- change complexity; and
- management capability

Traditional methods of sociodynamic profiling are also found to be useful as an analytical management approach to manage stakeholders in projects that are likely to experience high resistance to change. Stakeholder engagement mechanisms can cause some projects to fail or succeed, depending on the acceptance of the stakeholders' approach, but improved stakeholder communication methods can create a better understanding of resistance to or acceptance of change (Walley, 2013).

Practical Application of a Stakeholder Engagement Matrix

In summary, when a major change or project is envisioned, a stakeholder engagement matrix can serve as a simple but useful tool for the change management team, by following these steps:

1. Identify *all* stakeholders who are important to the change/project.
2. Assign each stakeholder to one or more of the groups described above (1. Involve; 2. Manage; 3. Acknowledge; and 4. Monitor) remembering that individuals of a particular stakeholder group (such as physicians) may have different levels of support and, therefore, could be assigned to different groups.

3. Develop engagement strategies based on the level of influence and support, with priority attention for early action being given to the key stakeholders in Groups 1 and 2.

The Eight Step Process of Successful Change

One of the most successful and popular approaches to change management is the theory of change published by John Koetter (Koetter and Rathgerber, 2006).

This approach can be applied in eight stages, as follows:

Set the Stage

1. Create a Sense of Urgency
   This first step to achieve the desired change needs to be strategically planned and prepared to ensure that the message is communicated in the right way, in the right place, and to the right people. The aim of this step is to help others see the need for change and the importance of acting immediately, or as soon as possible. When it comes to change, it's human nature to procrastinate and wait until circumstances are "ideal." Communications should be affirmative, informative, and carefully articulated, to be heard and clearly understood. A sense of urgency can be strengthened by adding important statistical or financial facts, showing the trends and projections of the unwanted scenario; for example, what will happen if there is no change? What are the consequences? Sources for such facts should be reliable and well checked, preferably endorsed by important and influential health-related organizations, such as, the World Health Organization (WHO) or important, well-recognized recent publications. The communications should be reinforced through the use of multiple methods and media formats at the same time (news, leaflets, social networks, etc.). Those messages could be a part of ongoing, well-timed public health campaigns, government initiatives, national, regional, or international strategic plans to immediately assure strong and well-recognized partners to reduce costs and multiply results.
2. Pull Together the Guiding Team
   The leader of the change needs to ensure that there is a powerful group guiding the change—one with enthusiasm, leadership skills, resilience, credibility, assertive communications, strong authority, good analytical skills, and a sense of urgency. The guiding team should be carefully selected, to assure a smooth process of change initiation, including affirmative atmosphere, inclusive approach, and participatory leadership. Responsibilities should be well-defined and shared, timelines set, and goals clearly visible to all members of the team. Communication should be carefully planned until the plan is ready to be announced.

Decide What to Do

3. Develop the Change Vision and Strategy
   The most important part of this stage of the process is to clarify how the future will be different from the past, and how that future could become a reality. Building the mind-map is one of the strongest accelerators to acceptance of the change in the mind of the target group. This is when marketing strategies and project planning will take place, including economic, clinical, and humanistic aspects of the change. In particular, possible benefits and results should be announced and accepted. Strategies to be adopted should demonstrate win-win situations to include and engage important stakeholders, especially targeting patient safety and outcomes, which can lead to financial savings in the health-care system, more efficient operational procedures, and sustainability.

Make It Happen

4. Communicate for Understanding and Buy-In
   In the third phase, which is connected to realization, it is important to make sure that as many others as possible understand and accept the vision and the strategy for the desired change. It is crucially important to design communication strategies to avoid any misunderstanding in this early implementation phase. Communication here includes stakeholders (with different strategies to engage them) and a process of announcements in the health-care system. Benefits for each stakeholder group and/or their constituents as well as the health system as a whole should be clearly described. In addition, the different roles and valuable contributions that specific stakeholders can make during implementation should be highlighted. Authors and deliverers of these messages should be well prepared to address all possible concerns and questions with evidence-based facts and published resources.
5. Empower Others to Act
   In this phase, it is important to remove as many barriers as possible so that those who want to make the vision a reality can do so. Education and training activities are essential here, including toolkits for application and evaluation of the

change process. All questions and concerns should be answered in this stage, building capacity and leading to the first results.

6. Produce Short-Term Wins
   In the change process, some visible, unambiguous successes should be assured as soon as possible. Establishing simple projects and objectives ("low hanging fruit") and collecting early evidence of success will assure a firm start and solid foundation and encourage and motivate stakeholders, leading to further success. On the other hand, setting unrealistic and over ambitious objectives may result in failure to achieve the desired results, lead to discouragement and demotivation of stakeholders, and provide an opportunity for cynics and naysayers to denounce the change. If possible, the success should be celebrated, champions recognized, and results published to advocate for the further developments and visibility of change. In this stage, some stakeholders can increase their level of support and join the efforts to bring the project to a higher level. It is important to communicate with them the further steps and strategies and to find a place where they can contribute to the process of change.
7. Don't Let Up
   Many good initiatives end after the first successes (e.g., adoption by "early adopters" or champions) or even earlier. This does not necessarily mean that there was a problem with the idea behind the initiative. After the early successes, there is a "gulf" (see later discussion in this chapter) when leaders of change should press harder and be relentless with implementing the change until the vision is a reality. It is crucially important not to disappoint the leading team and to not allow the initiative to "die" after the first promises have been fulfilled. There are many strategies to be used in this stage of the change process, such as, fostering publications, panel discussions, announcements of national projects, organizing educational programs, and meetings to inspire others to act and be a part of success.

Make It Stick

8. Create a New Culture
   This is the time to hold on to the new culture and new ways of behaving and make sure they succeed until they become strong enough to replace old traditions. New regulations can help here, if it is possible to change requirements and demand implementation of new services, new principles, and new standard operating procedures. The new culture should be promoted and visible, as well as set as a new standard to follow. This empowerment can be organized at institutional and organizational levels, to assure the clarity of standards and to avoid improvisations and failure.

Pilot Project to Manage the Change

A *pilot project*, *pilot test*, or *pilot experiment* is a small-scale preliminary project conducted to evaluate sustainability, feasibility, resources and materials, timeline, costs, and possible outcomes of the project that will introduce the change. The main purpose of piloting the project is to identify gaps and barriers of implementation, to improve the study design and/or appropriateness of materials and resources prior to full implementation of the change. Some stakeholders might like to wait until a pilot project has shown preliminary results to be fully engaged, which is also one strategy to consider when selecting partners for the project. The pilot project also needs to be properly designed, strategically planned, and include different aspects of implementation. If possible, indicators of successful implementation should be in place to allow improvements and check points (Billé, 2010).

Individual Response to the Change Process

Every change will have an impact on the individual level, for all participants included in the change process. The impact of change in different organizations or at the national level might have different responses from different groups of people. Research indicates that individuals find it difficult to engage with change in a meaningful manner as stress, fear, and anxiety prevail; therefore, a strong strategy in change management is required to assure change implementation and sustainability. Leadership must help individuals to accept the change and to adjust it in everyday practice with visible meaning and reasoning about the benefits of the change. The eternal question "Why do we need the change now? Why should it affect me?" should be addressed by well-organized strategy and planning, to avoid negative individual contributions (Vakola, 2014)

Rogers' Innovation Adoption Curve

One of the most cited and used models in explaining innovation adoption is Rogers' innovation curve, which portrays different group of people in their responses to the proposed change. Researchers have studied why some innovations spread more rapidly than others and which are slow in implementation. If the perception is that the innovation will be advantageous, compatible with existing values, beliefs, and experiences, relatively easy to comprehend and adapt to, observable or tangible, and divisible for trial, it is more likely to be adopted (Rogers, 2003).

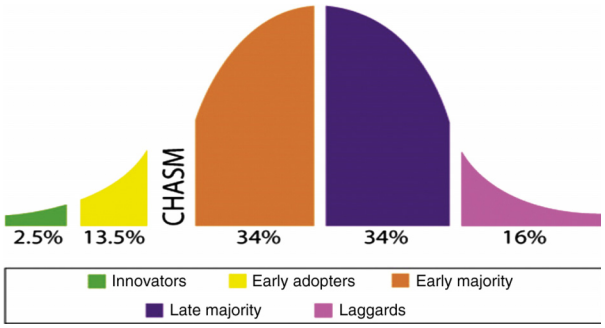

Figure 3 Rogers' innovation adoption curve.

Rate of adoption is described as the relative speed with which members of a social system will adopt an innovation. It is measured by the length of time required for a certain percentage to adopt an innovation and change. The dynamic is slow until the change adoption reaches the so-called "tipping point," at which time/point an innovation reaches critical mass and turns into a self-sustaining process to make change stable, effective, and visible (Fig. 3).

Innovators are people who will adopt change first; they could even invent and suggest change, bearing the need to describe the outcome and impact of innovation. They comprise 2.5% of a typical population. Considering pharmacy practice, they will need to adjust innovations to the existing law-frameworks and pharmacists' scope of practice, usually trying to fit into existing practice models. They are creative, affirmative individuals or groups, who will always investigate options and opportunities to improve practice and advance the roles of pharmacy practitioners. Usually, they belong to younger generations and highest social class, have the closest contact to scientific sources, and interaction with other innovators in their field. They are willing to take risks and initiate the change process under any circumstances.

The second fastest category of individuals who adopt an innovation is *early adopters* (13.5% of a population). They are easy to include in the process of change. Even though they didn't suggest or initiate the change, it will be easy to persuade them. They have the highest degree of opinion leadership, higher social status, advanced level of education, and willingness to try.

The next category would adopt an innovation after a varying degree of time. The time of adoption is significantly longer than with the innovators and early adopters. This group represents the *early majority* (34% of a population). These individuals seldom hold positions of opinion leadership, but they are of above average social status. To include them in the process of change, it would be helpful to introduce incentives and to explain clearly how the change will benefit them. They like to see large numbers of stakeholders supporting the change to be more convinced that change is important, realistic, and needed.

The *late majority* (34% of a population) are typically highly skeptical and will not be easily convinced that there is any need to change. They are likely to express that they have some reservations, not being sure that the change will work in real practice. In this group, members will adopt the innovation after they observe that it has been adopted by a majority of the population. Members of this group typically have below average social status and have very little opinion leadership.

The group, which will be the last to adopt an innovation, demonstrates little to no opinion leadership. They are called *Laggards* (16% of the population). They like to stick to tradition and do things in "the good old way." The need for change is something they will typically not see. They will often only change when forced to by their employer or through regulation. They tend to be advanced in age, are very likely to have the lowest social status, and have a poor network of experts they can rely on and consult in certain situations. Their resistance to change in general could be applied directly and personally on the innovators and agents of change and cause conflicts and distraction to the change management process.

There are two important points in the rate of adoption. The first is positioned between the early adopters and the early majority. It is described as a "chasm" or "gap" to signify the difficulty of making further progress in the change process after the innovators and early adopters. It is also a warning to change managers to persevere in the process and apply more effort and resources. This is an important stage to maintain the process of change at the desired level and not to allow the change to be compromized and prolonged. If this point is not recognized, there will be delays in the change process, which can cause loss of motivation and engagement of the innovators and early adopters and may ultimately lead to a breakdown of the change process.

The second point is positioned between the early majority and the late majority. When 50% of the population has adopted the change, the dynamic of the change process alters and change happens by itself. This point is graphically portrayed as the top of the curve and it is named the "tipping point" for change. After that point, the change process should be irreversible, maybe even facilitated by regulation or other forms of requirement and standard procedures.

Managers of change should use existing tools to navigate the process of change in a structured, strategic, and efficient way, avoiding delays and obstacles. Other skills that are helpful in achieving the desired implementation of change include time management, organizational skills, strategic planning, assertive and motivational communication, risk management, marketing skills, public speaking, presentation skills, and IT literacy.

Barriers and Facilitators of Change in Scope of Pharmacy Practice

Innovation in pharmacy services is growing and shaping pharmacy future in a patient-outcome oriented way. According to the Good Pharmacy Practice (GPP) guidelines, pharmacists in community and hospital settings, as well as nursing homes and other tertiary care positions, should introduce new services in collaboration with other health-care professionals, to meet societal needs and embrace new roles and responsibilities (Joint FIP/WHO Guidelines on Good Pharmacy Practice, 2011).

All these changes are on the agenda of many professional organizations, regulators, and private initiatives, confronting the change management process with many internal and external challenges. In many countries, regulation is not clear about the competency level of pharmacists needed to provide new services, and there are inconsistencies between countries and regions in this regard. There is a critical question about credentials and privileges of different groups of pharmacists to assure that services are introduced in safe and standardized ways to patients. Levels of clinical experience and skills of pharmacists differ across the globe, including the generational differences due to various curricular changes and clinical aspects of educational programs offered over the last 20 years. All these aspects should be observed through change management aspects, ensuring many stakeholders are included in the process of implementation of new services and roles of pharmacists in practice.

It is important to understand that every practicing pharmacist has developed clinical reasoning and judgment to a certain extent, and that there is a requirement for all pharmacists to perform on a certain clinical level. Pharmacists who are specialized in some clinical areas (such as ambulatory care, pediatric care, oncology, etc.) will be able to introduce services on a different level but that does not mean that all pharmacists cannot embrace new roles and responsibilities.

Besides pharmacists' traditional roles to prepare, procure, store, secure, distribute, and dispense medicines and medical products, there is a new demand to provide rational pharmacotherapy. Based on GPP guidelines, that means that pharmacists should assess the health status and needs of the patient, manage medicine therapy processes, monitor the outcomes of the treatment and progression of the patient, and provide information on medications and treatment procedures to patient and carers.

It is also required that pharmacists in all settings should achieve excellence and continuous improvement in their knowledge, skills, attitudes, and values by planning and implementing continuing professional development to achieve new competencies.

There is also requirement to contribute to effective functioning of the health system and public health activities by informing and educating patients about medicines, prevention, and health through active involvement in prevention and treatment outcome procedures. All actions need to be in line with the national context, guidelines, and legislation, providing active support and promotion of national strategies that aim for good outcomes of treatment and patient safety (FIP/WHO Guidelines on Good Pharmacy Practice, 2011).

Cognitive Services and the Change Process for Their Implementation

Innovative cognitive services are needed in rationalization of medicine therapy and patient education. Cognitive pharmaceutical services can be defined as professional services provided by pharmacists, who use their skills and knowledge to take an active role in patient health improvement, through effective interaction with both patients and other health professionals. There is growing evidence of the effectiveness of implementation strategies that ensure that changes in this aspect of pharmacy practice are successful.

To foster the success of the change management process, it is important to recognize the usual barriers and facilitators of change and to account for them in the strategic planning and implementation process.

Services that should be introduced in the process of change should be based on an *interprofessional, integrated approach to the patient* and include collaborative practice. To facilitate change, the main stakeholders, such as medical doctors, should be not just informed but invited to partner in the change management process. If that is not the case, and pharmacists try to work in isolation they will become one of the biggest barriers of service implementation.

Furthermore, the *selection of services* to be implemented in pharmacy practice should be based on public health, patient education, adherence, and patient safety, care systems. They belong to the specific expertise of pharmacists, not interfering with other health-care professional services but contributing to efforts to achieve safe and effective use of medication. It is also important to choose a service based on the real and carefully examined *needs of patients* through interviews, surveys, and expert panels, alongside considering *patient satisfaction* with the services provided in the health-care system. Seasonal immunization, as one example, was successfully implemented in more than 40% of EU countries, based on the real need and satisfaction of patients. If the implementation of a new service changes the perspectives of patients, thereby increasing the expectations and demand for the service, that is a very strong facilitator of change, and it is important to continue with the change process. *Communication with and counseling of patients* can be a strong facilitator for service implementation, using the principles of motivational interviewing and active listening skills. Proper selection of a new service obviously can facilitate the change, as the need to implement it is easily recognized and welcomed in the health-care system.

One of the most important facilitators to implement a new service is *well-organized team work and shared responsibility* of the pharmacy team, utilizing their competencies and specializations in certain aspects of pharmacy practice. For full-service implementation, it is recommended to include *external experts* with skills and knowledge that are needed to facilitate the process of change. Those could be experts such as educators, consultants, designers, project developers, IT managers, lawyers, and marketing experts. One of the biggest barriers to change implementation is the perception that members of the pharmacy team can manage all these

aspects of implementation themselves. It usually takes much more time, costs are higher at the end of the process, and the result is not always on the level of excellence.

Clearly defined *standards and quality control* of service provision can facilitate change; therefore, it is important to ensure that the legal framework and regulatory issues are ready before implementation starts. Pilot projects are always recommended and needed and, as regulation processes sometimes can be slow, it is good to start with collecting evidence that a new service is effective, needed, and well received by patients. For these aspects of implementation, *IT tools and applications for data collection* and processing can facilitate the change but also be barriers to implementation, as many pharmacists will still prefer to collect data in traditional ways.

A solid and sustainable financial base for a new service implementation can also be a strong facilitator, as the benefits of the implementation will be assured and visible quickly. It could be perceived that providing services for free can be a facilitator for implementation success, and payment for services can be seen as a barrier but much evidence shows that in real-life situations that is not the case. Patients are ready to pay for services when they see and respect the value of the service. If the service is provided for free, it might not be perceived as so valuable by the patient. Pharmacists wondering why they have to provide extra work for no financial gain can be a strong barrier to embracing new roles and changes in practice.

Marketing tools are important facilitators for change management. Marketing activities directly involve inviting messages, calls for participation in new services, and making the change more visible and desirable in society. Messages and signs in the pharmacy windows and/or dispensing area, together with reallocation of service provision (to the consultation room for example), as well as space designation are strong facilitators of change. They help both providers and customers to see the difference between old and new systems and realize the benefits that new services can provide. Visualization of change is helpful to maintain momentum, especially when the early majority starts to buy into a new concept of care.

Referring back to Rogers' innovation adoption curve shows that it is important to understand that one of the most important facilitators of change is the *development and visibility of internal "champions" and accelerators of changes* within any system that is introducing change. Those individuals are important in the process and serve as positive role-models for other colleagues. They provide examples in real-life situations that changes are possible. Generative systems, open to change, will always recognize and invest in the development of those champions as part of the change management process. It is important to celebrate success and excellence in accepting new roles and responsibilities and then set new standards for the pharmacy organization and all its departments. Achieving impact on patient outcomes and safety is probably the strongest facilitator of change, as it fosters pharmacists' motivation and professional satisfaction, which results in more change in practice (Roberts et al., 2008).

All barriers can be analyzed on multiple levels within a system and externally. A systematic analysis of internal barriers can include, but is not limited to: current organizational culture of the pharmacy, lack of an internal implementation champion, lack of priorities and goals, inappropriate layout (including the lack of a counseling room), lack of appropriate technology and resources, and lack of bibliographic resources and medicines-information support/assistance. At the pharmacy staff level, lack of leadership, lack of staff awareness about the relevance of the service, lack of priority to implement the service, inadequate workflow, and lack of staff training to provide the service are identified as the major barriers (Garcia-Cardenas et al., 2016).

If new services are oriented toward models of collaboration with other health-care professionals, such as nurses, general practitioners, specialists, there is evidence that demonstrates what is successful when integrating changes into an existing primary care team. After the determination of the needs and priorities of the team and its patients, it is recommended to clearly communicate and explain new roles to the health-care professionals and to develop new and updated pharmacist job descriptions. Then, it is necessary to train and educate the team about the new roles and collaboration, including all members of the team. It is also important to ensure that clinic infrastructure supports the new pharmacist's role and to ensure that pharmacists' skills are strongly developed and their knowledge is up to date, so they can provide proactive care and take responsibility for patient outcomes. In the process, it is highly recommended to regularly seek feedback from the team, as well as developing and maintaining professional relationships with other team members in the health-care system (Jorgenson et al., 2013).

The change in pharmacy practice should be considered as an essential part of the quality improvement and advancement. It is necessary and possible. Despite many obstacles, there are tools and paths to be used to achieve the desired change, and change management is a competency of the pharmacists that should be developed and nurtured providing new knowledge, new skills, especially new attitudes, and values. All stakeholders in pharmacy practice, education, and regulation have shared responsibility to maintain the good collaboration and mutual support in this noble task, rather than working in isolation. Innovation is a category we have to consider essential to provide better care and assure best possible outcomes for our patients.

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Professional Boundaries

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Introduction

Professionalism is considered by the American College of Clinical Pharmacy as one of the six competencies of practitioner pharmacists that can be described by the maintenance of the highest standards of integrity and honesty in the pharmacists' relationship with their patients (Saseen et al., 2017). In addition, the credibility and trustworthy interactions of the pharmacist with students, trainees, colleagues, and other professionals represent another perspective of professionalism. These interactions should exhibit the values and behaviors of a standard professional practice. To maintain the highest standards of professional practice, it is necessary to define professional boundaries to prevent the intentional or unintentional breaching of these professional standards.

Understanding the professional use of the term "boundary" is paramount in clinical practice. Boundaries in professional relationships have been highly dynamic throughout the years. It has been reported that professional boundaries between the healthcare workforce components dynamically recognize the unavoidable interrelationships to achieve the goals of medical care (Nancarrow and Borthwick, 2005). Moreover, it is well established that health-care professionals should be trained to practice therapeutic relationships that enable them to utilize their knowledge, abilities and experiences to meet the patient's care needs (National Council of State Boards of Nursing, 2018). The challenge in the practice of therapeutic relationships that insufficient patient's involvement because of too rigid professional boundaries may potentially lead to disengagement and lack of patient's trust (Smythe et al., 2018). While exceeding the limits of these therapeutic relationships may lead to violations in the professional boundary (Manfrin-Ledet et al., 2015). Historically, the professional boundaries have been developed over time from no well-defined boundaries (the Apothecary model) to strict boundaries (the product-oriented practice) until reaching the era of the patient-centred care whose boundaries are dynamic to support therapeutic relationships that meet the patient's care requirements. The expansion of the pharmacist's role and evolution in the disciplines of pharmacy practice have shifted some boundaries by identifying new domains of work or by adopting roles usually carried out by other providers (Bidwell and Thompson, 2015; Nancarrow and Borthwick, 2005). Among health-care providers, the pharmacy profession has experienced remarkable growth and development (Pearson, 2007). Overall, it can be said that professional boundaries in the health-care system have been moving on a sliding scale (Hart, 2017) from no boundaries to strict boundaries, and then, opening doors, finding new roles, and switching responsibilities from day-to-day (**Fig. 1**).

By the early 1990s, Helper and Strand had introduced the concept of pharmaceutical care: "The responsible provision of drug therapy to achieve definite outcomes that improve a patient's quality of life." Consequently, pharmacists are recognized as drug experts, whose role is to act collaboratively with patients, physicians, and other health-care professionals to optimize the use of medications and health outcomes (Helper and Strand, 1990). The widespread increase in chronic diseases and their complications in parallel with the increase in life expectancy and the demand for a better quality of life place a burden on the overall health-care system (King et al., 2015). Furthermore, increasing health costs and rates of drug-related morbidity and mortality have led to a need to shift boundaries and change the scope of practice of health-care providers, including pharmacists (Macleod-glover, 2011). In addition, the emergence of a considerable number of drugs places a professional and ethical responsibility on the pharmacist to contribute effectively to the health-care system in terms of promoting the efficient and safe use of drug therapy (Bains, 2009).

In a Canadian study aimed to assess the perceptions of pharmacists, pharmacy students and the public toward the pharmacy expanded scope of practice, it was found that transition to patient-centred practice has raised public expectations and impose greater responsibility on pharmacists to collaborate effectively with other healthcare members (Schindel et al., 2017). Therefore, the dynamics of pharmacy professional boundaries have been changed to accommodate the different shaping of public expectations and the introduction of new responsibilities including medication reconciliation, medication therapy management, pharmacoeconomic studies and policy making.

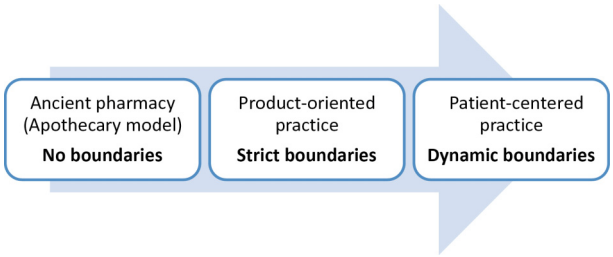

Figure 1 Professional boundaries progress in pharmacy profession.

The World Health Organization (WHO) and the International Pharmaceutical Federation (FIP) have framed new boundaries and expanded the roles of pharmacists to improve patient care and drug therapy outcomes (FIP and WHO, 2011). Moreover, collaborative prescribing by pharmacists has resulted in another shift in professional boundaries. Pharmacists, as prescribers, are empowered by a good professional relationship and mutual trust with doctors and other health-care providers (Lloyd and Hughes, 2007). The prescribing pharmacist's role is associated with many opportunities and responsibilities (Makowsky et al., 2013). These opportunities include improving patients' compliance and disease control, fewer drug interactions, better allocation of resources, reduction in patient waiting time, and increasing patients' access to medicines (Emmerton et al., 2005; Kay and Brien, 2004). The responsibilities are related more to the required additional and role-specific training such as physical examination and patient counseling (Dawoud et al., 2004). In summary, it is noticeable that the changing or evolving roles of pharmacists have contributed to a change in the dynamics of professional boundaries.

Patient-Related Professional Boundaries

The professional boundary with patients denotes the respect for the patient's psychological and physical integrity (Glass, 2003). Boundary violations can be defined as those actions that improperly disrespect patient's boundaries. These actions range from breaching the patient's privacy (e.g., disclosure of patients' information to unauthorized persons without their prior consent) to the extreme level where gross sexual exploitation is involved (Glass, 2015). Although this crossing of professional boundaries has been typically reported by patients against health-care providers as malpractice claims, it has also been reported by health-care givers as incidents against some of their patients (Bird, 2009).

The ethics that govern the pharmacist–patient relationship constitute the fundamental part of the ethical framework of the pharmacy practice. According to the code of ethics of the American Society of Health-system Pharmacists (ASHP), relationships with patients should be controlled by three main ethical principles in relation to the moral obligations, caring responsibilities, and respect of every patient's autonomy and dignity (ASHP, 2012). Moreover, the Australian Pharmaceutical Society (APS) has published a code of ethics that has been divided further according to the pharmacist's focus area such as patients, professionals, business, or community. A summary of the ethical principles relevant to the relationship between pharmacists and their patients from both the American and Australian codes of ethics are presented in **Table 1**.

Typically, the code of ethics provides general outlines that need to be abided by all practitioners. Nevertheless, many situations can be challenging for practitioners from an ethical perspective. At the beginning of a caring relationship with a patient, there are many views on identifying the proper ethical approach in accepting a gift from a patient who wants to show gratitude or even the initiative to help some cases through discounted service fees. It has been observed that accepting any form of informal relationship such as gifts, or making any sort of exception to a particular patient with regard to waiting time or service fees, is regarded as an early warning sign for the crossing of professional boundaries (Galletly, 2004). Therefore, a violation of professional practice ethics may occur if the practitioner is unable to identify the early warning signs of the crossing of professional boundaries. It can be argued that a

Table 1 Summary of the code of ethics relevant to the pharmacist–patient relationship

American Society of Health-system Pharmacists (ASHP) Ethical Principles
A pharmacist respects the covenantal relationship between the patient and pharmacist.
A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.
A pharmacist respects the autonomy and dignity of each patient.
Pharmaceutical Society of Australia (APS) Ethical Principles
Pharmacists recognize the health and well-being of the consumer as their first priority.
Pharmacists pay due respect for the autonomy and rights of consumers and encourage consumers to participate in decision-making actively.

proper balance between expressing care, compassion, integrity, and trustworthiness on the one hand, and maintaining limits and boundaries on the other hand, is crucial for relationships with patients.

Furthermore, in a Tanzanian study designed to explore the views and experiences of pharmacy workers in providing treatment services related to sexually transmitted diseases among homosexual men, the phenomenon of stretching the boundaries was observed (Larsson et al., 2016). This study highlighted the concept of "Stretching Boundaries for Pharmaceutical Responsibilities" to describe the dynamic process of changing workers' experiences from limited to regular engagement with providing services to this population. Emotional motivation and financial interests were found to have effects on the dynamic change of professional boundaries. Furthermore, another work in the same setting was conducted to qualitatively explore the perceptions and experiences of this group of care seekers toward pharmacy services (Agardh et al., 2017). The findings underpinned the perceived barriers to accessing pharmacy care services as low. However, further initiatives to improve the knowledge of care seekers and pharmacy workers are needed.

A Romanian study also assessed the dissatisfaction of patients with regard to the professionalism of their medical staff (Popa et al., 2017). Two main domains were the cause of dissatisfaction in patients: the first domain related to the lack of a proper explanation regarding the treatment choices, procedures, and duration, which might affect the patient's sense of security. The second domain was linked to the poor communication skills of medical staff in that they usually do not introduce themselves. Some patients perceived this lack of good communication skills as a sign of disrespect. These findings highlighted that shortcomings in the professional capabilities of health-care practitioners create unnecessary boundaries with patients. Consequently, it should perhaps be recommended that all health-care institutions reassess the professionalism of their health-care practitioners in terms of their attitude and practices in facing the challenge of unnecessary boundaries due to a lack of professionalism.

Any health education program should have a process known as professional socialization, which includes some components that contribute toward equipping future practitioners with professionalism (Arndt et al., 2009). Schools of pharmacy should have a strategy to imbue their students with professional qualities such as honesty and integrity, responsibility, commitment to excellence, respect for others, and care with compassion. In a pharmacy school in the United States, the positive impact of the implementation of a co-curricular professional development program on the promotion of the professional identity of the students was investigated (Hoffman et al., 2017). This program can be a role model for other schools of pharmacy to design customized contents to instill a professional character in future practitioners.

Despite the development and testing of instruments to assess the behavioral professionalism of pharmacy students (Hammer et al., 2000), it is worth highlighting that the evaluation of professionalism is still a challenge because of the multifaceted concept of professionalism that relies on idealized traits. An evaluation of these traits should take into consideration their important values in professional practice to assure applicable and fair evaluation outcomes. It has been suggested that a more practical and explicit method of implementing the theory of a value-based practice would be to include its three pillars, namely, education, regulation, and teamwork, in the professionalism assessment (Ahmadi and Hasan, 2017). Nevertheless, it has been highlighted that professionalism should not be limited to certain defined behaviors, attitudes, or values but should go beyond these traits toward a holistic approach that focuses on the formation of a professional identity through experiential learning and the alignment of the curriculum with work practices (Mylrea et al., 2015).

Patient Preferences as the Focus of Professional Boundaries

Professional boundaries with patients refer to the apparent separation between professional behavior that meets the patients' health needs and the pharmacist's views and feelings (Pharmacy Board of Australia, 2012). Shifting the pharmacist's role to a patient-centered model enables them to spend more time with patients. Pharmacists interview and assess patients, make specific therapeutic recommendations, monitor responses to drug therapy, and provide drug information (Tietze, 2012). Therefore, in a patient-focused health service, the patients' preferences should be taken into consideration (Gerard et al., 2012).

Patients and pharmacists may have different views about the latter's role in the patient/practitioner relationship. Researchers have examined the opinions of patients and pharmacists about their relationships. They both share the concept that clear information increases a patient's trust in the pharmacist (McCullough et al., 2016; Worley et al., 2007). The patients' expectations include consistent patient care services, greater pharmacist participation, and a sense of being patient centered (Schommer and Gaither, 2014; Worley-Louis et al., 2003). Also, the patients' trust is affected by the type of experience they have had previously with pharmaceutical services, where a positive experience increases trust (Patterson et al., 2013). Moreover, the lack of acknowledgment of the pharmacist's role might affect their motivation level in performing their professional duty (Schommer and Gaither, 2014). In addition, it may be necessary to revisit the scope of the roles, responsibilities, and practices of pharmacists so as to adapt it to the existing opportunities for making better use of pharmacists in direct patient care (Schindel et al., 2017).

Another issue in research involving patients is that pharmacists should respect the right of patients to withdraw from a study without judgment and without compromising the pharmacist–patient relationship or the care of the patient (Pharmacy Board of Australia, 2012). Professional boundaries must be maintained at all times; if these are crossed, patients may lose trust and confidence in pharmacists (General Pharmaceutical Council, 2012). Patients have the right to be treated with dignity and respect by helping them to make their own choices through a shared decision (Duggan et al., 2006). This can be accomplished through effective communication using professional knowledge, skills, behaviors, with honesty, integrity, and respect for the confidentiality of patients (General Pharmaceutical Council, 2016). The attributes of pharmaceutical care services should guarantee the quality of

the professional–patient relationship and indeed, the continuity of care (Gerard et al., 2012). Policymakers should develop clear objectives for the quality of the provided services.

Boundaries with Health-care Professionals (Interprofessional Boundaries)

Professions are engaged in an ongoing and dynamic process involving the appraisal and adaptation of organizational, skills, and knowledge bases (Nancarrow and Borthwick, 2005). Each health profession has a predefined role that relies on other related professions in different degrees to facilitate a patient care process (Frank et al., 2015). Highly elastic boundaries induce overlap in the scope of practice among different health-care providers that might give rise to friction among team members and initiate disputes of health-care role boundaries among professionals (King et al., 2015; McNeil et al., 2013). It has been reported that those professionals who have had more experience and interaction with pharmacists have better perceptions regarding potential professional disputes (King and Ross, 2004; McNeil et al., 2013). Consequently, they are more likely to be engaged in a collaborative relationship, where the members are willing to delegate and share responsibilities (Doucette et al., 2005; MacNaughton et al., 2013). Furthermore, the key elements for a powerful collaboration, such as interdependence, perceptions, skills, and interests, have a significant impact on the boundary dynamics (Bardet et al., 2015).

It is thought that a further elaboration of the scope of practice and health policies of pharmacists can help to enable healthy team-based interactions. Also, policymakers are expected to support flexibility in the professional role and provide innovations in the provision of health care derived from the health needs of the society (King et al., 2015; Nancarrow and Borthwick, 2005; Schindel et al., 2017). This will consequently ensure a mutually effective, respectful, and clear communication, and an acknowledgement of the contribution of each practitioner involved in the care of the patient (Pharmacy Board of Australia, 2012). Therefore, immovable professional boundaries should be dynamically shifted based on health policies and in the light of patient-centered care (King et al., 2015). In this regard, interprofessional professionalism is a model linked to professionalism and teamwork that precisely emphasises an individual health-care professional's ability to practice collaboratively with other health-care professionals (Hammer et al., 2012).

It is a well-established fact that patient care is an all-inclusive process that requires collaboration with all health-care providers, including physicians, pharmacists, nurses, and other allied health-care professionals. The findings of a recent UK study showed that effective communication and cooperation between physicians and pharmacists can potentially increase the optimization of medications and improve patient safety in primary health-care settings (Bradley et al., 2018). The interactive relationship between many health-care providers from different backgrounds both facilitates and obstructs the achievement of a productive collaborative relationship. It facilitates in the sense that health-care providers are interested in collaboration, are aiming to improve the quality of patient care, and are making use of opportunities to identify potentially new professional roles. By contrast, the barriers to a productive collaborative relationship are the lack of awareness among health-care providers of each other's professional competencies, their concerns about confidentiality when sharing information, inadequate efforts toward setting a team-based mentality, and the planning of interprofessional training (Supper et al., 2014). According to the results of a qualitative study of the perceptions toward interprofessional collaboration between general practitioners and community pharmacists, shared trust and appreciation were identified as important influences on the quality of interprofessional interaction (Löffler et al., 2017). The findings highlighted that pharmacists are focused on their need for a well-defined and clear pathway for professional communication with physicians, while physicians value the potential professional contribution of pharmacists in the challenge of providing care to an increasing population of elderly patients and patients with chronic diseases.

Interestingly, the introduction of an interprofessional collaboration model that concentrates on predefined outcomes has had a positive impact on ensuring successful collaboration, while maintaining professional boundaries (Rathbone et al., 2016). Moreover, the determinants of a successful collaborative practice include trust, interdependence, awareness, and expectations with regard to the other health-care professionals, curiosity for a collaborative practice, role description, and communication (Bardet et al., 2015). These determinants can be the framework for any initiative aimed at maintaining good control of interprofessional boundaries in clinical practice. Furthermore, it is worth highlighting the significant association between the extent of collaboration between health-care professionals and the possibility of implementing the recommendations of a medication review process (Kwint et al., 2013). This finding is fundamental in assessing the potential impact of collaborative practice on the quality of patient care. Therefore, efforts and initiatives should be directed at facilitating interprofessional collaboration by addressing commonly perceived barriers and professional boundaries. **Table 2** presents a summary of the interprofessional boundaries with their relevant facilitating suggestions.

Professional Boundaries with Students with a Focus on the Emerging Role of Social Media

Social media has been utilized widely by pharmacy students, faculty members, and practitioner pharmacists in relation to facilitating pharmacy education and practice (Benetoli et al., 2014). However, there are reported cases where open use of social media could adversely affect professionalism such as describing opinions, feelings or attitudes toward patients, colleagues or faculty members even if they were kept anonymous. Therefore, the concept of e-professionalism has emerged to define a set of behaviors and attitudes that refer to the paradigm of professionalism through digital media networks (Cain and Romanelli, 2009).

Facebook provides an informal learning environment for expanding the learning content to involve current topics in the context of optional professional participation (Cain and Policastri, 2011). Moreover, the use of Facebook in pharmacy education shows

Table 2 Summary of interprofessional boundaries with its relevant facilitating suggestions

Concerns related to interprofessional boundaries	*Suggestions to overcome concerns of interprofessional boundaries*
Lack of awareness of one another's professional competencies	Early introduction of interprofessional education involving all health-care students.
Inadequate professional responsibility (sharing information & confidentiality).	Clear job description for each professional role with its relevant roles and responsibilities. Revisiting the pharmacist's roles, and responsibilities.
Lack of mutual trust and appreciation.	Health-care institutions should focus on initiatives that foster interprofessional trust and appreciation between all health-care providers in daily clinical practice.
Poorly defined communication framework between physicians and pharmacists.	Health-care policy makers should take initiatives to regulate professional communication between physicians and pharmacists.
The need for setting team-based mentality and planning the interprofessional training.	Future medical and pharmacy training curricula should be directed toward a comprehensive interprofessional interaction at early stages within professionals' education, training, and career.

potential benefits in terms of facilitating the pharmacotherapy course-related discussion between students and faculty members (Divall and Kirwin, 2012). The popular use of Facebook has made the issues of privacy, identity protection, and e-professionalism the focus of discussions related to professional and organizational impacts (Mattingly et al., 2010), particularly in the context of lacking robust evidence that regulates the proper interaction between social media use and pharmacy professional boundaries (Hammer et al., 2003).

In a study conducted by Hall et al. to explore the views and use of social networks among the UK pharmacy students, it was found that the wide use of social networks is associated with potentially inappropriate professional attitudes. The same study highlighted that male students seem to be less concerned about professional issues related to their use of social networks and have a less comprehensive view of professionalism than female students (Hall et al., 2013). Furthermore, the evaluation of social interactions between faculty members and students or residents has shown that the students, especially at a public university, were more concerned that "friending" on Facebook represented a violation of professional boundaries. In addition, the students reported that they had to be cautious as to what content to share if it could be seen by faculty members (Bongartz et al., 2011).

From the perspective of faculty members regarding the professional way of interacting with their students on social networks, there is no clear consensus about professional boundaries in this regard. It was reported in a US study that the majority of faculty members agreed that they should not initiate friendships with current students on social networks, but they varied in their acceptance rate and response to friendship requests sent by students (Schneider et al., 2011). Most faculty members considered that social media connections with current students could compromise the boundary of lecturer–student relationship (Cain et al., 2013). It is essential for faculty members to investigate further the proper context for the use of social media for educational, professional, and networking purposes (Cain et al., 2013). Overall, all social interactions involving students and their mentors or faculty members should be kept professional to overcome potentially inappropriate attitudes and behaviors that constitute threats to maintaining professional boundaries (Bongartz et al., 2011). In conclusion, it should be noted that the framework regulating the professional aspect of social interactions involving pharmacy students, pharmacists, and faculty staff members is not clear, and further explicit working definitions of professional boundaries in this context are needed.

Conclusion

Professionalism in pharmacy practice and education is affected by the ability to recognize the different types of professional boundaries while dealing with patients, health-care professionals, trainees, and students. The promotion of knowledge concerning professional boundaries, important warning signs, behaviors, and attitudes should be considered as early as during the health-care education of undergraduates. It is the responsibility of educational institutions, management of health-care facilities, and policymakers to exert continuous efforts and initiatives to maintain professional boundaries and facilitate a professional identity in daily practice.

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Drug Misuse and Dependence: The Role of Community Pharmacy

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Introduction

The use of psychoactive drugs for pleasure and ritual purposes is not a new phenomenon, and the use of psychoactive substances obtained from plants based materials such as betel, khat, tobacco, and coca have a long history (Sullivan and Hagen, 2002). The notions of addiction and dependence (see Section "Misuse, Addiction and Dependence—A Brief Review of Concepts and Terminologies") are a modern framing of substance use, which sees the use of most psychoactive substances (excluding alcohol and nicotine) as deviant and problematic and, in many cases, an illegal activity as a result of international treaties and conventions. Health professionals tend to frame substance misuse and dependence in a medico-legal context, but may also see it as deviant.

This chapter will describe a predominantly 20th and 21st century role for community pharmacists in the treatment of drug dependence, as well as describing community pharmacy's role in a harm reduction approach to substance misuse. In doing so, the chapter will focus mainly on developed countries, using European (mainly United Kingdom), Australasian and the North American evidence. A brief description of concepts and terminologies will be followed by a description of the changing role of community pharmacy, using the UK as a case study, from the late 19th century through to the mid-1980s. The major paradigm shift towards harm reduction in the post HIV/AIDS era will then be described, followed by a more detailed exploration of pharmacy's role in newer initiatives in treatment and harm reduction, followed by brief crystal-ball gazing into the future. The chapter does not specifically focus on the pharmacist's role in the management of risky alcohol consumption, nor on smoking cessation.

Misuse, Addiction and Dependence—A Brief Review of Concepts and Terminologies

As with any area of medicine, shared terminology is critical in supporting effective communication. The importance of language has been highlighted in a number of recent commentaries in the field (Botticelli and Koh, 2016; Kelly et al., 2016). These reflect concerns about how stigmatising the language of health professionals can be, and the negative impact this can have on patient care. For example, two separate studies of commonly used terms identified that when a patient was referred to as a 'substance abuser' they

were more likely to be considered to be deserving of punishment, or a greater social threat compared to when the words 'person with a substance use disorder' (SUD) were used (Kelly et al., 2010; Kelly and Westerhoff, 2010).

The term 'abuse' and 'abuser' are no longer used by the World Health Organization, and SUD is now the term used in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (O'Brien, 2011). Similarly, when urine samples containing substances are referred to as 'dirty' this can also imply a value judgement, and conversely, a person being described as 'clean' when they are not using any substances may also imply that a person who is using a drug is 'dirty. The term 'addict' is also considered pejorative, labelling a person by their substance use. In the following section we provide definitions of three key terms in the addiction field: misuse, dependence, and addiction.

Misuse

The World Health Organization defines misuse as the 'Use of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications' (https://www.who.int/substance_abuse/terminology/abuse/en/).

Dependence

The International Classification of Disease (ICD-10) definition of dependence is a cluster of physiological, behavioural, and cognitive symptoms, whereby the substance takes on a much higher priority in a person's daily life. Where a drug takes prominence in someone's life, this can also be referred to as 'salience'. Further characteristics of dependence include strong desires to take the substance, sometimes referred to as 'craving'. There are psychological aspects of dependence, which centre on the loss of the control over the use of a substance and cravings for the substance. Physical aspects of dependence include 'tolerance', where more of a substance is required to produce the same effect, and 'withdrawal' where a group of symptoms emerge on cessation of the use of the substance. For substances such as opioids when used in the context of treating pain, the development of physical neuroadaptation is expected with long-term use, and this alone is not considered 'dependence' in the absence of psychological aspects such as loss of control over use, salience or craving.

Addiction

The term 'addiction' has fallen in and out of favour over time, though the term is broadly understood by the public, and is often used interchangeably with 'dependence'. The term 'addiction' is not currently used to define problems with substance use in the widely used ICD-10 or DSM. The term addiction is often preferred in the pain field to avoid confusion with the term 'dependence', which is used to refer to physical dependence in the absence of the psychological or behavioural aspects of substance use disorders.

Sociological Constructs of Addiction/Dependence

Drug misuse and dependence are very emotive subjects and they form a common theme of political and sociological discussion. How society should, and does, address drug use depends on a multitude of factors including the society in question, the drug, and historical views of the use of the drug. At times, certain drugs have been vilified in 'moral panics'.

In general, the use of alcohol and tobacco is legal. In Western society, alcohol use is both legal and socially acceptable, and in some ways positively encouraged, particularly in social settings. The use of most other 'drugs' is largely deemed socially unacceptable, in line with legislation prohibiting their sale and use. Alcohol and tobacco (nicotine) are largely ignored as drugs, even though that is what they are. As will be explored further in this chapter, the social rules and legislation that Western society has drawn up in respect to drug use are not always firmly rooted in scientific evidence.

Legislation has formed over centuries in response to experience and sometimes to aforementioned panics, which have been artificially created (most classically illustrated by the 1936 film, 'Reefer Madness') and may bear little relation to the harm posed by each individual drug. In 2010, a seminal paper by Nutt et al. (2010) described the harms of drugs (as assessed by a group of experts) and found that these were not reflected in the legal approaches to each drug in the UK.

Earlier in the chapter, the term addiction was defined from the medical/scientific point of view. However, another aspect is the perception of dependence by those who are using a drug, and society at large. The medicalisation of dependence is challenged by many. They argue that SUDs are associated with a combination of personal and sociological issues, where the drug alleviates or ameliorates negative emotions that an individual is experiencing. This was demonstrated in a series of experiments during the 1970s, which have been colloquially termed 'rat park' (Alexander et al., 1978). These suggested that rats caged alone experienced negative psychological effects, which were not experienced when rats were housed with other rats in a community. The rats that were caged alone drank a morphine solution in preference to water, which did not occur in the social 'park'. Studies of United States soldiers returning from the Vietnam conflict found that, in the same way that solo rats used drugs to cope with stressors, the soldiers in Vietnam had used the easily obtainable opioids there to deal with the stress of witnessing death and destruction, along with the risk of death they faced on a daily basis. Upon returning to their homes in the United States at the end of their tour of duty, most troops ceased opioid use, indicating the use was linked to their situation, rather than the individual or the drug (Hall and Weier, 2017; Leshner, 1997; Robins et al., 1974).

However, in healthcare, it is generally accepted that a SUD is a chronic, relapsing medical condition. It is sometimes referred to as a chronic 'disease' (Volkow et al., 2016). Pharmacists involved in the care of individuals with SUD need to be aware of its relapsing nature and to support the individuals when necessary. Substance use affects not only the person who uses a drug, but other people, both friends and family, as well as the wider community. Direct harm from the drug or complications from use (to the individual using the drug) are obvious consequences of drug use. Effects on those close to the individual are also clearly witnessed and may include worry, frustration and sadness over the individual's drug use, to physical harm for example from drug or alcohol induced violence or aggression. However, individuals not known personally to those with a substance use disorder may also suffer through events such as being the victim of a vehicle accident caused by an intoxicated driver, or being a victim of an acquisitive crime committed to fund drug use.

A Historical View of Pharmacy and Addictive Drugs—The British Experience

Contemporary pharmacy manages substance use and addiction within a framework of the legal regulation of psychoactive substances. This is in line with international conventions on narcotic drugs and psychoactive substances, and classifies drugs into legal groupings, which describe their manufacture, distribution, possession, use, prescribing, and dispensing. The most tightly controlled substances (e.g. lysergic acid diethylamide (LSD); 3,4-methylenedioxymethamphetamine (MDMA) commonly known as ecstasy) are deemed to have no recognised medical use. Other substances may be prescribed only by authorised doctors, whilst other substances may be prescribed more widely according to specific regulations. Many countries control access to potentially addictive substances through laws such as the Controlled Substance Act in the United States (1971), The Misuse of Drugs Act (the United Kingdom, 1971), The Narcotic Drugs Act (Australia, 1967), and The Misuse of Drugs Act (New Zealand, 1975). However, this has not always been so and the following brief description of the history of British drug laws serves as a case study.

In formulating this following section, we acknowledge the BMA Board of Science "Drugs of Dependence: The Role of Medical Professionals" report (2013). In the 1800s, there was unrestricted access, for example to opium, and there was an estimation of opium consumption at 6.5 people per million in Britain in 1894 although this fell to 4.9 per million by 1903 (Berridge, 1999). Products containing opium, such as laudanum, could be freely obtained from pharmacies with no restriction. However, concerns about consumption led to the first attempt in the UK to control access through the Pharmacy Act 1868 (BMA Board of Science, 2013). The Act changed access to these substances from pharmacies only, and pharmacists were required to keep records of sales and supplies, although there was little restriction on the quantity that could be supplied. In the early 1900s, a subsequent Act also controlled morphine and cocaine. It was not until World War I, when concerns were raised about troops using cocaine, that for the first time, a prescription was required for the supply of cocaine, and the subsequent Defence of the Realm Act 1914 meant that "it was an offence for anyone except physicians, pharmacists and vets to be in possession of, or to sell or give cocaine" (BMA Board of Science, 2013, p. 88).

In 1920, as a result of it being a signatory to the 1912 International Opium Convention, the UK government enacted the Dangerous Drugs Act, which expanded control over drugs such as morphine, cocaine and heroin, and also allowed doctors to prescribe these drugs. Lack of clarity over whether prescribing to people dependent on these drugs was a legitimate medical activity led to the convening of the Rolleston Committee which, in its Report (Ministry of Health, 1926), confirmed that doctors could prescribe opioids to people dependent on opioids for the treatment of addiction. This was the beginning of what has become known as the "British System", which saw a "balance of a medical approach within a penal framework" (BMA Board of Science, 2013, p. 89). This situation, with a small number of patients being prescribed heroin long term, remained unchanged until the 1960s when concerns were raised about younger people becoming dependent on heroin. In 1965, the Brain Committee ruled that prescribing of heroin should be by licenced doctors only and saw the setting up of specialist drug clinics (Ministry of Health and Scottish Home and Health Department, 1965). This resulted in a decline in the prescribing of diamorphine (pharmaceutical heroin) with replacement by methadone—a longer acting, orally bioavailable opioid agonist, which had emerged from the USA. It is interesting to note that the "British System" was at odds with the American approach, which had prevented doctors prescribing for addiction.

One of the biggest changes to the way pharmacists could supply addictive drugs to patients came in 1971 with the introduction of the Misuse of Drugs Act (1971), which classified drugs into schedules laid out by the UN 1961 Single Convention on Narcotic Drugs. These schedules defined restrictions on manufacture, prescribing, supply, possession and use. For pharmacists, this meant becoming familiar with a whole new set of regulations and legal requirements on the storage and dispensing of such drugs.

In the 1980s, in the UK and many other countries, there was a rapid increase in the number of people using illicit 'street' heroin. In the UK, the government released its strategic policy "Tackling drug misuse" (Home Office, 1985), which included the wider use of doctors beyond specialists to prescribe methadone for addiction and thus a greater number of prescriptions being presented at community pharmacies. However, the biggest change to the role of pharmacy and indeed to the way in which substance misuse and dependence were framed did not really occur until the recognition of the HIV/AIDS epidemic in the 1980s, and the acknowledgement that the HIV virus was blood borne and could be transmitted from one individual to another through the use of shared injecting equipment, as well as through unprotected sex. The UK Governments' Advisory Council on the Misuse of Drugs (ACMD) produced its first report "AIDS and drug misuse", which contained the highly influential statement that: "The spread of HIV is a greater threat to individual and public health than drug misuse" (Advisory Council on the Misuse of Drugs, 1988) and led policy-makers to embrace a different approach to the management of drug misuse and dependence—a harm reduction approach.

HIV/AIDS and the Emergence of a "Harm Reduction" Approach

Harm reduction has many definitions, but the basic premise in the 1980s was a pragmatic approach to preventing the spread of HIV. The approach accepted that people would continue to inject drugs, and set in motion a number of interventions, which were designed to reduce the HIV transmission, without the aim of reducing use of drugs *per se*. The two main harm reduction interventions which impacted on community pharmacy practice were the introduction of needle exchanges, and the expansion of OAT from mainly detoxification regimes to maintenance treatment, with the aim of reducing drug injecting.

Needle exchanges (often known as needle syringe exchanges), were set up to supply sterile needles and syringes to people who injected drugs and also offered a means of safely disposing of used injecting equipment. Research indicates that in cities with needle exchange schemes, HIV seroprevalence reduced in comparison with cities with no needle exchange (Hurley et al., 1997). It was recognised that another avenue for the supply of sterile injecting equipment was through community pharmacies. At the same time, there was a rapid expansion of oral methadone prescribing through primary care in the context of methadone maintenance (also known as opioid agonist treatment (OAT)), designed to reduce injecting, as opposed to being primarily directed at detoxification and abstinence. By the late 1980s, a national survey of community pharmacies in England and Wales, indicated that 3% of pharmacies were involved in a needle exchange scheme and 23% were involved in the provision of methadone to people who inject drugs (Glanz et al., 1989). Almost a decade later, 19% and 51% respectively were providing these services (Sheridan et al., 1996).

Pharmacy needle exchange services were not standardised, and evolved according to local need, with a range of methods for financing the scheme, and the range of equipment provided free of charge to pharmacies for distribution at no cost to people who inject drugs, also varied (Sheridan et al., 2000). Provision of needle exchange services was not without problems, with pharmacists reporting issues such as shoplifting; however, concerns about violence appear to have been unfounded with pharmacists generally positive about providing the service (McVeigh et al., 2017; Sheridan et al., 2000, 2005). Even in the USA in the late 1980s, where regulations made it difficult for pharmacists to sell sterile injecting equipment, a study in Maryland found a considerable level for support for needle exchange schemes (Gleghorn et al., 1998).

The prescribing of oral opioid substitutes as maintenance treatment, also increased around this time and in the period between 1998 and 1995 the proportion of community pharmacies in England and Wales dispensing prescriptions for controlled drugs such as methadone, for the management of drug misuse, increased from 23% to 51% (Sheridan et al., 1996). Since that time this role has expanded to providing supervised dosing of methadone and buprenorphine, in monitoring patients to identify where they may need clinical review, and providing support to patients to achieve their treatment goals (Chaar et al., 2011). The early adoption of these harm reduction services by community pharmacies was not universal, and research indicates that motivating factors include awareness of local need, and wanting to reduce the spread of HIV (Matheson and Bond, 1999). It has been suggested that overt support from government agencies, professional bodies and pharmacy professional associations may have had a positive impact on participation (Matheson and Bond, 1999; Myers et al., 1996).

The 1990s and 2000s saw a proliferation of research interest in this field, with studies being carried out on service development and implementation, service delivery, and pharmacist attitudes towards HIV and drug misuse. Research on attitudes towards the provision of needle exchange and OAT found a proportion of pharmacists with very positive attitudes, and a relationship between positive attitudes and service provision (Matheson et al., 1999; Sheridan et al., 1997). However, a small proportion of community pharmacists were not comfortable providing the services, indicating it was not their role.

Pharmacists also had concerns about the impact that providing these services might have on their business (Matheson et al., 1999; Sheridan et al., 1997, 2007). However, a study of public perspectives of pharmacy harm reduction interventions indicated generally positive support, although with a preference for these services to be provided in a private area (Lawrie et al., 2004).

Importantly, the opinions of people who use drugs on the role of pharmacists in harm reduction have also been explored. Both qualitative and quantitative research with people who inject drugs revealed a number of key themes, one of the most significant being that of stigma. People who inject drugs reported feeling stigmatised (Matheson, 1998), and if they are too embarrassed to access pharmacy services this could have a negative impact on harm reduction interventions (Simmonds and Coomber, 2009). Stigma has also been a theme in research exploring clients' perspectives on OAT (Anstice et al., 2009) and there have been reports of negative treatment by staff (Matheson, 1998). However, OAT clients find that community pharmacies are accessible, and note the importance of positive and supportive attitudes of pharmacists and their staff (Laird et al., 2016; Matheson, 1998).

Harm Reduction Beyond HIV/AIDS—Take Home Naloxone

Harm reduction as a concept has expanded beyond the prevention of the spread of HIV/AIDS to embrace a broader perspective of harm. One of the harms associated with substance misuse is drug overdose. Opioid overdose is a significant issue. If a person overdoses on opioids they experience respiratory depression which can ultimately be fatal. Opioid overdose deaths can be prevented through the timely use of opioid antagonists such as naloxone.

Naloxone is a competitive opioid antagonist with a relatively fast onset of action, usually within a few minutes depending on the route of administration (Dowling et al., 2008). When naloxone is given to a person who has been administered (or taken) an opioid agonist it displaces the opioid agonist from the opioid receptor, effectively reversing the effects of the opioid agonist. Naloxone is an

effective antagonist for most prescribed and illicit opioids (e.g. heroin), though higher doses are thought to be required with partial agonists such as buprenorphine, and high potency opioids such as fentanyl and its analogues (Dahan, 2006).

Naloxone has can be administered via a range of routes including intramuscular, intravenous, subcutaneous, and intranasal. Since it was discovered, it has been in routine use paramedic and hospital settings. In these settings has been shown to be safe, reliable and effective. More recently naloxone has been supplied to trained laypeople who may witness an opioid overdose, enabling earlier naloxone administration. This is often referred to as 'take-home naloxone'.

Take-Home Naloxone Programmes

Take-home naloxone programmes have been recommended by the World Health Organization in response to rising opioid-related mortality (World Health Organization, 2014). Systematic reviews have confirmed that community naloxone supply is an effective way to reduce overdose mortality, with few serious side effects and no abuse liability (European Monitoring Centre for Drugs and Drug Addiction, 2015; McDonald and Strang, 2016; Olsen et al., 2016). Most overdoses are witnessed, so there is an important opportunity for naloxone to be administered if a trained bystander is present (Strang et al., 1999).

Over the past decade in the United States, a trebling in opioid overdose mortality has led to a recommendation for a rapid expansion of naloxone distribution (Rudd et al., 2016; Straus et al., 2013). By 2010 over 50,000 take-home naloxone kits had been distributed, and more than 10,000 successful overdose reversals were reported. There are now naloxone programmes in many countries including the United Kingdom, Australia and Canada.

Naloxone in Community Pharmacy

In 2016, naloxone was downscheduled to a pharmacist only medicine in Australia, making Australia one of the first countries with naloxone widely available without a prescription. In the United States and the United Kingdom, different supply strategies have also been devised to remove the need for a prescription, including the use of standing orders in many US pharmacies, and patient group directives to enable supply within the UK healthcare system (Nielsen and Van Hout, 2016). These supply mechanisms mean that pharmacists have an increasingly important role in the supply of naloxone. Community pharmacies have wide geographic distribution and long hours of operation. This means that take-home naloxone can be accessed widely in the community, particularly in rural and regional communities and outside opening hours of many drug treatment services.

Community pharmacy is a key primary health care hub, and most people at risk of opioid overdose and other opioid related harms are already in contact with community pharmacists, either through the supply of opioid agonist treatments such as methadone and buprenorphine or through receiving pharmaceutical opioids for the treatment of pain. Research has demonstrated that interventions in healthcare settings can significantly reduce opioid overdose risk compared to standard care (Bohnert et al., 2016), and that training laypeople to administration naloxone is an effective way to reduce overdose mortality (European Monitoring Centre for Drugs and Drug Addiction, 2015; McDonald and Strang, 2016). As skilled health professionals, pharmacist can combine these two effective strategies of overdose risk education and naloxone supply.

Challenges with Expansion of Naloxone Supply

Expansion of naloxone availability in community pharmacy is not without challenges. Research in Australian pharmacies has indicated that pharmacists have low confidence in identifying who to supply naloxone to, and how to train people about its use (Nielsen et al., 2016). Research in the United States and Canada has confirmed that not all health professionals are confident to supply naloxone (Edwards et al., 2017). A recent study of Canadian pharmacies found one in four had naloxone available, with less than one in five anticipating that they could supply it within a week (Cressman et al., 2017).

Additional barriers to naloxone supply have traditionally been the need for a prescription, though rescheduling, standing orders and other supply channels have gone some way towards addressing this. A further significant barrier to naloxone supply is cost. Where naloxone is not covered through government programmes or insurance the cost to the individual can be considerable, with wholesaler prices of USD$75 for an intranasal dose and exceeding USD$450 for autoinjector devices (Gufford et al., 2017).

Naloxone in the Future: New Formulations

Traditionally, take-home naloxone programmes provide naloxone through either ampoules or prefilled syringes for intramuscular injection, or prefilled syringes with atomisers for intranasal administration. The use of injectable products can be a barrier for those not familiar with administering injections (particularly for family members or carers) and in criminal justice settings. In some settings the carrying of injecting equipment may be illegal, adding an additional concern with injectable formulations.

New intranasal formulations address this barrier, but raise new queries about the ideal dose of naloxone. The dose of naloxone in intranasal formulations was determined through healthy volunteer studies aiming for comparable pharmacokinetics to intramuscular doses, though ideally this will be supported by experience in the field with use of these products to reverse overdoses. With expanded use of high potency opioids such as fentanyl and carfentanyl, it is possible that higher doses of naloxone may be required to reverse an overdose, although the onset of respiratory depression may be so fast, and the depression so severe that naloxone may be ineffective.

Consumer Education with Naloxone Supply

When providing naloxone to those who may witness and overdose, it is critical to firstly provide education on the signs of an opioid overdose so that the need to administer naloxone can be established.

A first step when supplying naloxone in pharmacy settings, is for the pharmacist to establish what is known about recognising and responding to a potential opioid overdose. Many people who are likely to witness an overdose may have already attended formal training on overdose management, and/or have previously administered naloxone. Conversely, concerned family members or carers, and those prescribed opioids for chronic pain may have had little exposure to opioid overdose, and may not be familiar with the signs of opioid overdose to look for. Open ended questions to establish baseline knowledge may help to target information more based on the patients existing knowledge.

In addition, information on naloxone administration and where naloxone fits into broader overdose management, including the importance of calling an ambulance, are key counselling points.

Other Overdose Risk Factors

Pharmacists may be ideally placed to identify other known contributors to opioid overdose risk. In addition to naloxone supply, pharmacists can advise patients on potential drug interactions when combining sedatives such as alcohol and benzodiazepines with opioids, and can identify those pain patients on higher opioid doses that are associated with increased overdose risk (doses of 50 mg oral morphine equivalents [OME] have been shown to increase the risk of overdose 4-fold, and doses of 100 mg OME have been shown to increase the risk of overdose 9 fold compared to people receiving doses of 1–20 mg OME per day) (Dunn et al., 2010). Patients who report using of multiple central nervous system depressant substances, and those with other mental health comorbidities, may also be at increased overdose risk (Park et al., 2016).

Medicinal Cannabis and Pharmacy

The medicinal use of cannabis has occurred for millennia, with recorded use for over at least 4000 years. Historically, the drug has been used for an array of conditions. The absence of proven effective medical use for cannabis resulted in it being placed within the strictest levels of control in the legislation introduced in the early 1970s. However, for certain medical conditions, effective treatments still do not exist and demand for cannabis products persists to this day, and there is limited evidence of efficacy for some conditions. In a form of a vicious circle, the tight controls placed upon it have hindered any research into possible medical use.

In 1996, the people of the state of California in the US voted to introduce the 'Medical Marijuana Initiative'. This would enable the use of cannabis for a range of medical conditions for which cannabis 'provides relief'. Subsequently, many States have introduced similar legislation with others having also legalised it for recreational use (National Conference of State Legislatures, 2017). In the States in the US where it is approved, medicinal cannabis is available as a range of products for use including smokeable matter, capsules/tablets, edible forms (such as cookies), and tinctures. Some States prohibit some forms; for example, New York does not permit forms for smoking or edibles (New York State Department of Health, 2017).

The pharmaceutical industry has attempted to develop cannabis over a number decades. One of the first products to be launched was the synthetic cannabinoid, nabilone, which was primarily used for nausea and vomiting in patients undergoing chemotherapy. In 2005, a product, Sativex™, a standardised formulation of cannabis extract containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), was approved for use in Canada. The manufacturer claimed "the world's first prescription cannabis medicine" (GW Pharmaceuticals, 2010).

The use of cannabis for medical purposes remains controversial, most crucially because evidence of efficacy for most indications is still lacking. However, cannabinoids are currently an area of significant research and interest; therefore, further data on safety and efficacy are expected in the near future.

Pharmacy Distribution of Cannabis

Medicinal grade cannabis has been available on prescription through community pharmacies in the Netherlands since 2003 (Hazekamp, 2006). More recently, in late 2013, Uruguay legalised access to cannabis for both recreational and medical reasons. It introduced changes that allowed the growing of plants and the purchase of limited quantities of the drug. An important deviation from that of all other jurisdictions is that Uruguay chose for the sales of cannabis to be made from pharmacies (Walsh and Ramsey, 2016). The new law was explicit in its aim to improve public health, and therefore the distribution from a healthcare setting appears a logical choice. Furthermore, in Australia, in 2016, the federal government legislated to allow medicinal cannabis (TGA). State-based legislation and guidelines have been introduced which will allow patients to obtain a prescription from a doctor and have their prescription dispensed at a pharmacy. This new role for pharmacists is likely to require additional training and education. Very little research to date exists on pharmacist knowledge and attitudes towards medicinal cannabis.

From Illegal to Legal—The Growing Problem of Prescription Drug Misuse

Over time there has become less of a distinction between illicit and legal substances. Traditionally illicit substances such as cannabis are being intensively studied for therapeutic use. Widely used 'illicit' opioids such as heroin (also known as diacetylmorphine) have historically been used for medical treatment. Diacetylmorphine is still used as an analgesic in some clinical settings, in addition to its provision as Heroin Assisted Treatment (HAT) for addiction in countries including the Netherlands, the United Kingdom, Switzerland Spain, Germany and Canada (Strang et al., 2015). Over the past two decades there has been increasing non-medical use of over-the-counter and prescription opioid medicines. The rising mortality associated with prescription drugs has placed a sharp focus on their supply, misuse and associated harms. As such, there is an increasing role in pharmacy practice to prevent, identify and respond to the non-medical use of pharmaceutical drugs.

Pharmaceutical Opioids

Large increases in opioid prescribing have been observed in Australia, North America, and Europe (Berterame et al., 2016). These increases have largely been due to the increasing use of opioids for acute and chronic pain. This increase in therapeutic use has been associated with dramatic increases in harms including dependence, morbidity, and mortality (Bohnert et al., 2011; Fischer et al., 2013, 2016; Roxburgh et al., 2011). The non-medical use of prescription opioids is well established, though problems also emerge in the context of therapeutic use. Studies in Australia and the United States have found that between 10% and 35% of people using long-term opioids for chronic pain are estimated to meet criteria for opioid dependence or opioid use disorders (Boscarino et al., 2015; Degenhardt et al., 2015).

There in an international trend for mortality from prescription drugs to exceed mortality from illicit drugs (Martins et al., 2015). The increase in mortality has paralleled increased in use of prescribed opioids for pain (Martins et al., 2015). This highlights the need for interventions that address overdose risk in medical settings.

Other Prescription Medicines

Benzodiazepines have been widely available since the 1960s and were thought to have a lower dependence liability (Wick, 2013). In recent decades the risks of dependence have become clear. On their own, benzodiazepines are unlikely to cause death with overdose; however, benzodiazepines are commonly implicated in mortality statistics when taken in combination with opioids, alcohol or other sedatives (Bachhuber et al., 2016).

Emerging concerns have been identified with the non-medical use of the gabapentinoids pregabalin and gabapentin (Schifano, 2014). Descriptions of misuse have emerged in case reports (Bonnet and Scherbaum, 2017), and gabapentinoids have also been implicated in increasing numbers of opioid-related deaths (Gomes et al., 2017). The risk for dependence is thought to be greater in those with a history of substance use disorder (Bonnet and Scherbaum, 2017), suggesting care should be taken when gabapentinoids are prescribed for this patient group.

Whilst the misuse of antipsychotics is not new, an emerging body of cases reports and case-series describe the misuse of atypical antipsychotics, with quetiapine the most commonly identified drug (Montebello and Brett, 2017). Misuse is described in a range of contexts and settings, for example in correctional settings (e.g. prisons) where other substances may be less available (Montebello and Brett, 2017). Reasons for non-medical use of atypical antipsychotics commonly centre on their sedative effects (Malekshahi et al., 2015). Atypical antipsychotics are also used off-label as to treat anxiety and insomnia, though evidence to support this practice is lacking (Thompson et al., 2016).

Stimulants such as dextroamphetamine or methylphenidate are indicated for the treatment of attention-deficit/hyperactivity disorder. Misuse of stimulants is most commonly described among adolescents and student populations, with an estimated 5–9% school aged children and 5–35% of US college aged students reporting past year non-medical use (Wilens et al., 2008). Use of pharmaceutical stimulants by this group is described primarily to assist in studying, and medications commonly supplied to peers (i.e. shared or sold between students) (Benson et al., 2015).

Anabolic–androgenic steroid steroids such as testosterone and its synthetic derivatives are indicated for conditions such as muscle wasting with HIV or hypogonadism. These drugs are used by professional athletes to build muscle mass and improve performance; however, much misuse is thought to occur among recreational sportspeople (Sagoe et al., 2014). While not considered to be psychoactive, there are concerns with dependence with steroid use.

The Pharmacists' Role in Management of Prescription Drug Dependence

The community pharmacist has a key role in prevention and management of prescribed medication misuse. Many patients have low awareness that the consumption of widely used medications such as opioids and benzodiazepines may result in dependence. A discussion between the pharmacist and patient about the potential for medications to lead to physical tolerance and psychological dependence may be warranted. Treatment contracts between patients and healthcare providers are a useful way of managing and documenting these risks, in addition to other structural approaches to treatment that can minimise misuse. For example, community pharmacy interventions include supervised dosing, facilitating daily or weekly medication collection and monitoring for signs of escalating dose or non-medical medication use. With the increasing availability of prescription

monitoring programses, pharmacists have the potential to be central in identifying problematic use and providing responses to reduce harms (Lynas, 2013).

Where medications are known to have a significant dependence liability, care should be taken in populations with known vulnerabilities to SUD. This includes those with histories of trauma, mental health co-morbidity and family histories of substance use. These risk-factors do not preclude the use of effective medications where clinically indicated, but additional precautions actioned by pharmacists such as discussing the risks prior to commencing a medication, only dispensing the amount required or dispensing smaller amounts more frequently and monitoring for early requests for further supplies and signs of loss of control can all increase patient safety.

There is a paucity of research into pharmacist perspectives on prescription drug misuse and even less into prevention and treatment interventions. In a study in New Zealand on issues for primary care, both general practitioners and community pharmacists reported problems with managing inappropriate requests and dealing with aggressive behaviours (Sheridan and Butler, 2011). In the same study it emerged that participants tended to take a binary view of prescription drug misuse, classifying people into those who purposely misuse drugs and those who had become addicted through no fault of their own, with the latter being seen more sympathetically, and more likely to be offered support. However, such support for this group was hard to access (Butler and Sheridan, 2010).

The Future

There are clear roles for community pharmacy in harm reduction, prevention and treatment of SUD that go far beyond medication supply. For example, pharmacist prescribing of OAT has become standard practice in some services in the United Kingdom (Hill et al., 2014) and is being considered in other countries. Proactive identification of opioid overdose risk and naloxone supply is another example of extending pharmacist roles to provide life-saving interventions. There may be a broader role in the routine screening for SUD in the future.

If drug laws continue to change as in the case of Uruguay, supply of psychoactive drugs from pharmacies, possibly dedicated specialist pharmacies, may become a standard. The concept of distribution of drugs for recreational purposes from pharmacies is not new. In 2009, the Transform Drug Policy Foundation released "After the War on Drugs: Blueprint for Regulation" (Transform Drug Policy Foundation, 2009) and the legal supply of drugs through the community pharmacy was proposed as one prospective route of supply. Indeed, in 2012, The Foundation joined the experts advising the regulation model in Uruguay; the pharmacy supply model was launched in July 2017 and will be the first test of this model anywhere worldwide. The issue of supply of recreational drugs through pharmacies was also proposed in early 2013 (All-Party Parliamentary Group for Drug Policy Reform, 2013). It was argued that some recreational drugs, such as ecstasy (MDMA), could be supplied in a purified form from community pharmacies to reduce harms from the illicit supply chain. The idea was rebutted in a response from the President of the Royal Pharmaceutical Society stating that "The role of a health professional is to improve health, which seems completely incompatible with selling cigarettes and any other substance for recreational use which we know causes harm without any health benefit" (Royal Pharmaceutical Society (News Team), 2013). However, in a world of ongoing change with regard community pharmacy, this is a possible future role.

Whatever the future holds, there will always be a role for community pharmacists to play in managing substance use and addiction given their role in the supply and control of these substances. Pharmacists need to be well prepared for such roles and pharmacy curricula should embrace this and ensure they provide appropriate education and training.

List of Relevant Web Pages

http://prescribetoprevent.org/
https://www.hri.global/what-is-harm-reduction
http://www.who.int/substance_abuse/en/

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Corporatization of Community Pharmacy

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Introduction

Traditionally, reimbursement in community pharmacies has principally been linked to medicine distribution or the sale of medicines, where the medicine, for the most part, is considered a commodity of retail exchange rather than a health service. Consequently, community pharmacists have always lived with the tension of providing a healthcare service within a retail business environment. Being retail enterprises, community pharmacies can only continue operating if they are financially viable, and consequently one of the primary focus areas of any pharmacy owner or manager, has to be profitability. Therefore, within a retail business environment, the commercial interests and the need for profit generation constantly compete with the altruistic motives of providing a healthcare service. This issue—the tension between the commercial interests and the altruistic provision of a healthcare service—has been central to pharmacy's age-old struggle to claim its role and status as a profession (Bush et al., 2009; Denzin and Mettlin, 1968).

Over the past few decades, the practice of pharmacy has progressed through many phases, mirroring periods of constraint and expansion in the role of the pharmacist, relative to their relationship with society and patients. More specifically, the phases are aligned with changes in role orientation between what can be described as a business, commercial or product orientation and a professional, service or patient orientation. Consequently, the phases also reflect fluctuations in the professional status of pharmacy (Daughton and Ruhoy, 2009).

Within recent years, this tension or the dilemma for role definition and professional status of pharmacists has become exacerbated by the deregulation of pharmacy ownership laws to allow for open ownership and the "corporatization" of community pharmacy. Corporatization of community pharmacy refers to the shift in ownership type of community pharmacies from independent, pharmacist owned private pharmacies to small, medium, and large pharmacy chains owned by corporate organizations.

Corporatization of community pharmacy worldwide has largely been permitted, and even encouraged, as a means to increase access, availability, affordability, and quality of medicines and pharmaceutical services. The consequences, however, of open ownership on the professional status have to be questioned. In this chapter, we will explore the rationale for deregulation of pharmacy law worldwide, which has led to open ownership and corporatization, the state of pharmacy ownership, and the consequences on the profession. We will conclude by discussing the implications for the future of community pharmacy.

Corporatization of Community Pharmacy

Because of a public interest in healthcare delivery and the need to deliver quality pharmaceutical services to society, community pharmacy worldwide has evolved within a milieu of wide-ranging regulations and operational standards. By placing restrictions on key issues governing the ownership, establishment and operation of community pharmacies, these regulations and standards have

essentially created a controlled and restricted environment within which community pharmacy has been practiced. The primary focus of these restrictive laws has been on:

- market entry and the establishment of new pharmacies, together with geographic and demographic criteria to open a new pharmacy;
- ownership, including restrictions on who may own a pharmacy and the number of pharmacies that may be owned by an individual or group;
- operating or opening hours;
- pricing regulations relating to the sale of medicines; and
- competition.

Within this controlled and restricted environment, and with the growth of the pharmaceutical industry and the entry of increasing numbers of new medicines onto the market, community pharmacies were able to capitalize and "build profitable enclaves with limited competition" (Strong, 2015). By the 1980s, the pharmacy retail business worldwide was dominated by relatively small-sized independently owned businesses, with comparable management and organizational structures, all offering relatively similar products and service provision, and generating analogous fiscal results. Employing comparable organizational and operational strategies meant that pharmacies largely competed with one another based on location and convenience. For the most part, costs and productivity became a secondary focus even though market growth and the development of the chronic medicine industry resulted in greater dispensing volumes and contributed to the stability and profitability of independent pharmacies (Strong, 2015).

Until the 1980s, in many parts of the United States (US) and in the United Kingdom (UK) where ownership laws were less restrictive, the development of corporate and chain pharmacies remained mostly contained or regional. By the early 2000s, the less restrictive regulations and relatively free market nature of pharmacy in the US and UK resulted in an extensive entry of corporates, including supermarkets and discount stores, into the pharmacy and over-the-counter (OTC) medicines market.

Even though regulations governing pharmacy practice within a country or state are relatively stable, there has been a developing global trend toward a more liberal approach to pharmacy regulation. The move toward liberalization of pharmacy regulations, particularly relating to pharmacy ownership, is often termed "deregulation" of pharmacy ownership. The term deregulation is used to describe varying degrees of relaxation of the regulations regarding pharmacy ownership, and can refer to anything, from a reduction of restrictions in some countries, to a complete abolition of restrictions in other countries. An important result of the deregulation of ownership laws has been the opportunity for corporatization of the community pharmacy sector.

Rationale for Deregulation of Pharmacy Ownership

The global trend of deregulation toward open ownership and corporatization has been driven by various motivations. The primary intention is often cited as the creation of a free market environment, which encourages competition. Central to the creation of competition within a retail market are low barriers of entry—creating the opportunity for multiple potential competitors to enter the market. Therefore, pro-competitive policies, often driven by competition authorities, play a pivotal role in driving deregulation (Anell, 2005; Helen Suzman Foundation, 2016; Lluch and Kanavos, 2010; Pharmaceutical Society of New Zealand, 2017).

Primary arguments for increased competition and allowing new entrants into the community pharmacy market center on four main issues: access, affordability, consumer choice, and quality of services.

Access to Medicines and Pharmaceutical Services

Arguments and motives for deregulation of pharmacy ownership laws have often focused on the role of competition in creating greater access to medicines and pharmaceutical services, particularly in previously underserviced and rural areas (Helen Suzman Foundation, 2016; Lluch and Kanavos, 2010; Vogler et al., 2014). Availability of medicines and pharmaceutical services can be described in terms of greater or lesser access to pharmacies due to increased or decreased numbers of pharmacies, shorter or greater distances between pharmacies and longer or shorter operating hours.

In South Africa, changes to the Pharmacy Act in 1997, allowing for open ownership, were based on the understanding that prospective entrepreneurs and businesses would be enabled to open pharmacies in underserved areas and provide highly needed pharmaceutical services (Helen Suzman Foundation, 2016). Liberalization of ownership laws in Sweden in 2009 was also based on the rationale that open ownership would increase availability of pharmacies and consumers' access to medicines (Wisell et al., 2015).

In North Dakota, proponents for deregulation of ownership laws have argued that it would increase access to medicines and pharmaceutical services in rural areas, where it is ordinarily difficult to attract pharmacists to work (Haarsager, 2010). Similarly, the Ministry of Health in New Zealand is pushing for deregulation of ownership rules, with the expectation that this will result in an increase in the overall number of pharmacies and longer operating hours, particularly in underserved or rural areas (Pharmaceutical Society of New Zealand, 2017).

Affordability of Medicines to the Consumer

Since pharmaceuticals, comprise a large share of healthcare expenditure, in the international context of a constrained financial environment, there is intensifying pressure to contain medicine costs. Consumer access to affordable medicines is an imperative for all governments. Competition is believed to stimulate efficiency, and particularly when corporate chains enter the market, economies of scale, enhanced buying power and lower distribution costs are anticipated to result in lower prices and more affordable medicines for consumers (Helen Suzman Foundation, 2016).

The promotion of competition and the lowering of medicine expenditure and consumer costs has been cited as the rationale for deregulation by many governments, including Iceland, Norway, Portugal, South Africa, and Sweden (Anell, 2005; Martins and Queirós, 2015). The Office for Fair Trading—a UK government department tasked with ensuring markets function favorably for consumers—in its 2003 report, "The control of entry regulations and retail pharmacy services in the UK," suggested that removing the control of entry regulations into the prescription medicine market could result in consumer savings in two ways:

- entry of corporate discount pharmacies and supermarket chains into the market could promote the availability of low prices to consumers and
- promoting price competition between pharmacies, would result in lower medicine prices in all types of pharmacies.

Increase Consumer Choice and Quality of Service

In a competitive market, the need to keep up with rivals is believed to stimulate the range and quality of products and services provided. Competition is also believed to drive innovation to deliver better services, and more integrated patient-focused services (Lluch and Kanavos, 2010; Pharmaceutical Society of New Zealand, 2017). In arguing for deregulation of pharmacy ownership laws, the New Zealand Ministry of Health states that ownership restrictions are not necessary for ensuring safe and rational medicines use, and that there is no direct link between the percentage shareholding of a pharmacy by a pharmacist and the safety of patients. Furthermore, the Ministry contends that restrictive ownership laws, by reducing the scope for competition and investment in community pharmacy, have the effect of hampering rather than promoting innovation. The Ministry further suggests that "more flexible ownership arrangements could assist in achieving the mutual goal of the pharmacy profession and the Government of helping the sector move toward better, integrated and consumer centered care" (Pharmaceutical Society of New Zealand, 2017).

Despite the existence of some common arguments for deregulation of ownership laws and increased market competition, there is considerable diversity in community pharmacy systems across the world because of differences in prevailing legal, political, and healthcare structures. Consequently, there is a multiplicity of ownership rules worldwide.

Pharmacy Ownership Types

Pharmacy ownership rules lie on a continuum between the more restrictive forms on one end, where pharmacy ownership is the exclusive right of pharmacists, and the less restrictive, deregulated forms on the other end, where open ownership of pharmacies is permitted and encouraged.

Along the ownership continuum, various types of pharmacy ownership exist. Although the exact nature and details of these vary from country to country, in general the following types can be identified.

Pharmacist-only Ownership

These are pharmacies, which are owned solely by pharmacists, either individually or in groups. Examples of countries with regulated pharmacy systems and pharmacist-owned pharmacies include Australia, Denmark, Finland, Germany, Greece, Luxemburg, and Turkey (Danish Medicines Agency, 2014; Employed Community Pharmacists in Europe (EPhEU), 2017; Government of Western Australia Department of Health, 2017; The Association of Finnish Pharmacists, 2014; Vogler et al., 2014). In many low-income countries, including India, Nigeria, Côte d'Ivoire, Vietnam, Cameroon, and Lebanon, ownership is restricted to pharmacists (Lowe and Montagu, 2009).

In highly regulated pharmacy systems, where ownership of a pharmacy is the sole domain of pharmacists, there are often restrictions placed on the number of pharmacies each pharmacist may own. In Germany for example, a pharmacist may own a maximum of three pharmacies with the proviso that they are located in the same or adjacent district, and each pharmacy must have a pharmacist in place as branch manager. In Finland, pharmacists are restricted to ownership of one pharmacy, while in Greece, a pharmacist may own one pharmacy and have a minor share-holding in a second (EPhEU, 2017; The Association of Finnish Pharmacists, 2014). In Australia, the restriction on the number of pharmacies owned by one pharmacist varies from territory to territory. For example, there is no restriction in the Australian Capital and Northern Territories, while Tasmania and Western Australia have a restriction of four pharmacies, New South Wales, Queensland, and Victoria a restriction of five, and South Australia a restriction of six (Government of Western Australia Department of Health, 2017). Limitations on multiple ownership, except for a limited number of branch pharmacies, prevent the formation of chain pharmacies. The establishment or entry of new pharmacies into the market is also often tightly controlled by the need for a state concession or a license, and by geo-demographic criteria, including population quotas per pharmacy and distance from existing pharmacies. Although terminology varies, when

ownership is restricted to one or more pharmacists, and they own five or fewer pharmacies, the pharmacies are generally termed independent pharmacies.

Mixed Ownership

Partial deregulation in many countries has resulted in mixed ownership types. These comprise pharmacy systems where ownership of a pharmacy must include shareholding by a pharmacist but may include non-pharmacists or corporate entities as shareholders. The extent of shareholding required by a pharmacist or group of pharmacists varies considerably from country to country. In some systems, pharmacists must be the majority shareholders, for example, in Austria, Cyprus, and Latvia, a pharmacist or pharmacists must own at least 51% of the business, while in Lithuania and Spain, pharmacist shareholding must be at least 75%. Furthermore, in many of these countries it is a requirement that the pharmacist who holds the pharmacy license must have the exclusive power of management and representation (EPhEU, 2017). In New Zealand, current legislation specifies that a registered pharmacist or a company with the majority share capital held by a pharmacist or pharmacists must have at least 51% ownership. There is also a restriction on prescribers holding any interest in pharmacies (Pharmaceutical Society of New Zealand, 2017).

North Dakota, the US state with the most stringent pharmacy ownership laws, requires 51% of the ownership interest of every pharmacy in the State, to be held by a pharmacist licensed in the State. Furthermore, the laws in North Dakota require that the pharmacists with the controlling interest in the pharmacy are actively employed in the pharmacy and have managerial control over the pharmacy. Although there is no ban on corporates entering the market, this law has effectively discouraged corporatization and the formation of chains within the State of North Dakota, since large-scale retailers are statutorily restricted to entering the pharmacy market as minority shareholders (Haarsager, 2010).

The only other US state with restrictive ownership laws is Michigan, which requires that a pharmacist or pharmacists have at least a 25% shareholding in a pharmacy. Michigan, however, has no corresponding requirement that the pharmacist owner has managerial or operational control over the pharmacy (Legislative Council - State of Michigan, 2017). Haarsager (2010) makes the point that, despite comparable ownership laws, corporate "retail giants" have penetrated the retail pharmacy market in Michigan but not in North Dakota, suggesting that corporates are not willing to own pharmacies in which they are not the majority, controlling shareholder.

Open Ownership

On the more liberal end of the ownership continuum, pharmacy ownership rules have been deregulated and there are few or no establishment rules for the entry of new pharmacies into the market and almost no restrictions on who may own a pharmacy. Examples of such countries include Belgium, Bulgaria, England, Iceland, Ireland, Italy, the Netherlands, Norway, Portugal, Romania, Slovakia, South Africa, Sweden, Switzerland, most US states, and some Canadian provinces (Helen Suzman Foundation, 2016; Lovells, 2017; Pharmine, 2016; Vogler et al., 2014). Within an open ownership system, there are frequently some common but minor exceptions to ownership, for example, a limitation on ownership by prescribers or manufacturers of medicines (Vogler et al., 2014).

Globally, corporatization has been a major trend in the retail industry and the pharmacy retail industry is no exception. It is within these deregulated environments where open ownership is permitted, that corporations have entered the retail pharmacy market, resulting in the corporatization of community pharmacy. In deregulated countries chain pharmacies are now the norm, for example, approximately 96% of pharmacies in Norway, 86% in Sweden, 64% in the US, and 61% in the UK, are owned by corporate chains (National Community Pharmacists Association, 2017; Sukhar, 2016; Vogler et al., 2014).

In some countries, the establishment of pharmacy chains is limited by restrictions on the number of pharmacies that any person or business entity may own. This has resulted in wide variations in the extent of corporate penetration into the market and has given rise to various levels of chain pharmacies, including small, large, and multiple chain stores. Entry of supermarket retailers into the market in countries such as the UK, US, and South Africa has also resulted in the creation of supermarket chain pharmacies. In more regulated countries where, the establishment of chain stores is limited, franchising or branding is used to develop and create de facto chains (Helen Suzman Foundation, 2016; Lowe and Montagu, 2009). Franchising or branding is a business relationship in which the franchiser or owner permits another party—the franchisee to use their brand, products, or business systems, and in return, the franchisee pays an upfront fee and ongoing royalties. In many European countries, and in both Australia and New Zealand, where ownership is restricted to pharmacist-only or mixed ownership types, franchising is effectively leading to chains or networks of privately owned pharmacies. Franchising enables an individual pharmacy owner the opportunities and efficiencies of operating as part of a larger group while retaining independence and professional autonomy (Pharmaceutical Society of New Zealand, 2017).

Impact of Deregulation of Ownership Laws on the Community Pharmacy Market

In this section, we will review the evidence and experience of the reduction or removal of restrictive pharmacy ownership regulations. The intention of deregulation in many countries was the creation of a more competitive pharmacy market, with the anticipation of a consequent improvement in accessibility to affordable medicines, increased consumer choice and improved quality of services.

Although we will consider the impact of deregulation on each of these aspects, we will also review the influence of deregulation on levels of competition within the market, and on issues of professionalism and the practice of pharmacy.

Unbalanced Increase in Accessibility

In countries with deregulated pharmacy markets, there is normally a general increase in accessibility of medicines because of the entry of new players into the market and the establishment of new pharmacies, resulting in an overall decrease in the number of inhabitants per pharmacy. Deregulation, however, tends to favor the more densely populated and affluent areas, most of which already had good accessibility to medicines and pharmaceutical services (Vogler, 2014).

In a study to evaluate the impact of deregulation in community pharmacy ownership on accessibility of medicines, Vogler et al. (2014) compared community pharmacy systems in five deregulated countries (England, Ireland, the Netherlands, Norway, and Sweden) with four regulated countries (Austria, Denmark, Finland, and Spain). Vogler et al. (2014) concluded that deregulation of pharmacy ownership laws was associated with opening of new pharmacies, an increase in the number of pharmacies, and a corresponding decrease in the number of inhabitants per community pharmacy. New pharmacies, however, were clustered in established urban areas and there was no apparent increase in the number of pharmacies in rural and previously under-served areas, or in the accessibility of medicines in these areas. Furthermore, they suggested that the opening of new pharmacies appears to be a short-term trend or phenomenon in the early years following deregulation but diminishes with time and the increased competition that is created can ultimately lead to pharmacy closures.

Examination of the evidence by Anell (2005), following deregulation of the pharmacy market in Iceland and Norway, showed similar trends to those described by Vogler et al. (2014). The relaxation of restrictive ownership laws in Iceland in 1996 stimulated an initial increase in the number of pharmacies. The increases, however, were largely focused on the more densely populated and urban areas, such as Reykjavik, which experienced positive benefits. The benefits sometimes came at the expense of parallel closures of pharmacies in the more rural areas. With the opening of new pharmacies came the formation of strong chains, and by 2004 two pharmacy chains controlled 85% of the market. Pharmacies in these two chains, however, were only available in Reykjavik and in Akureyri, the two largest cities in Iceland, creating a major difference in access between the urban and rural areas. Similar changes in the Norwegian pharmacy market were evidenced following deregulation in 2001. Within a three year period (2001–2004) there was a 32% increase in the number of pharmacies. The majority of these new pharmacies, however, opened in city centers and shopping malls, close to existing pharmacies with high sales volumes. With only a few exceptions, the changes in policy did little to stimulate the availability of pharmacies in rural areas.

Proponents of the deregulation of pharmacy ownership laws in North Dakota have used the potential for greater access to medicines in the more rural areas as a large component of their argument. A comparison of North Dakota with its neighboring deregulated state, South Dakota, provides insight into the strength of this argument. There are, geographically, more local pharmacies in North Dakota, spread evenly throughout the State, while in South Dakota; pharmacies are mostly located in large cities and high population areas. In North Dakota, 53% of rural census tracts have pharmacies, compared to only 35% in South Dakota (Haarsager, 2010; LaVecchia and Mitchell, 2014).

Based on the Portuguese experience, Martins and Queirós (2015) purport that deregulatory changes can lead to an unbalanced distribution of pharmacy services which favors already well serviced, more affluent urban markets. The concentration of chain and supermarket pharmacies in more affluent areas has also been described in the UK. Bush et al. (2009) suggested that in the UK, independent pharmacies tend to be located centrally within communities and were easily accessible to those without transport while supermarket pharmacies were found on the peripheries in retail parks and were more difficult to access without transport—in other words by those who are generally also the socioeconomically disadvantaged (Bush et al., 2009).

In an effort to improve access in the UK, through longer operating hours, an exemption from a licensing requirement to prove new pharmacies were "necessary and desirable" was introduced in 2005, and granted to all new pharmacies which opened for "100 hours" per week. Although this exemption saw a tenfold increase in the number of new licenses being issued, these were mainly to large multiples protecting their high street and retail park businesses and to new supermarkets entering the market. This exemption law was withdrawn in 2012 as it was viewed by the Pharmaceutical Services Negotiating Committee as creating "clustering of additional pharmacies that bring about little improvement in access." Regulations that are more restrictive were reintroduced, requiring new entrants to the market to pass a new market entry test centered on a pharmaceutical needs assessment (Pharmaceutical Journal News Team, 2012).

In South Africa, permitting of open ownership was specifically intended to increase access and provide medicine in underserved areas. Therefore, at the time of the amendments to legislation, it was widely understood that the establishment of new pharmacies under lay ownership would be focused in previously underserved areas. In addition, the general understanding of the pharmacy profession was that the issuing of new pharmacy licenses would be preceded by the distribution of a notice of intent to existing pharmacies in the area, giving them an opportunity to provide reasonable objections (Helen Suzman Foundation, 2016). No geographical restrictions, however, have been applied and the entry of corporates and the formation of chains have been largely facilitated by what Lowe and Montagu (2009) describe as "the existence of an urban middle-class market." This has resulted in a two-tier community pharmacy market, where rural areas are underserviced and the majority of pharmaceutical services are provided in suburban areas and city nodes (Adams, 2011).

Despite a global trend toward deregulation and corporatization, in some Eastern European countries, for example, Estonia and Hungary, a lack of increased access to medicines following a period of open ownership has actually resulted in the reintroduction of

stricter regulatory control of pharmacy ownership, often referred to as "reregulation" (Gross and Volmer, 2016; Helen Suzman Foundation, 2016). Estonia, a country with liberal pharmaceutical policies and ownership laws introduced in the 1990s, has re-introduced legislation which from 2020, will again restrict ownership of community pharmacies to the pharmacy profession. This is because liberal ownership laws, which were related to economic factors and not improved patient care, resulted in an uneven geographical distribution of community pharmacies and vertical integration between community pharmacies and wholesalers. Following deregulation in the 1990s, there was a significant increase in the number of community pharmacies. The majority of the new pharmacies, owned by corporate chains, operated in larger towns. The legislative changes being introduced to reregulate pharmacy ownership have been a consequence of the perceived threat to the viability of small community pharmacies in rural areas and the potential this has to limit access to medicines and community pharmacy services in the future (Gross and Volmer, 2016). Similar changes resulting in reregulation of pharmacy ownership laws have also taken place in Hungary. In 2010, the Hungarian government legislated that at least 51% of shares in community pharmacies must be held by Hungarian pharmacists. This decision was based, in part, on a lack of improvement in the supply of medicines in rural and economically disadvantaged regions, despite an overall increase in the number of pharmacies post-deregulation.

Affordability of Medicines and Pharmaceutical Services in Deregulated Community Pharmacy Environments

As discussed previously, pro-competitive moves toward deregulation of ownership laws are often aimed at increasing the affordability of medicines and pharmaceutical services. Experience has, however, demonstrated that anticipated financial savings on medicine costs are not generally realized for either the patient or the government (Vogler et al., 2014). Basing their conclusions on both their study to evaluate the impact of deregulation of community pharmacy ownership on European countries, and an extensive literature review, Vogler et al. (2014) concluded that there was "no indication for an association between the extent of regulation and the amount of total, or public, pharmaceutical expenditure." Furthermore, they suggested that there was a range of policies and factors affecting pharmaceutical expenditure and the cost of dispensing medicines was only one aspect.

Although, as Strong (2015) argued, deregulation and consequent corporatization has generally been associated with a fall in prices, prices tend to fall faster than costs, and margins have been negatively impacted. In the context of the pharmacy environment where core dispensary reimbursements, ordinarily paid by governments and third-party agents such as pharmacy benefit management companies (PBMs), are being constantly reduced, this trend is putting pharmacies, especially independents, under severe economic strain.

Corporates, with their economies of scale and widespread geographical reach are viewed as having sufficient financial muscle to negotiate with governments and third-party agents. For example, community pharmacists in the UK believe that corporate pharmacy chains are well positioned to attract disproportionate financing through the National Health System (NHS) commissioning processes (Bush et al., 2009). Similarly, in South Africa, medical schemes, medical benefit, and insurance companies enter into agreements with pharmacies to provide their members with medicines, in an effort to contain costs. Through a system of designated service providers (DSPs), these third party agents then negotiate reduced dispensing fees. To be appointed as a DSP, the pharmacy has to enter into a contract that sets the dispensing fee payable for the supply of medicines at a lower price than the upper limit set by government. Thus, for the advantage of becoming a preferred provider, an agreed level of price reduction or incentive is provided to the third party agent. Although such agreements are in principle open to all pharmacies, in reality, the chain nature of corporate pharmacies, their geographical coverage, together with the economies of scale that they are able to offer, makes the negotiation of such contracts easier and simpler for them, and smaller independent pharmacies are therefore largely excluded from such negotiations (Helen Suzman Foundation, 2016).

With the global movement toward open ownership, there has been an accompanying trend toward both horizontal and vertical integration in the pharmaceutical distribution chain. Vertical integration is the merging or fusion of business entities with complementary business interests, and a vertically integrated company participates at multiple levels of an industry's distribution or value chain. Open ownership has led to the merger of pharmacies at the retail and wholesale levels, and more specifically in the UK, US, and several European countries, to large pharmaceutical wholesalers merging with or owning pharmacy chains. Within three years of deregulation in Norway, horizontal integration had resulted in 97% of all community pharmacies being aligned with the three major pharmacy chains (Apotek 1, Alliance Unichem, and Vitusapotek), all of whom had formed vertical alliances with the three main wholesalers in Europe (Phoenix, Alliance Unichem, and Celesio). In the US, vertical integration between pharmacy chains and PBMs has also become common place (Barlas, 2018). Horizontal integration, the fusion of business entities conducting the same line of business, such as the merging of multiple community pharmacies, has also resulted in the creation of powerful corporate chains (Anell, 2005; Kanavos et al., 2011; Vogler et al., 2014).

The current financial climate has also seen an unprecedented increase in vertical integration between corporate pharmacy chains and PBMs in the US. A reduction in drug prices, aimed at assisting consumers to manage costs while improving health outcomes, is cited as the prime motivating factor behind these mergers. Barlas (2018) argued, however, that although there were some small indications of point of sale discounts, these cost reductions were for the most part not being passed on to consumers. Agency theory suggests that the primary goal of a corporate business is to increase profit (Dobson and Perepelkin, 2011). Therefore, since logically the prime reason for the existence of a corporate organization is to fulfill its responsibility to its shareholders by making a profit, it is not surprising that deregulation of ownership has little effect on the sale price of pharmaceuticals and that financial savings are not passed onto the consumers.

In the context of a drive for profit maximization, when price savings in the dispensing and selling of medicines in corporate pharmacies are passed on to the consumer, they are viewed as a "loss leader" and a means of drawing customers through the stores. Within corporate chains, dispensary operations are frequently not considered to be a significant contributor to profits; as Strong (2015) stated the role of dispensaries is shifting from being a "profit-driver to a traffic driver." Honeysett, a former CEO of the Clicks Group, the largest retail pharmacy chain in South Africa, summed this up when he said: "dispensaries ensure greater footfall in Clicks stores, thus increasing sales volumes across the brand" (Trevor Honeysett, Former CEO—Clicks Group, cited by Bolin, 2005).

Experience of deregulation in many countries has demonstrated that corporate ownership of pharmacies has led to the development of oligopolies where a small number of organizations become dominant and hold the majority of the market share. In the US, two corporates—CVS Health Corporation and Walgreens Boots Alliance—hold approximately 40% of the prescription medicines market share between them (Statista, 2017). Walgreens Boots Alliance is the world's largest pharmacy operator and the owner of the UK-based Boots pharmacy chain. In the UK, 12 large multiple corporate chains own approximately 50% of the community pharmacy market, with the largest of these, Boots, owning approximately 17% (Sukhar, 2016). In Ireland, Norway and Sweden, the three largest community pharmacy chains respectively own approximately 79%, 81%, and 68% of the market share. In fifteen years, since the deregulation of pharmacy ownership laws in South Africa in 2003, two companies, Clicks and Dis-Chem, have captured nearly 45% of the retail pharmacy market.

The development of oligopolies within the community pharmacy market has, in many deregulated countries, given rise to a substantial reduction in competition, and could even result in higher prices for consumers. Furthermore, within a market characterized by oligopolies, consumer choice becomes more limited.

Implications of Deregulation on Consumer Choice and Quality of Services Provided

As Strong (2015) contended, within a regulated community pharmacy environment, small independent pharmacies, all offer similar products and services and consumer choice is limited. Community pharmacy patronage decisions within these restricted markets are largely based on location and convenience. Consequently, the intentions of deregulation to create increased competition and resultant consumer choice are generally realized fairly soon after new competitors enter the market. New entrants enter the market with fresh strategies, frequently targeted at specific customer segments; for example, low-price, volume driven corporates and supermarkets often target the more cost-conscious consumer. With time, however, vertical and horizontal integration and the development of oligopolies leads to reduced consumer choice, especially when small-scale independent pharmacies are being placed under severe pressure and sometimes squeezed out of the market. Although consumer choice of a pharmacy is most frequently driven by location and convenience, range and quality of professional services is increasingly becoming a factor (Strong, 2015).

Bush et al. (2009) investigated the implications of corporatization on community pharmacy in the UK, focusing on service provision, public health function and professional status. Although the researchers reported no relationship between the pharmacy type and the provision of essential services such as health promotion and the collection of waste medicines, they did identify an association between the provision of enhanced services and pharmacy type. The decreased levels of provision of services such as domiciliary visits, palliative care, out-of-hours, and home delivery services—none of which offer any immediate, short-term financial benefits—by large chain and supermarket pharmacies were notable. There was also a tendency for supermarket chains to limit the services they provide to those which might be considered socially acceptable or less controversial such as the supply of emergency hormonal contraception (EHC) to persons younger than sixteen years without a prescription. A high proportion of supermarket and multiple chain pharmacies, however, did offer medicines use reviews (MURs). These findings with regard to MURs confirmed the outcomes of a 2008 study by Bradley and colleagues, which identified ownership type as the most significant determinant in the uptake of MURs by community pharmacies in England (Bradley et al., 2008). These findings need to be viewed in the context of MURs being classified as a Tier Two, advanced service, in the national contractual framework for pharmacies in England and as such attract reimbursement from the NHS per MUR conducted. Bradley et al. (2008) demonstrated that MUR provision by multiple pharmacy chains was almost twice that of independent pharmacies. The results of their study also highlighted a difference in the manner in which multiple chains and independent pharmacies approached MURs. Interviews with five pharmacists employed in multiple chain pharmacies reported being pressured by the chain management to achieve MUR targets, often to the detriment of quality. When the work of pharmacists is measured by the achievement of targets, the purpose and quality of their work becomes compromised. For example, MURs serve the purpose of optimizing medicine use, but when under pressure to achieve targets, pharmacists may opt to perform MURs for patients with fewer medicines or simpler medicine regimens rather than for patients with more complex regimens with multiple medicines (Latif et al., 2011).

The case of MURs in the UK highlights an important issue concerning the professional autonomy given to employee pharmacists within corporate environments and the impact of corporatization on professionalism. This is an issue not unique to the UK and has been noted in many other countries including the US, Canada, South Africa, Norway, and Sweden (Canadian Pharmacists Association, 2016; Gaither et al., 2008; Vogler et al., 2014).

Professional Implications of Deregulation

Changing models of pharmacy practice require greater levels of professional autonomy, increased service-orientation, increased patient focus, and greater emphasis on clinical skills. Corporatization is often associated with a loss of the pharmacists' autonomy,

decision-making abilities, and level of control, due in part to the more inflexible and fixed structures of these organizations, the focus on profit, and the resultant commoditization of pharmacy services (Perepelkin, 2008; Sukhar, 2013).

In considering an appeal for greater liberalization of ownership rules in Italy and Germany, the European Court of Justice drew attention to the unique nature of medicinal products, stating that the therapeutic effects of medicinal products "distinguish them substantially from other goods." For this reason, because the unnecessary or incorrect consumption of medicinal products poses a very real public health risk, the Court stated that medicinal products were best sold by a pharmacist. In addition, the ruling alluded to the notion that the safe sale of medicinal products is most probable when a pharmacist has "genuine professional independence" and any breach of laws governing the sale of medicines would both threaten his/her professional existence and financial investment. The Court ruled that although the restriction of pharmacy ownership to pharmacists constituted "a restriction on the freedom of establishment and the free movement of capital" it was justifiable as necessary for the reliable provision of good quality medicinal products (Commission of the European Communities, 2009).

Irrespective of the type of ownership, at an operational level, the presence of a licensed or registered pharmacist is required in almost all countries for the operation of a dispensary. Licensure or registration as a pharmacist carries with it professional responsibilities and obligations and compliance with laws and regulations, the goal of which is to optimize medicine related health outcomes and safety. A full appreciation and knowledge of the legal and ethical issues related to medicines and their supply are essential requirements of competency, registration, and practice as a pharmacist. In a corporate pharmacy environment, however, pharmacists are not only bound to pharmaceutical regulations but also corporate institutional policy decisions, which are often centralized and removed from the operational level (Dobson and Perepelkin, 2011; Perepelkin, 2008; Pharmaceutical Society of New Zealand, 2017). As the Helen Suzman Foundation (2016) report suggests, in a corporately owned pharmacy "there is a separation between principal and agent." While the organization or principal may be tempted to comprise on professional standards, it is the pharmacist—the agent, carrying out the functions of the organization—who has to carry the primary concern of maintaining professional and ethical standards. In an independent pharmacy, the pharmacist generally understands that upholding professional standards is a means of protecting their investment; however, when employed by a corporate organization, the cost of maintaining professional standards, especially if it involves opposing the employer, is much more personal in nature (Helen Suzman Foundation, 2016).

Within corporate pharmacy businesses, pharmacists are often viewed as a necessary but costly human capital expense; this results in corporations trying to either economize or maximize on the expenditure on pharmacists (Dobson and Perepelkin, 2011). Maximizing involves seeking to gain the maximum benefit from employee pharmacists and results in increased workloads and work pressure for pharmacists. As a further means of maximizing, pharmacy chains are increasingly employing non-pharmacists as store managers. This is viewed as a means of freeing pharmacists from non-pharmaceutical related managerial tasks and allowing them to focus on providing pharmacy services. Many pharmacists, when forced to work with a non-pharmacy manager, feel that their authority is undermined and they are uncomfortable with the lack of clarity over responsibilities (Elvey, 2011). The other tendency in corporate environments is to try to economize on the services of pharmacists by employing fewer pharmacists and more pharmacy support personnel, such as pharmacist assistants and technicians. Attempts to either maximize or economize on the services of pharmacists have the potential to compromise the quality of pharmaceutical services provided and might ultimately pose a threat to patient safety. Furthermore, non-pharmacist owners and managers are likely to be more focused on production efficiency rather than the professional objectives related to patient outcomes and safety (Dobson and Perepelkin, 2011). Consequently, in many countries, corporate ownership of pharmacies has been associated with increased workloads and a more stressful work environment for pharmacists. Excessive workloads and constant challenges to their professional status by non-pharmacist managers, often leave employee pharmacists in corporate pharmacies feeling "jaded" (Kubashe, 2017).

The Changing Community Pharmacy Landscape and the Way Forward

Challenged with the tension of providing a healthcare service within a retail business environment, community pharmacy exists within complex economic and social structures. Consequently, the international movement of the retail industry toward corporatization has not escaped community pharmacy. Corporatization has and is undoubtedly changing the community pharmacy landscape with pharmacy chains of varying sizes and supermarket pharmacies now the norm in many countries.

We have seen that international evidence and experience does not support a claim to superiority of any of the ownership types. As Lluch and Kanavos (2010) contended, there are useful lessons to learn from all types. Countries with liberal or deregulated pharmacy systems could learn from the policies applied in more strictly regulated countries, which increase the equity and professional status of community pharmacies, while highly regulated countries could consider some of the policies from liberal countries to increase efficiency in the pharmacy system.

A final word of warning may be apposite, however, based on the work of an American sociologist, George Ritzer, Harding and Taylor (2000) referred to corporatization as the "McDonaldization" of community pharmacy. Harding and Taylor explained how the four dimensions described by Ritzer, as characterizing the working practices of large corporations in rationalizing products and services are similarly apparent in corporate pharmacies. The four rationalizations are:

- *Efficiency*—the carrying out of tasks in the most optimal and rational manner, with no freedom for individualization, is achieved through the routine following of standard operating procedures (SOPs).

- *Calculability*—relates to the commodification of medicines and services, where they become a unit of supply and a cost item, rather than a unit of therapy and healing.
- *Predictability*—refers to the standardization of experience in any outlet within a chain, regardless of geographic location. It is achieved by the standardization of store layout and service, uniformity of products and the implementation of centrally driven company policies, protocols, and procedures.
- *Control*—achieved through the minimization of skilled activities by staff and the use of automation and technology wherever possible.

These rationalizations in the pharmacy domain have resulted in the formation of pharmacy chains or "McPharmacies" in which the standardization of policies, procedures, and processes become routinized, and, thus, products and services standardized. Even the store layout and fittings are uniform in design. Through in-house training programs, all staff, including pharmacists and managers, are socialized into the corporate ethos and way of providing services and even interacting with clients. Essentially, throughout a corporate chain of pharmacies, the consumer experience becomes uniform and standardized (Harding and Taylor, 2000; Taylor and Harding, 2003).

Within the context of this standardized corporate milieu, where the pharmacist's work becomes measured by "speed and efficiency" and pharmacists become "McPharmacists," there is little space for individualized, patient-centered care. Taylor and Harding (2003) asked searching questions about the challenges this raises for the future of the pharmacy profession. They contended that the changes brought about by the "McDonaldization" of pharmacy have implications for all levels of the pharmacy profession, including practitioners, professional bodies, researchers, and educators. The pharmacy profession has to capitalize on the rationalization and routinization of practice to create greater opportunities to "extend and promote their professional activities" (Taylor and Harding, 2003). Even within corporate environments, this could mean striving for greater community and patient focus through increased pharmacist availability, development of their advisory and health promotion roles, provision of pharmaceutical care services, medicines management activities, and pharmacist prescribing. All community pharmacists need to be fully integrated into primary care and resourced to deliver value-for-money, efficient, individualized, and patient-centered healthcare. Their role needs to be supported by supportive and proactive professional bodies and by pharmacy educators focused on developing critical thinking, decision-making pharmacists, who are willing to exercise autonomous professional judgment, albeit as employee, manager or owner pharmacists (Taylor and Harding, 2003).

Glossary

Chain pharmacy: A retail or community pharmacy, belonging to a group of more than five pharmacy outlets, co-owned by a pharmacist, multiple pharmacists, and/or non-pharmacists, business entities or corporations.
Community pharmacy: A business or for-profit organization providing pharmaceutical and primary healthcare services and products to a community.
Community: A group of people living within a specific geographic area, sharing both similar or different characteristics and needs.
Corporate pharmacy: A retail pharmacy forming part of a corporation-owned small, large, multiple, or supermarket pharmacy chain, having more than five pharmacy outlets centrally managed.
Corporation: An organizational form typically found in business, characterized by clearly articulated corporate objectives, centrally managed, with a separation between senior management and operations.
Corporatization: Although generally referring to the process of bringing businesses under the control of a corporation, in this chapter it will be a reference to the shift in community pharmacy ownership, from private independent pharmacies to chain pharmacies.
Deregulation: The revision, reduction, or removal of laws and regulations that hinder free competition in the supply of products or services.
Horizontal integration: The merging or fusion of business entities conducting the same line of business. In the pharmaceutical distribution chain, this usually refers to the fusion between wholesalers or the fusion between retail or community pharmacies to create chains.
Independent pharmacy: A retail or community pharmacy owned by a pharmacist or multiple pharmacists, who have five or fewer pharmacy outlets.
Large chain pharmacy: A pharmacy forming part of a group of more than 20 but fewer than 200 pharmacy outlets, co-owned by a pharmacist, multiple pharmacists, and/or non-pharmacists or business entities.
Mixed ownership: Ownership form of a community or retail pharmacy or chain that requires a pharmacist or pharmacists to be co-owners.
Multiple chain pharmacy: A pharmacy forming part of a group of 200 or more pharmacy outlets, co-owned by a pharmacist, multiple pharmacists, and/or non-pharmacists or business entities.
Oligopoly: A market structure in which a small number of organizations hold the majority market share and become dominant.

Open ownership: Ownership form of a community or retail pharmacy or chain that does not require a pharmacist as a co-owner.
Pharmacy-only ownership: Ownership form of a community or retail pharmacy or chain that restricts ownership to licensed or registered pharmacists only.
Reregulation: The process of reinstating laws and regulations that restrict free competition in the supply of products or services.
Retail pharmacy: A business or for-profit organization selling medicines, in quantities intended for personal use, direct to the consumer.
Small chain pharmacy: A pharmacy forming part of a group of more than five but fewer than 20 pharmacy outlets, co-owned by a pharmacist, multiple pharmacists, and/or non-pharmacists or business entities.
Supermarket pharmacy: A pharmacy outlet within a supermarket chain.
Vertical integration: The merging or fusion of business entities with complementary business interests. In the pharmaceutical distribution chain, this usually refers to the fusion between wholesaler and retailer, or manufacturer, wholesaler and retailer.

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Stigma Surrounding Medicine Use—HIV Exemplar

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Introduction

This chapter explores the notion of stigma surrounding medicines use and utilizes as its example human immunodeficiency virus (HIV). HIV is a significant social and public health issue and by the end of 2016, there were 36.7 million people in the world living with HIV; 1.0 million of whom died in 2016 through infection and corelated illnesses (WHO, 2017). HIV is the precursor condition to acquired immune deficiency syndrome (AIDS) and The World Health Organisation (WHO) plans to end the public threat that is caused by the AIDS epidemic by 2030 (Rintamaki et al., 2006).

The HIV pandemic which started in the 1980s, brought to society a new type of stigma, associated with this relatively unknown and significantly lethal disease. The origin and the epidemic characteristics of the disease were not publicly known at that time, therefore, people living with HIV (PLHIV) were perceived by society in a largely negative way. Since the WHO launched the Special Programme on AIDS in 1982, a radical increase in the number of patients covered by antiretroviral therapy (ART) has been observed. Nevertheless, there is still a number of common challenges related to HIV/AIDS and stigma experienced by PLHIV certainly remains as one of the considerable social issues they deal with (Rintamaki et al., 2006).

The definition of stigma is a reaction, negative in its nature, to a discrediting or undesirable trait of an individual in a social setting. Stigma occurs when one group of people hold a biased/prejudicial opinion against another group, who happen to be identified with a mutual attribute (Martinez et al., 2018). Stigma can manifest in several ways. In addition to stigma in its most common understanding (discrimination by society), stigma can also occur as "anticipated stigma," where an HIV-positive person expects negative reactions from people who may learn about their serostatus, or as internalized stigma, where a person living with HIV assumes that their personal and societal worth is in some way compromised by their disease. This thinking can lead to self-destructive health behaviors and has a negative impact on the quality of life for PLHIV's (Helms et al., 2017). The Social Cognitive Model is a popular theory related to HIV stigma; the theory outlines the process of development of HIV stigma in an individual who becomes aware of negative perceptions of HIV/AIDS and therefore is able to accept them as valid and truthful. For that reason, when the individual becomes HIV-positive, they perceive their serostatus as meaning they are now part of the discriminated group, which perpetuates the negative beliefs further (Travaglini et al., 2018).

What is more, discrimination and stigmatization which may correlate with access to anti-HIV treatment, is significantly dependent on such factors as gender and age, geography and belonging to key populations (WHO, 2016b). These key populations, as identified by The Joint United Nations Programme on HIV and AIDS (UNAIDS), include sex workers, men who have sex with men (MSM), transgender people, intravenous drug users (IDUs), and prison inmates (UNAIDS, 2016b, 2018). These populations have been socially marginalized throughout history, even before the negative connotation related to HIV emerged (Vanable et al., 2006). These key populations experience multifaceted issues related to discrimination and stigma, which may negatively influence these peoples' adherence to medication regimens (WHO, 2016a). In some regions, such as Sub-Saharan

Africa and the Middle East, there is still a lack of tools available for effective measurement of stigma in those populations (Fitzgerald-Husek et al., 2017).

HIV infection has been associated with the increased likelihood of mood disorders, substance abuse, and addiction, posttraumatic stress disorder (e.g., related to their HIV diagnosis) and serious mental health issues such as schizophrenia (Travaglini et al., 2018). It has also been proven that HIV stigma can be associated with bidirectionally maladaptive coping behaviors such as hazardous drinking. A "self-medication" alcohol consumption model (i.e., drinking to relieve stress) has been observed among people living with HIV. This type of alcohol consumption tends to cause more alcohol-related negative consequences than other forms of excessive drinking, e.g., binge drinking in social situations (Wardell et al., 2018).

Overview of HIV Medication Stigma

It has been established, that for ART to be successful, medicines adherence in an HIV-positive person must be 95% or higher (Martinez et al., 2018). Otherwise, anti-HIV medications will not be sufficiently effective in terms of increasing CD4 counts and lowering viral load (Dlamini et al., 2009). It has been proven that HIV stigma can make PLHIV three times more likely to be nonadherent to their therapy recommendations, compared to PLHIV not experiencing such concerns (Martinez et al., 2018).

Nonadherence may be a nondirect consequence of, for example, mental instability caused by stigma. A study in South Africa suggested that internalized stigma, which led to cognitive-affective depression, consequently caused nonadherence (Bhatti et al., 2016). Poor medication adherence may cause the antiretroviral therapy to be unsuccessful, but also has a wider impact on public health, giving rise to drug-resistant HIV strains (Rao et al., 2007). Consequently, the resistant virus strains might be transferred to other individuals, and limit their options in terms of effective anti-HIV therapy (Rintamaki et al., 2006). Another stigma-associated factor that negatively impacts the HIV epidemiology is avoidance of HIV testing by people with anticipated HIV stigma. That can lead to a delay in starting treatment and the virus to be transmitted to, for example, sexual partners of the HIV-positive person. Moreover, the fear of being stigmatized might, in fact, lead to risky sexual behaviors such as not using a condom; PLHIV with anticipated stigma might worry that initiating a discussion on safe sex hints that the person has a sexually transmissible disease (STD) (Vanable et al., 2006).

In 2006 a study found that people who struggle with HIV stigma are less likely to be adherent to their medications as well as correctly interpreting their CD4 counts (Rintamaki et al., 2006). PLHIV also tend to hide their status from their acquaintances which may lead to lapses in medication adherence. Being seen taking medications or with medication bottles related to HIV might induce questions and consequently force them to reveal their disease (Vanable et al., 2006). It has also been theorized that stigma might be related to poor social support and psychological status of HIV-positive individuals and therefore impact on medication adherence (Vanable et al., 2006). One study suggested that stigma is commonly associated with "attachment-related anxiety." This type of anxiety can impact medicines adherence due to anticipated stigma and fear of being negatively judged by a close person when they witness the person living with HIV, taking their medications (Helms et al., 2017). Another example of nondesirable behaviors of HIV-positive patients who want to conceal their antiretroviral medication intake was reported in South Africa—patients ground their medicines into powder, which caused a risk of inconsistent dosing (Mills, 2006). The effect of different types of stigma (e.g., anticipated vs. experienced) on adherence should be further analyzed in this context (Helms et al., 2017).

Moreover, some anti-HIV medications might be stigmatizing due to their side-effects. For example, atazanavir can cause clinical jaundice, which although not causing a clinical threat to the patient, can be potentially stigmatizing (WHO, 2016a). A study in Thailand found that women who gained weight due to anti-HIV medication were concerned about their looks and the potential for associated discrimination (Liamputtong et al., 2015).

Apart from the multidrug combinations that are designed for HIV-positive patients, it is important to remember that antiretroviral therapies include those that are intended to prevent the infection. Oral preexposure prophylaxis (PrEP) is a prevention tool for individuals exposed to substantial risk of HIV infection. It has been proven that PrEP is highly effective where adherence is satisfactory. Unfortunately, even in the case of PrEP, stigma might cause insufficient adherence. WHO guidelines on the use of HIV drugs outline that if PrEP recommendations reach beyond specific populations such as MSM and if PrEP is properly implemented within health care systems, the associated stigma might be reduced, while general access to the therapy can be increased (WHO, 2016a).

HIV stigma is not only associated with inadequate adherence but also lack of HIV testing and implementation of HIV prevention as appropriate (Quinn et al., 2017). Being infected with HIV can also cause patients to be wary of treating other diseases as this would require them to disclose their serostatus (Madhombiro et al., 2018). Therefore, it is crucial that all data collected from HIV patients needs to remain confidential, not only to respect their privacy but also to prevent any stigmatization (WHO, 2016a). As an example, a study on alcohol use associated with HIV treatment showed that HIV stigma can be a barrier for people to seek help for alcohol-related addiction (Madhombiro et al., 2018).

Even people who are in stable romantic relationships with HIV positive people can face stigma when they disclose their partners' serostatus. The so-called "courtesy" stigma can be experienced by people in serodiscordant relationships due to their friends and family who might, for example, not appreciate and stigmatize their partners (Siegel et al., 2018).

Review of HIV Stigma in Key Populations

MSM and Transgender

MSM accounted for 12% of new known HIV infections worldwide as of 2015 (UNAIDS, 2017). Sexual minorities suffer from all types of stigma, including enacted stigma such as verbal harassment, discrimination, or physical assault. It has been proven that enacted stigma can be associated with a higher occurrence of risk-related sexual behaviors, e.g., anal intercourse without the use of a condom (Balaji et al., 2017).

PrEP has been recognized as a means for reducing HIV susceptibility among MSM. HIV stigma and antigay prejudice have been identified as important factors discouraging MSM to consider PrEP for HIV prevention in two cities in the United States. Another important barrier was presented by lack of trust for health professionals, especially widespread in the black MSM community (Cahill et al., 2017). A New York based qualitative study conducted in 2017 on 37 MSM showed that participation in the PrEP regime can trigger stigmatizing behaviors. The study participants reported that when people saw them taking antiretroviral medications they assumed that the cause for that was being HIV-positive or the PrEP users' promiscuity and willingness to have unprotected sex. They also experienced anticipated stigma which led them to hide their medications from their sexual partners (Franks et al., 2018). Another study on African American MSM found that the use of PrEP can make people wary of other people's undesired presumptions such as participants' homosexuality, promiscuity, or having AIDS (Weathers et al., 2017). A study on young MSM and transgender women showed that PrEP stigma is more common in areas with high concentration of racial minorities, while lower stigma was observed among people with prior knowledge about PrEP, as well as among white and nonmale participants (Mustanski et al., 2018).

A study of young black MSM suggested that some specific aspects of stigma might have more influence on their health outcomes than others, whereas total stigma did not impact their adherence. What is more, the study demonstrated that anticipated stigma can be associated with a higher likelihood of optimum adherence (Quinn et al., 2017). Another study on a similar population suggested that stigma and hostile environments might serve as a "daily reminder" for people to take their medications (Radcliffe et al., 2010). Both studies showed that MSM who experience a high level of stigma are more likely to participate in high-risk sexual behaviors while intoxicated or under the influence of drugs. One of the reasons to take drugs before having sex among HIV-positive MSM may be to suppress feelings of shame and guilt (Quinn et al., 2017; Radcliffe et al., 2010).

Results of a four-country study conducted in Indonesia, Malaysia, The Philippines, and Timor Leste showed that significantly more transgender people experience stigma and discrimination by health care providers compared to MSM. The most common form of stigma was verbal discrimination, however, over 18% of the questioned transsexual people had experienced being refused access to health care services (Cortes, 2017).

Women

In 2016, worldwide there were 17.8 million HIV-positive women (aged 15+) (UNAIDS, 2017). HIV positive women tend to have insufficient coping strategies and less social support when compared to male PLHIV (Martinez et al., 2018). Barriers to adherence that women face can be gender specific, such as family obligations and physical abuse (Roberson et al., 2009). A study of American adolescent females aged 15–24 did not show a direct relationship between stigma and adherence. It suggested, however, that when there was a low satisfaction level related to health care, stigma might have decreased adherence. If patients found their experiences with health care highly satisfactory, the impact of stigma was lower. Also, various coping strategies such as spiritual coping or seeking support from family helped participants to maintain better adherence, despite enduring stigma. The study failed to demonstrate a direct relationship between depression and stigma (Martinez et al., 2018).

Mother-to-child-transmission (MTCT) is the main reason for HIV infections in children. Nevertheless, as of 2017, only 62% of pregnant women living in low and middle-income priority countries were covered by prevention of MTCT services (McMahon et al., 2017). A research study conducted in Tanzania in 2017 showed that stigma was the main barrier to obtaining HIV-related health services for women, affecting, therefore, the number of infant infections. Study participants felt especially vulnerable when they were subject to stigma as well as having to face health care facility limitations at the same time. It was suggested that peer support networks and "mother-2-mother" groups could be effective forms of intervention for HIV-positive mothers to encourage them to become engaged in prevention of MTCT (McMahon et al., 2017).

HIV burden among Black women is an example of race-related disproportions in HIV epidemics. It has been forecast that in the US, 1 out of every 48 Black women will be diagnosed HIV positive. In the case of US White women, the prevalence for HIV diagnosis is 1 out of 880 (Lambert et al., 2018). In a study of 220 Black women, anticipated HIV stigma was correlated with fear of disclosure of their serostatus as well as increased likelihood of mental health symptoms, and use of dysfunctional/negative coping strategies (Travaglini et al., 2018). Twenty African American women, who participated in a study in 2003, experienced HIV stigma as "being marked by the disease"; it also caused social isolation and was an important barrier to medicines adherence (Edwards, 2006).

Children and Youth

As of 2016, there were an estimated 2.1 million children (<15 years old) living with HIV globally (UNAIDS, 2017). Great progress has been made in regard to the survival of children, who were infected through HIV vertical transmission, into adolescence. Their

survival, however, also implicates complex challenges related to access to medications and adherence for this group of patients. Their situation is unique, since they often face the perspective of taking medications for the rest of their lives, from their early childhood and never having lived without the illness (Bernays et al., 2017). What is more, HIV-positive adolescents, especially those belonging to key populations, experience stigma and discrimination in high levels (WHO, 2016a).

In a study involving 25 young PLHIV, over 90% of the patients acknowledged the fact that their health condition could get worse unless they follow their therapy recommendations. That contradicted the popular opinion that young people feel invulnerable and therefore tend to be reckless with regard to their health. Stigma was identified as the reason for poor medication adherence for half of this young age group, which was caused by fear that the medicines could disclose their serostatus to their relatives and friends (Martinez et al., 2018).

Young people require a friendly environment in places where health services are provided, which should also reinforce the importance of ART adherence (WHO, 2016a). A study from 2017, however, showed that clinics, where the highest pressure was put on adherence (which was presented, for example, as a young patients' moral duty), could also create a stigmatizing environment. A group of young PLHIV, who participated in one study, when asked about their reaction to their own nonadherence talked about their deep shame and feeling of failure. This feeling created a barrier for them to seek support from clinicians when they missed their doses (Bernays et al., 2017).

Disclosure to children of their HIV positive status is an additional challenge that parents and caregivers face. According to WHO, children at school age should be informed about their disease which, as defined in the WHO guidelines, means that a child that has "cognitive skills and emotional maturity of a normally developing child of 6–12 years" (WHO, 2011). Caregivers must also face their concerns and fears related to HIV stigma. A study in China revealed that parents and caregivers of young patients sometimes did not disclose the disease status with the child or forbade the child from talking about their medications with their friends and playmates. One child in the study confessed that she was asked about her medications numerous times at school and once her HIV status was disclosed, she felt separated from others (DeSilva et al., 2018). Children and young people might benefit from the provision of accessible and culturally aware mental health counseling in conjunction with their classical ART (Quinn et al., 2017).

Prison Inmates

Around 3.8% of inmates worldwide are estimated to be HIV-positive, however, it varies significantly between regions (AVERT, 2018). In the United States, in 2010 there were around 20,000 HIV-positive prison inmates, and a high racial disproportion was observed (e.g., male African Americans were five times more likely to be diagnosed with HIV compared to white men) (CDC, 2018). A study in the United States of 17 former male inmates showed that there is a need for better education on HIV stigma in jails, which should cover both incarcerated people and staff. Inmates might avoid HIV testing due to HIV/AIDS stigma and related stereotypical views on PLHIV. One participant of a study admitted that even though other inmates were aware of the existence of antiretroviral drugs, the inmates did not believe these medicines could prevent the death of an HIV positive person who should be taking them. In the same study, it was also noted that incarcerated people often do not distinguish between being HIV positive and having AIDS (Derlega et al., 2010).

As of 2015, more than 700,000 women and girls were imprisoned throughout the world, including more than 200,000 in the United States. The population of female inmates has grown since the new millennium by around 50% (ICPR, 2015). It has been proven that female inmates, in general, have their HIV status diagnosed later after being infected compared to incarcerated men. Women also tend to hide their serostatus more often than men (Roberson et al., 2009). A plethora of incarcerated women have been victims of psychological, sexual, and physical abuse, experienced drug and alcohol addiction or have been infected with STDs. Their complex and unmet health and psychological needs impact the general health status of the population, including HIV epidemics (Sprague et al., 2017). Incarcerated women experience many barriers to adherence to antiretroviral drugs, one of the main ones being stigma. A study of 12 HIV-positive female inmates showed that the other important barrier is the lack of privacy in jail. Participants of the study complained that they often had to wait for long periods in queues to have their medications prescribed, which could potentially aid in disclosing their serostatus to other inmates if they were taking a lot of medications (Roberson et al., 2009). In an interview series with 25 previously incarcerated HIV-positive women, which took place in the US in 2015, the interviewees shared stories of being separated from other inmates, experiencing discrimination from prison staff and breaches of confidentiality regarding their serostatus (Sprague et al., 2017).

The "HIV prison paradox" has been defined in the United States as a situation where HIV-positive inmates-to-be increase their chance of being covered by ART by entering prison—an environment widely recognized as unhealthy (Sprague et al., 2017). Moreover, a study from 2009 showed the routine of living in jail can facilitate their adherence to ART (Roberson et al., 2009).

Drug Users

Out of 13 million people estimated to inject drugs worldwide, 1.7 million are expected to be HIV-positive (WHO, 2018). A series of qualitative interviews with 52 HIV-positive drug users in 2007 found that they had experienced stigma resulting in a feeling of loneliness and marginalization, which was further exacerbated by drug use (Ware et al., 2006). A study of 40 former and current drug users living in Bali showed that stigmatization was one of the main barriers to HIV testing, while 15% were concerned about the confidentiality of the testing process (Ford et al., 2004).

A 2010 study conducted in Ukraine, a country with one of the highest HIV epidemics in Europe, showed that among IDUs stigma was one the most significant barriers to medicine adherence (including stigma experienced from interaction with health care providers), along with discrimination by police and ART side effects. Discrimination and harassment by police, the barrier which was most commonly discussed by the studied patients, was related to possession of anti-HIV medication. It was noted that police officers misidentified people's medications as narcotics and confiscated them from HIV-positive individuals (Mimiaga et al., 2010).

Estonia and Russia have some of the highest rates of HIV outside of Sub-Saharan Africa and many of those PLHIV are IDUs. Participants of a study on HIV-positive IDUs living in Kohtla-Järve, Estonia and St. Petersburg, Russia, reported that they experienced simultaneously high levels or four types of stigma: internalized HIV stigma, anticipated HIV stigma, internalized drug stigma, and anticipated drug stigma. In Estonia, however, due to better developed harm reduction programs, stigma was less associated with poor health outcomes (Burke et al., 2015).

Sex Workers

Prevalence of HIV among sex workers can be very high in some regions such as Southern Africa where prevalence rates of 50%–70% have been reported (UNAIDS, 2016b). Sex workers are a highly stigmatized key population, suffering from such forms of discrimination and abuse as police repression, physical and sexual violence, and insufficient access to health care and even detention. This group is often not sufficiently protected by law and state policies, as their occupation is criminalized in many countries (Decker et al., 2014). Low uptake of ART has been observed in those HIV-positive women who are sex workers and also inject illicit drugs. This group is also at high risk of HIV infection due to having multiple partners who do not always use condoms. A study on 159 female sex-workers in Vancouver showed that these participants had to face not only a high risk of HIV infection (and other infectious diseases), but also unstable living conditions, discrimination, and poverty. Only 9% of the participants were taking anti-HIV medications at the time of the study, however, high levels of injection/noninjection drug use were observed (Shannon et al., 2005).

Sex workers' fears of being stigmatized are a critical barrier to adherence to anti-HIV therapies. What is more, sex workers might fear that if they start taking anti-HIV medications, it could disclose their serostatus to their clients and therefore reduce their own income (Decker et al., 2014). The stigma might also reduce adherence to PrEP among sex workers, as they might be required to take medications after coitus and therefore in the presence of their clients (Mutua et al., 2012).

There are around seven million sex workers in China, even though sex work is officially prohibited there. A study on 517 sex workers (of different genders) in China revealed experiences of various forms of discrimination, and some participants reported an increase in their HIV infection vulnerability, e.g., confiscation of condoms by the police (Shen and Csete, 2017; Decker et al., 2014). Participants of a study in South Africa, among whom there were sex workers, expressed that they often felt blamed and discriminated by health workers who were supposed to provide them with help (Duby et al., 2018). In a study in Zimbabwe, female sex workers living with HIV reported that they more often felt stigmatized because of the sex work than being HIV positive. They were also more likely to be refused help from health professionals because of their occupation rather than their HIV serostatus (Hargreaves et al., 2017).

Review of HIV Medication Stigma in Selected Regions

Africa

Close to two-thirds (64%) of new HIV infections globally are reported to occur in Sub-Saharan Africa (UNAIDS, 2017). Botswana is a country with one of the highest HIV infection rates in the world (with the prevalence rate of 21.9% for adults aged 15–49 as of 2016) (UNAIDS, 2016a). In a study involving over 100 patients and 60 health care providers in Botswana, stigma was identified as one of the most important barriers to medicines adherence. This study also recognized other implications of HIV stigma in Botswana, such as keeping HIV infected people's status confidential from patients' families and the community. Patients who felt that their adherence was compromised by stigma did not feel that they could take their medications at home or at work. They also did not feel comfortable about getting medication refills in clinics, being wary of other people learning of their disease status (Weiser et al., 2003).

A study on 158 Tanzanian PLHIV showed that involuntary disclosure of their serostatus was related with higher perceived stigma. Also, the participants who voluntarily disclosed that they were HIV positive, experienced a lower level of self-stigma. Lower adherence to ART was observed among patients who were in denial of their serostatus and/or had higher alcohol intake (Lyimo et al., 2014).

In a study involving over 1000 HIV-positive women and men living in Cape Town, South Africa, an anonymous survey found that 40% of the studied population had been discriminated against due to their disease. More than one in three individuals experienced self-induced stigma, caused by shame, guilt, or feeling "dirty" (Simbayi et al., 2007).

South, East, and Southeast Asia

In China, a high prevalence of HIV is observed in key populations (Shen and Csete, 2017). Family honor in China is cherished by the culture, which creates a barrier to disclose one's serostatus (DeSilva et al., 2018). Similarly, in India, a country where there were

2.1 million PLHIV in 2016 (UNAIDS, 2016c), being HIV-positive can be seen as a dishonor for the family (Nyamathi et al., 2018). A study in India with 60 PLHIV showed that the main barriers to adherence included stigma, cost savings, and perceived benefits of nonadherence to medicines (e.g., lack of side effects or even death). Over one-fifth of the participants did not disclose their serostatus to their relatives, which might have made taking medications more difficult for them (Kumarasamy et al., 2005).

Almost 40% of HIV positive people in India were female as of 2016 (Nyamathi et al., 2018). A study which included 400 HIV-positive women and their children living in a rural state of India (Andhra Pradesh) showed that the women experienced lack of social support as well internalized stigma and a generally low quality of life (Bagley et al., 2017). In a study with health care staff in India, over 80% of nurses and doctors admitted that if they had to face a situation that would expose them to body fluids, they would not treat HIV positive patients equally (Nyamathi et al., 2018).

Thai HIV-positive women, who participated in a 2014 study, presented a very optimistic view of antiretroviral medications. According to them, ART helped to reduce stigma and fear in society and made others more compassionate about the disease. They still did not feel comfortable enough, however, to take their medicines openly. The women reported that in order to take them, they would hide, e.g., in a bathroom or lied that the medicines were related to some other "socially acceptable" disease (Liamputtong et al., 2015).

Middle East

Prevalence of HIV in the Middle East and North Africa (MENA) remains relatively low; in 2016, there were around 230,000 PLHIV in MENA. PLHIV, however, are highly stigmatized and discriminated against in that region (Gökengin et al., 2016; UNAIDS, 2017). Sexual transmission seems to be the main way by which people are infected in MENA; however, this remains understudied for various reasons specific to the region. The main issue being that sex between men is generally unaccepted and penalized (Gökengin et al., 2016).

A study on 162 male college students from Saudi Arabia showed that HIV/AIDS shame was the most significant predictor in that population in relation to HIV stigma (Badahdah, 2010). Another study conducted also among students (in the United Arab Emirates), showed that 53% of them believed that PLHIV should be separated from society, while only 27% considered HIV-positive children as being able to attend school (Ganczak et al., 2007). Over half of Yemeni students who participated in a study in 2010, confessed that in their opinion "people with AIDS should be ashamed of themselves" and that they would be humiliated if someone from their family suffered from AIDS. Over 40% of the students felt anger and lack of sympathy toward PLHIV (Badahdah and Sayem, 2010).

Iran has been recognized as the HIV prevention pioneer in the Middle East, thanks to its needle-exchange program. HIV related stigma and discrimination, however, are still present there (Oskouie et al., 2017). A study of 25 HIV-positive women living in Iran showed that they had experienced frustration, fear, shame, and rejection. One of the women was afraid to disclose to her own daughter that the medication she was taking was for HIV, because she believed the daughter would reject her own parents. Some of the study participants also expressed that people surrounding them did not have sufficient knowledge about HIV and, therefore, avoided contact with PLHIV based on misconceptions. One participant admitted that the fear of stigmatization affected their medicines adherence as they did not want to be seen taking their medication. Stigma was also recognized as the main reason to withdraw from therapy follow-up visits and for instituting self-medication or trying alternative medicines (Oskouie et al., 2017). A similar study was conducted in Kerman, Iran. The participants experienced both internal (shame, isolation, nondisclosure of the serostatus) and external (from their family and health care professionals) stigma. One woman admitted to lying to her family members that she had cancer and therefore had to take medications (Karamouzian et al., 2015).

Parallels With Stigma Associated With Other Diseases

Prejudice and stigma are observed in many diseases other than HIV/AIDS, such as tuberculosis (Yan et al., 2018), mental illnesses (Corrigan and Al-Khouja, 2018), leprosy (Susanti et al., 2018), obesity (Brewis et al., 2018), and STDs (Ross et al., 2017). Stigma is also experienced by patients with opioid use disorder who are treated with medications (Bagley et al., 2017) even though there is evidence that methadone/buprenorphine therapy reduces the risk of death due to overdose and relapse of use of opioids. In the case of opioid addiction, additional stigma is the consequence of the illness being perceived as the addict's choice, alongside HIV where it is sometimes treated as the result of PLHIV's life decisions (Wakeman and Rich, 2018).

As with HIV, stigma in key populations or regions can be even more challenging to tackle. For example, it was found that in Saudi Arabia a high number of hospital staff working in King Abdulaziz Hospital had a stigmatizing attitude toward patients with mental illnesses (Sewilam et al., 2018). Military service members tend to avoid mental health services, wary that it might cause stigma, harm their career and reduce the trust of their superiors (Hernandez et al., 2017). MSM who participated in a study in Tanzania reported that when they were suffering from STD symptoms, health care professionals were not polite in response to the majority of symptoms (Ross et al., 2017).

A 2016 analysis suggested that encouragement of uniformed and civilian leaders of military service members should help them overcome stigma related to the use of mental health services. Military leadership should emphasize the value of these services in the overall health and encourage preparedness of military service members (Hernandez et al., 2017). A study in Indonesia showed that early diagnosis of leprosy and support of self-care groups can help with increasing adherence and motivation for healing (Susanti

et al., 2018). A case study from 2018 suggested that stigma associated with opioid agonist treatment among young adults can be tackled by increasing access to the treatment, through implementing public education campaigns, educating health professionals, changing stigmatizing language, and involving the media in campaigns (Hadland et al., 2018).

Discussion and Way Forward

Changes in legislation and public health policy as well as media initiatives should be utilized to help eradicate the stigma associated with HIV positivity and treatment. Effective strategies for tackling stigma in different regions of the world should be advanced (Vanable et al., 2006). WHO suggests that integration of services tackling various HIV-related issues, which includes provision of those services in the same location (e.g., the same clinic), might positively impact stigma over time. Moreover, an involvement of HIV-positive people in the training of health workers, or providing support to other patients can have a positive impact on overall stigma (WHO, 2016a). A study, which showed that internalized stigma can be associated with suboptimal medicines adherence, suggests that confronting interpersonal challenges that PLHIV face (such as low self-esteem and fear of being seen while taking medications) through Cognitive Behavioral Therapy (CBT) techniques can empower people to believe they can challenge stigma if they ever face it (Helms et al., 2017). A study in Ghana found that HIV-positive MSM are mainly motivated to engage in anti-HIV therapy by their fear of mortality, social support, and better knowledge of the treatment options available (Ogunbajo et al., 2018).

To really challenge multidimensional stigma among key HIV populations, it is crucial to understand other aspects of social hostility these people face in their daily lives, such as transphobia, homophobia, racism (Quinn et al., 2017), and sexism (Logie et al., 2011). A study of 135 older HIV-positive gay and bisexual men showed that participants were subject to internalized sexual minority stigma and enacted sexual minority stigma in health care settings, which was associated with increased likelihood of high-risk sex behaviors and less frequent presentation to health care facilities (Emlet et al., 2017). Furthermore, HIV-positive MSM who are also illicit substance abusers experience more limited access to anti-HIV therapy in comparison to nonsubstance abusers (Shoptaw, 2017).

Cultural awareness has to be applied, especially when approaching highly stigmatized communities such as Black MSM, who should be covered by HIV-education and stimulated to have open discussions on HIV that would encourage nonrisky sexual behaviors and the use of appropriate prevention (Weathers et al., 2017). A study in China showed that HIV-positive MSM believed that developing an HIV cure would significantly reduce all types of HIV stigma (anticipated, internal, enacted). This group, however, also did not believe this would meaningfully impact stigma against MSM, as its roots reach well into societal beliefs of MSM's levels of promiscuity and high rates of STD (Wu et al., 2017).

One study of male sex workers in Vietnam demonstrated that a population that suffers complex stigma (in this case related to sex work, their sexuality, and HIV status) can be positively influenced by health promotion interventions that would increase their knowledge on sexual health, sexual diversity, stigma management, and so forth. The authors expressed their belief that interventions promoting health knowledge might benefit even the most stigmatized and difficult to reach groups (Goldsamt et al., 2017).

Stigma can also be worse in patients suffering from comorbidities such as Hepatitis C coinfection, however, mental health problems are still the most common comorbidities that PLHIV suffer. A study published in 2016 tried to trace how mental health problems associated with HIV positive people living in London evolved during the decade 2004–14. The data showed that despite the significantly more effective anti-HIV therapy, PLHIV continued to experience significant mental health issues (Adams et al., 2016).

Reduction of HIV stigma in the health care setting should be treated as a priority. Health care providers should be aware of the existence of stigma and benefits that can be achieved by its reduction, such as better adherence to antiretroviral medication (Nyblade et al., 2009). In South Africa, results of a three-year research project suggested that collaboration between traditional healers and health care professionals could have a positive influence on global HIV health outcomes (Maleke et al., 2017). It has been proven in many studies that an effective social support network significantly improves HIV-positive patients' health and adherence to medications (Nyamathi et al., 2018). Self-stigma, of an HIV-positive person, can also be significantly reduced by loving support in a relationship (Yang et al., 2017). A randomized controlled trial in Kenya showed that HIV patients benefit from open communication and a feeling of being treated with compassion which helps to deal with stigma (Lowther et al., 2018).

Injectable long-acting anti-HIV medicines might be a promising alternative for people who struggle with HIV stigma. Taking medication less frequently not only improves the overall quality of life of patients but also has been reported, in one US and Spanish study, as more "discrete" and as reducing internalized stigma due to not having pills that serve as a daily reminder of the disease (Kerrigan et al., 2018).

New prevention technologies (NPT), such as PrEP, vaginal rings containing antiretroviral medications, rectal microbicides (compounds used to prevent infection), and HIV vaccination might bring positive change to highly vulnerable populations (the last three of these are still in development). Concerns have arisen, however, in regard to expected adherence to these prevention tools. A study in South Africa showed that participants were initially enthusiastic about using NPT. They felt that it would help them not only in the situations where they fail to negotiate using a condom during sexual intercourse but also in the event of rape, which is especially relevant for women and MSM. NPT also has the potential to empower women to make their own decisions in societies where they experience gender inequality and assist in protecting themselves against infections without seeking their partners' permission. The participants of this study, however, were mainly concerned about long waiting times and the stigmatizing approach

of clinic staff where they would receive NPT (Atujuna et al., 2018). What is more, PrEP stigma is still observed which negatively effects already disadvantaged populations in significant ways (Golub, 2018).

Web and mobile-based communities are increasingly common with support groups that can be easily accessed by people who are challenged by HIV stigma. Posts that were analyzed in a study on PositiveLinks, a mobile health intervention, showed that the community helped each other to cope with stigma by sharing their stories, and talking about companionship, positive thinking, finding hope in one's religious beliefs and so forth. Participants expressed that PositiveLinks helped to look at HIV/AIDS in a "hopeful light" and to increase HIV positive people's self-worth through positive affirmations (Flickinger et al., 2018).

Summary

Stigma related to HIV remains one of the most significant and challenging problems related to HIV infection and management with ART. Various research studies have proven that ART, even though currently highly effective and with a good risk-benefit ratio, might cause distress for patients who tend to hide the real cause for their taking of medications and who are constantly worried that the medicines might disclose their HIV serostatus. Stigma related to ART is unambiguously related to HIV/AIDS stigma and interlinked with the discrimination of various key populations. Some of those vulnerable populations might overlap (e.g., transsexual sex workers) and therefore their members experience even more complicated and severe stigma.

HIV stigma in some populations remains understudied, which might be the reason why some study results contradict each other when, for instance, trying to measure the correlation between stigma and adherence to medicines. Continuing studies are required to understand how different aspects of stigma affect various populations and how they relate to the lives of people living with HIV.

Stigma might negatively impact not only the mental health status of people living with HIV, but also their physical well-being, either through inadequate access/adherence to ART or discrimination by health workers, and even physical violence. For that reason, it is crucial that policies and programs in every region of the world should protect key populations and reinforce public education about HIV/AIDS, especially among health care professionals. It is of the utmost importance that there is greater access to programs dedicated to increasing access to harm-reduction services, reduction of high-risk sexual practices, and learning about active coping strategies.

New biomedical prevention technologies give hope that the most vulnerable populations, such as women, men who have sex with men, and IDUs will be able to defend themselves against HIV infection without being stigmatized. Similarly, new technologies and web-based communities should serve as a source of information and support for people living with HIV, a large number of whom suffer from stigma.

Glossary

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
IDUs	Intravenous drug users
MENA	Middle East and North Africa
MTCT	Mother-to-child-transmission
NPT	New prevention technologies
PLHIV	People living with HIV
PrEP	Preexposure prophylaxis
STD	Sexually transmissible disease
UNAIDS	The Joint United Nations Programme on HIV and AIDS
WHO	The World Health Organisation

Disclaimer: Irmina Wlodarczyk (the corresponding author) is an employee of ViiV Healthcare, however, the opinions expressed in this article are the corresponding author's own and do not reflect the view of ViiV Healthcare.

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External Reference Pricing and Medicines

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Introduction

The increasing price of medicines and growing pharmaceutical expenditure are becoming a major concern for governments, policy makers, and health insurers worldwide (Espin et al., 2011). These high prices can make essential medicines inaccessible and unaffordable hence compromising one of the Millennium Development Goals (MDGs) of United Nation (UN), i.e., "access to essential medicines" (Sachs and McArthur, 2005). Different price regulation policies are adopted by countries to contain medicine prices specially of the new medicine products, which are protected by some exclusive market rights, such as patents and external reference pricing (ERP) is one such cost containment strategy (Espin et al., 2011).

Currently, many countries (HICs) (Nguyen et al., 2014; Rémuzat et al., 2015) are using the ERP or International Reference Pricing (IRP). The ERP uses benchmarking or taking the price of a medicinal product as reference from one or more other countries to set or negotiate the local price of that product (Espin et al., 2011). Besides being feasible for adaptation by many high-income countries, this system can also be conveniently applied with limited technical resources, thereby justifying its use by small countries. There is a scarcity of evidence about its actual impact, limitations and scope, especially from LMICs, but some objective information is available regarding its use and implications from Europe and OECD countries (Espin et al., 2011). It may, however, pose some negative impacts as well, such as delayed launch of products, deceptive published prices, and higher priced generic products (WHO, 2015).

This chapter gives practical understanding of the concept of ERP together with prerequisites for adopting the ERP system in detail. The potential impact of employing ERP on local prices of medicines in different countries and on the pharmaceutical manufacturing firms has also been discussed.

Need for Pharmaceutical Pricing Policies

One of the main goals of a sustainable health policy in any country is the provision of cost-effective, accessible, and affordable pharmaceutical care services, as a vital component of the health-care system (Borowitz, 2010). Medicines account for a large portion of health-care expenditures across the globe, e.g., 20%–60% in LMICs and around 20% in the HICs (Acosta et al., 2014; WHO, 2015). The HICs have the major share in the pharmaceutical market. The LMICs have 84%, and HICs have 16% of the world's population, but global pharmaceutical expenditure by LMICs is 22% compared to 79% for HICs (Lu et al., 2011). This results in significant differences in per capita expenditures ranging from US$7.61 in LMICs to US$431.60 in HICs (Acosta et al., 2014). The increasing prices of medicines are becoming a major reason for unaffordability and inequitable access to medicines, making it necessary to include some price regulation strategies into the overall health policies. The purpose of pharmaceutical pricing policies is to determine the prices of drugs, which are suitable for both manufacturers and users of drugs, and to ultimately ensure the equitable access to medicines (Acosta et al., 2014).

Medicine Price Regulation: Policies and Strategies

Setting the maximum price of drugs that is fair and appropriate is of great concern for every country, no matter which mechanism of pricing is used (Rietveld and Haaijer-Ruskamp, 2003). There are different definitions of maximum price of drugs among all countries. It largely depends on their demography, pharmaceutical needs, share of the pharmaceutical industry in the national economy, and prescribing trends (Mossialos et al., 2006).

A fair price regulatory system should comprise certain features. Relevance to the particular health system and policy objectives, financial sustainability, affordability, and promotion of quality assured pharmaceutical products are probably the most important components of price regulation (Espin et al., 2011). WHO recommends the use of a mix of pricing policies such as cost-plus pricing, profit ceiling, price negotiations, internal and ERP, which cater for the individual needs of the countries and address both demand and supply issues. Such policies should be aimed at promotion of affordable medicines and should consist of a proper legislative framework and implementation, which must be reviewed on a regular basis. The transparency of pricing policies and international collaborations to promote the exchange of information regarding policies' impact is also endorsed by WHO (WHO, 2015).

When improving affordability is the sole target, prices are directed to lower than the prevailing prices but if a country has other targets such as promotion of research, innovation, new drugs development, availability, and local production, then a different set of policies will be required (Espin et al., 2011). Research and development may not be a main concern for many of the developing countries as they usually do not contribute much in this area but for developed countries this is of great importance. For research and development, drug prices serve as the main incentive for manufacturers especially when market competition is poor. The lowered prices of drugs will lead to lack of interest in manufacturing or importing essential drugs by many countries. So, patients might be deprived of many life-saving drugs, leaving a negative impact on their health. Hence, access to medicines will be compromised. This explains the significance of customizing the pricing policies according to country-specific needs (Espin et al., 2011). So, different countries use varying sets of pricing policies based on their particular objectives.

External Reference Pricing

ERP is also known as International Reference Pricing or External Price Benchmarking. It has been defined as "the practice of comparing pharmaceutical prices across countries" and "there are various methods applied and different country baskets used" (OECD, 2008). The OECD definition has been adopted by many pricing policy reports. The World Health Organization (WHO) defines ERP as, "the practice of using the price of a pharmaceutical product (generally ex-manufacturer price, or other common point within the distribution chain) in one or several countries to derive a benchmark or reference price for the purpose of setting or negotiating the price of the product in a given country". It is also indicated that, "Reference may be made to single-source or multisource supply products" (WHO, 2015). Under ERP, the manufacturer is guided by the country to set a product charge according to the price of the same product in selected foreign countries. The set of selected foreign counties is termed as that country's reference basket (Geng and Saggi, 2017).

It is noteworthy that another term called as "internal reference pricing" is a different type of reference pricing and shall not be confused with ERP. Under internal reference pricing, the price of a drug is set by taking the prices of other domestic drugs that are its therapeutic equivalents, as a reference. This system is usually used for pricing new drugs that already have their therapeutic equivalents in the local market. If the new drug has proven superior therapeutic advantage over the already existing therapies then it is given the benefit of a percentage increase in the price. Internal reference pricing can also be used for pricing generic medicines by setting lower prices than for brand medicines. This method is mostly used when adding medicines to the reimbursement list (Vogler et al., 2008).

In the past, different cost containment strategies such as cost-plus methods or internal reference pricing have been used by the majority of countries but recently ERP is being considered as a major price control mechanism by many countries across the globe. In the 1990s, when many new drugs (with superior therapeutic value) were introduced into different countries, ERP became an important instrument in setting fair prices of individual drug products rather than setting average price levels of drugs (Persson and Jönsson, 2016). Over time, ERP has been adopted by many countries because it is uncomplicated compared to other pricing models that need data on profits, costs, and cost effectiveness, that is, pharmacoeconomic evaluation, etc. (Geng and Saggi, 2017).

The purpose of ERP is to facilitate pricing by regulatory bodies by providing them with a reference price or a benchmark to set or negotiate the price of the drug in a domestic market. García Mariñoso et al. (2011) stated that "External referencing (ER) imposes a price cap for pharmaceuticals, based on prices of identical products in foreign countries," which they contrast with "directly negotiating the drug's price with the firm" (Garcia Mariñoso et al., 2011).

Requirements for Implementation of ERP

WHO states that the following factors must be considered when adopting ERP policy (see **Fig. 1**)

- Justified criteria for selection of countries in a reference basket.
- Availability of true data for prices rather than a falsified price.

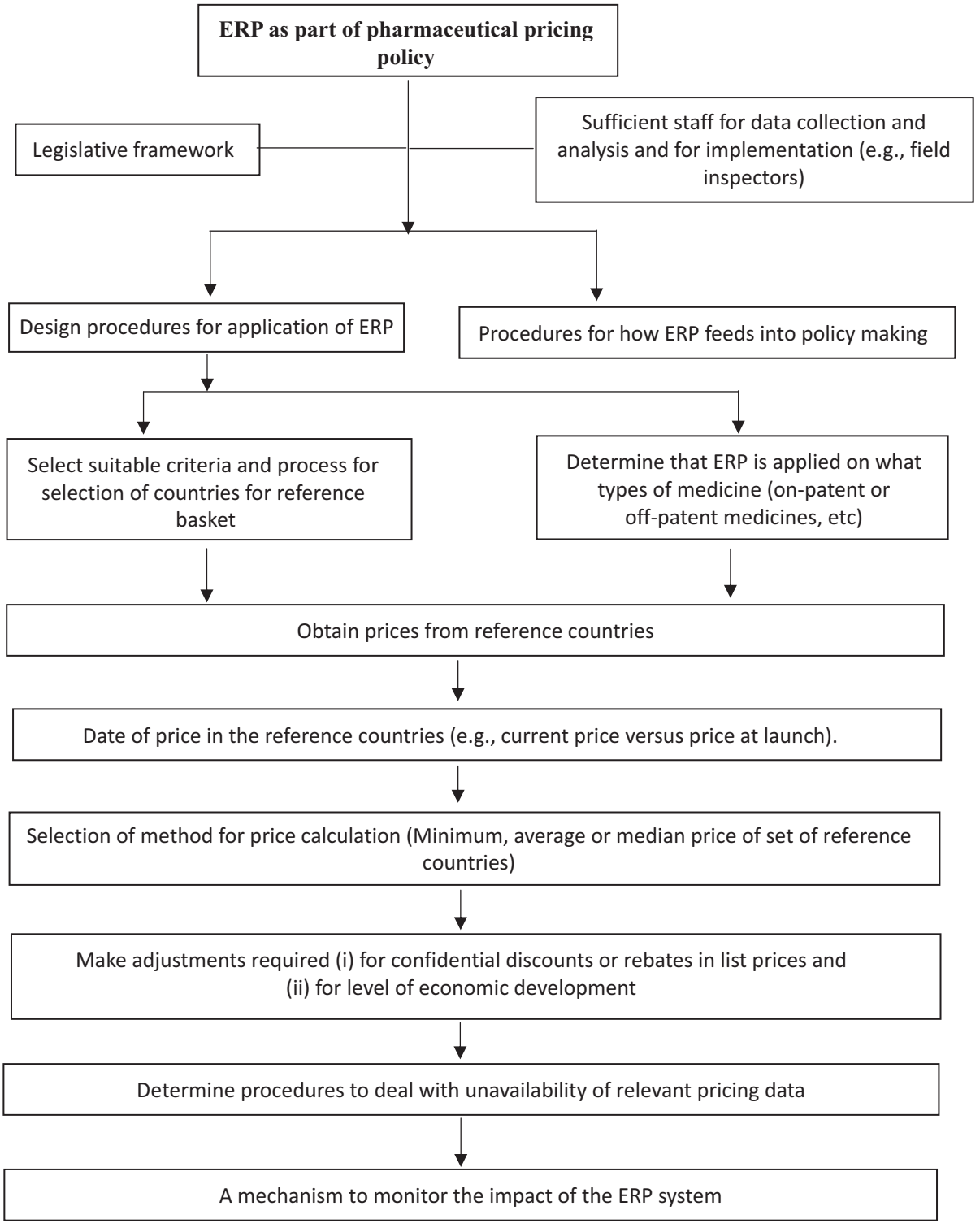

Figure 1 Process to implement the external reference pricing system. *Source: Adapted from the WHO guidelines on country pharmaceutical pricing policies. Geneva. (World Health Organization 2015).*

- Scope of ERP policy: selection of the type of drugs on which ERP will be applied (e.g., new drugs) and the level at which ERP will be applied (e.g., ex-factory price, procurement price, or manufacturer's price).
- Determination of method of calculating the ERPs, such as lowest price in that particular drug group, average price of all products, or median price of all products.
- Predefined procedures for application of ERP and regular monitoring of medicines prices backed by legislative framework.
- Management of database and data analysis.
- Making adjustments according to the current currency exchange rate with the reference country, and also considering the level of economic development (WHO, 2015).

Potential Benefits, Harms, and Risks of Using ERP

The potential benefits of using ERP as a pricing strategy are as follows:

- It is easily applied compared to other systems, such as economic evaluations.
- Lesser technical skills are required to manage its implementation (Nguyen et al., 2014).
- It provides quick evidence to policy makers even with limited availability of resources.
- It allows for international comparisons (Espin et al., 2011; WHO, 2015).
- It can develop a sense of security and satisfaction in the general public that they are not paying more than other countries to get the medicines (Persson and Jönsson, 2016).

Potential risks and harms of using ERP are as follows:

- The inappropriate selection of countries in a reference basket can lead to increased drug prices.
- Manufacturers and payers can falsify or hide true prices on the official list of medicines prices, so it can become hard to sustain the ERP in a true sense (Geng and Saggi, 2017; Persson and Jönsson, 2016).
- Patients in LMICs might experience limited or delayed launch of new drugs because the manufacturers will aim to launch the drugs first in high-income countries where they can charge higher prices to consumers (Espin et al., 2011; Geng and Saggi, 2017; Nguyen et al., 2014; WHO, 2015).
- Data sources for price comparison might be dubious (WHO, 2015).
- Consumers from high-income countries might not be able to pay in accordance with their buying power and their wish to contribute to the research and development of innovative drugs (Persson and Jönsson, 2016).

Implications of ERP Use in High-income Countries

As most of the countries from Europe (EU) are high-income countries, it is noteworthy that approximately 23 out of 27 of these are using ERP as the main drug pricing strategy (Rémuzat et al., 2015). European countries observed a 76% rise in pharmaceutical expenditure in the outpatient sector from 2000 to 2009 (Vogler et al., 2011). To deal with this situation and also under pressure from the global financial crisis of 2008, many price containment strategies were employed such as price reduction, changes in medicines value added tax (VAT), and in co-payments. Among the other pricing methods ERP was also widely applied in EU member states. The United Kingdom is important in the world's ERP system as it is taken as a reference country by many other countries, irrespective of their regions, because in the UK drug prices have been reported to be relatively low (Espin et al., 2011; Rémuzat et al., 2015; Ruggeri and Nolte, 2013). Many non-EU high-income countries such as Canada, Australia, Japan, and Norway have also applied ERP and are including EU countries in their reference basket (Leopold et al., 2012; Ruggeri and Nolte, 2013). The majority of the European countries are using the ERP system, which is backed by a legislative framework (Rémuzat et al., 2015). Other pricing mechanisms, such as direct price control, that is fixed maximum prices, profit ceiling, and internal reference pricing are also being used for different types of drug products by EU member countries. The less common methodology is "free pricing," which is being used mainly by Germany and the UK for specific products such as patented medicines (Mrazek and Mossialos, 2004). Most of the high-income countries use ERP to control the prices of medicines with patent protection or other intellectual property rights (pricing monopoly). Among the EU countries, some are using ERP for off-patent drug products, including Slovenia, Austria, Slovakia, Croatia, Poland, Czech Republic, the Netherlands, Iceland, Italy, Lithuania, and Latvia. ERP is used mostly for drugs that are reimbursed by the government in the European countries. Among EU members, France, the United Kingdom, and Germany are the top three most referenced countries. Japan has a different strategy compared to other high-income countries, as it uses ERP either to increase or decrease the local prices of medicines according to an adopted formula (Espin et al., 2011). The reference price used to calculate the external reference price varies among high-income countries but the majority use ex-factory prices. Drug prices are reevaluated regularly in the majority of countries. Among the EU member states, reevaluation ranges from every 3 months (Greece) to every 5 years (France) (Rémuzat et al., 2015).

There is scarcity of evidence on the impact of ERP (Kaiser et al., 2014; Ruggeri and Nolte, 2013). It is reported by two studies, conducted in both EU and non-EU countries that substantial decreases in drug prices has not yet been observed (Kyle et al., 2008; Leopold et al., 2013). With the widespread use of ERP by high-income countries, pharmaceutical manufacturers are developing strategies to counter any negative impact on them, such as reduced drug prices. So, many countries are facing delayed launch of

new drug products into the market. For example, Belgium faced delayed dossier submission by manufacturers because Belgian prices are usually not among the highest prices in EU member countries (Konijn, 2007). Another study reported that in Germany and New Zealand, the prices of some medicines (e.g., ACE inhibitors and atorvastatin) were deliberately kept high because manufacturers knew that these countries would be used later as reference countries (Kyle et al., 2008; Richter, 2008). This behavior can compromise the main purpose of ERP, which is to reduce prices and make medicines more affordable. Counter strategies by manufacturers put a big question mark on the sustainability of the ERP system. Price convergence, reported to be another result of ERP based systems, has led to reduction in funding of research and development of new products due to decreased revenues (Rémuzat et al., 2015). It has also been revealed that changes in prices in one country (i.e., a reference country) can result in changes in prices in other countries. It is estimated that if medicine prices are reduced by EUR1 in Germany, it can cause a decrease of EUR0.15–0.36 in 15 other European countries using the ERP system (Stargardt and Schreyögg, 2006). This evidence also puts emphasis on the importance of the selection of countries in the reference basket. So, if a country's aim is to reduce drug prices, then it should select a reference country that has low prices and is at the same level of economy. If the purpose is to promote research and development, however, then the choice should be made accordingly. Use of the ERP system by five high-income countries has been summarized in **Table 1**.

Implications of ERP use in Low- and Middle-Income Countries

In view of increasing global pharmaceutical expenditure, almost all high-income countries (except the United States) have adopted different pricing and procurement policies to reduce medicines' prices to cope with this situation (Critchley, 2006; Rietveld and Haaijer-Ruskamp, 2003). The situation has become worse for the LMICs, however, due to the lack of a regulated system, that is, stringent pricing, purchase, and reimbursement policies, which is making these countries "price acceptors" and increasing out of pocket expenditures (Sengupta et al., 2008). It has been reported that 61%–77% (per capita) of total pharmaceutical expenditure is private expenditure in LMICs (Lu et al., 2011). Health-care information systems are also lacking in the LMICs, making designing and the application of policies difficult compared to high-income countries (Nolen et al., 2005). Despite all of this, the situation is changing, as some LMICs are adopting different approaches to deal with increasing pharmaceutical expenditures. Some LMICs are now using one or more of the techniques (ERP, cost plus, internal reference pricing, profit controls, economic evaluation, and direct fixation, etc.) to set fair maximum prices for drug products (Vogler et al., 2008). The widespread use of ERP by high-income countries and its comparatively easy application is leading to its use by many LMICs. The applicability of ERP is due to lesser technical and analytical requirements compared to other methods of pricing such as cost plus or pharmacoeconomic analysis (Espin et al., 2011). In the ERP system, the selection of countries in the reference basket should ideally be from the countries with similar economies and within the same region, but lack of pricing data from these countries is a big obstacle for LMICs. So, in the absence of price information from reference countries, while implementing the ERP system, these countries also rely on international medicine pricing from the latest International Medical Products price guide produced by Management Sciences for Health (MSH, 2015).

There is very limited literature available on pricing policies and hence the use of ERP in LMICs. WHO and Health Action International (HAI) started reviewing the policies in 2011 under their broader project on prices and availability of medicines. Thirteen LMICs were selected for review. It was observed that the procedures for design and implementation of ERP varied among all the selected countries. For price referencing, average or minimum costs were reported as selected by the majority of these countries. Many European countries were observed to be taking reference countries from the same region. Slovakia takes eight European countries in its reference basket and the price regulator demands that the product's manufacturer provide information about its price in the other European countries and in the product's country of origin. The price setting commission of Iran uses ERP for ex-factor and wholesale prices of only on-patent and imported medicines taking Turkey, Spain, Greece, and the country of origin as reference (Espin et al., 2011). Pakistan is using the ERP system for setting a fair price for new molecules, taking India and Bangladesh as reference countries (DRAP, 2015). The Czech Republic takes an average of ex-factory prices in all EU countries to set prices of drugs in the government's reimbursement list of medicines (Espin et al., 2011). Indonesia adopted ERP along with other pricing strategies such as cost-plus pricing in 2010, for setting the prices of generic medicines. A price reduction in LPGs of about of more than 2000% for some drugs but not for the branded drugs was observed because of the lack of such policies for originator brands (Rida and Ibrahim, 2018). Turkey had also adopted ERP system (revised in 2011) and was used for all medicines. A decrease in the pharmaceutical expenditure (as a part of total health-care expenditure) was observed to be from 36% in 2004 and 27% in 2011 (Rida and Ibrahim, 2018). This decrease in prices both in Indonesia and Turkey can be linked to the ERP implementation up to some extent, but there is no objective evidence about it in the literature and there could be many other contributing factors leading to such results.

The increasing uptake of the ERP system by the LMICs serves as an index to its ease of use and applicability (Espin et al., 2011; Persson and Jönsson, 2016). It is hard to analyze the direct impact of pricing policies on drug prices in these countries because LMICs lack monitoring reports and relevant studies (Espin et al., 2011). Two Cochrane reviews were conducted which aimed to measure the impact of reference pricing on the health outcomes and medicine prices in 2006 and 2014 but none of these reviews included any LMICs (Acosta et al., 2014; Aaserud et al., 2006). Although the use of ERP seems justified for LMICs due to its comparatively easy application, still there is a dire need for these countries to strengthen their legal framework for better regulation of pharmaceutical prices, followed by sustainable monitoring and reporting systems (Nguyen et al., 2014). Use of the ERP system by five LMICs has been summarized in **Table 1**.

Table 1 Use of External Reference Pricing System in five high-income countries and five low- and middle-income countries

	World bank high-income countries					*World bank low- and middle-income countries*				
Country	*Netherlands*	*Canada*	*Japan*	*Portugal*	*Norway*	*Iran*	*Malaysia*	*Pakistan*	*South Africa*	*Jordan*
Number of reference countries	4	7	3	8	9	>3	6	2	4	17
Reference countries or institution	Belgium, France, Germany, UK	The federal governments reference USA, Germany, Switzerland, Sweden, the United Kingdom, Italy, and France.	France, the United Kingdom, Germany, and the United States	France, Italy, and Spain	Austria, Bulgaria, Germany, Denmark, Finland, Ireland, Netherland, Sweden, UK	Greece, Spain, Turkey and country of origin	Australia, Bulgaria, Brazil, Cyprus, Korea, Rep., New Zealand, Romania, Saudi Arabia, Turkey, Taiwan, South Africa	Bangladesh and India	Australia, Canada, New Zealand, and Spain.	UK, France, Spain, Italy, Belgium, Greece, Netherlands, Australia, Cyprus, Hungary, Ireland, New Zealand, Portugal, Czech Republic, Croatia and Austria, Canada, and countries of origin
Year implementing ERP	1996 (Price of Drugs Act)	NA	NA	2007	2000	NA	2012	NA	2014	29th January 2004
Availability of national price regulatory department	Evaluation is undertaken by the Pharmaceutical Care Committee (CHF) outside government., The Ministry of Health takes the ultimate decision on pricing	Patented Medicine Prices Review Board (PMPRB)	NA	Directorate-General for Trade and Competition	NA	The Medicines Agency (Pricing Commission)	It is within the MOH	Drug Pricing Committee, Drug Regulatory Authority of Pakistan (DRAP)	Pharmaceutical Economic Evaluations (PEE) Directorate	Pricing Committee of the Jordan Food and Drug Administration (FJDA)
Criteria used to determine medicine price	The average price of reference countries	The median of reference used as maximum price	When the highest price is 3X higher than the lowest price, the average of all the prices is used. Prices can range from 150% above or below 75% of reference countries' prices	Average of all reference countries	Average of three of the lowest price reference countries	Patented drugs are priced using the median price from reference countries, while for generics, the median price among the local manufacturers and the lowest price from reference countries	NA	NA	Minimum price	Median prices of reference countries.

Price basis	Pharmacy retail prices	Ex-factory is mostly searched for, if it's unavailable, retail price is then searched for.	Drug price list	Price control for prescription only medicines at manufacturer level; for all medicines at wholesalers' and pharmacists' level	Retail prices	Ex-factory and wholesaler	Wholesale price	Retail price	Ex-manufacturers and import prices	Ex-factory price of the reimbursed price
Review of medicines price	Prices reviewed every six months	Prices reviewed annually	NA	Quarterly	A schedule for review is published when the price of a different product within the same ATC is reviewed[i]		Price is reviewed annually on a case by case basis	NA	NA	The price is reviewed annually and verified by an external auditor
Legal document for medicine pricing	Price of Drugs Act (Wet Geneesmiddelprijzen, WGP)	Section 85 of the Patent Act of 1978	NA	NA	NA	NA	NA	Drug Pricing Policy 2015	Medicines and Related Substances Act (101/1965)	NA
Type of medicines or medicinal substance ERP applicable	Applied ERP for all prescription only medicines, as well as for high cost medicines and orphan drugs for in-patient care	Patent products/ Innovative medicines	NA	Portugal which excluded hospital-only medicines from its ERP system	Prescription medicines only.	Patent and imported medicines	NA	On-patent generic and imported medicines/(for medicines in the third category: new molecules)	Branded generic and schedules substances. On- and off patent products	All products
Response to change in medicine price in reference country	NA	Do not revise price	Do not revise price	NA	NA	Do not revise price	Do not revise price	Do not change price. Change can occur when manufacturer requests a higher price.	NA	Do not revise price when reference countries price changes. Price is reviewed two years after registration or the 5th year which is the re-registration period.
Source	Ruggeri and Nolte (2013) and Rémuzat et al. (2015)	Espin et al. (2014) and Ruggeri and Nolte (2013)	Espin et al. (2011) and Espin et al. (2014)	Leopold et al. (2012), Mossialos et al. (2004) and Vogler (2012)	Leopold et al. (2012)	Espin et al. (2011) and Espin et al. (2014)	Espin et al. (2014)	Espin et al. (2014) and DRAP (2015)	Espin et al. (2011) and Espin et al. (2014)	Espin et al. (2014)

NA, Information not available.

ERP and Pharmaceutical Manufacturers

The pricing of pharmaceuticals is a complex process that involves expertise and is influenced by the dynamics of demand (consumers) and supply (manufacturers). How well these market forces harness the institutional policies of government or private sector (e.g., health insurers) will determine access, availability, and affordability of medicines to consumers. It is worth emphasizing that the primary objective of manufacturers is maximizing profit by marketing their drugs at the highest cost possible (Babar, 2016). ERP is an excellent tool that has been shown to reduce end user and public-sector health expenditure cost (Espin et al., 2014; Babar, 2016; Miraldo, 2009). The effectiveness of this pricing practice, however, depends on how well market monopoly is discouraged, the transparency of the negotiated price (Miraldo, 2009), and the country in which manufacturers first launch their products.

The market dynamism for pharmaceutical products differs from other consumers goods. Mostly, buyers are not the end users, but institutions are given the responsibility to provide for the population. Two scenarios come into play in this instance: protecting manufacturers' business from external referrers and cutting health expenditure. Countries tend to achieve the former by offering a relatively high ex-factory price to manufacturers or fail to publish the actual transaction price and letting the manufacturer determine the product price (Leopold et al., 2012; Espin et al., 2014). The latter is achieved by providing a platform for companies to compete, which prevents exploitation of the payers (Leopold et al., 2012).

Nonetheless, ERP does not prevent pharmaceutical companies from price manipulation. Leopold et al. used the term *"gaming"* to explain the pattern used by manufacturers to launch their product, targeting high-income countries where there will possibly achieve a higher price for their product (Leopold et al., 2012). This explains why the majority of countries using ERP are high-income countries because countries tend to reference countries with the same economic status (Espin et al., 2014). Furthermore, companies can get to the point of withdrawing their product from countries referencing the lowest possible price to avoid decline in revenues (Remuzat et al., 2015) or refuse to sell their product abroad if the domestic market is lucrative (Geng and Saggi, 2017).

Generally, ERP is a working pricing system that ensures health system sustainable by lowering overall cost; however, since it is a complex process it must be implemented with caution to protect the interests of both pharmaceutical companies and patients. Thus, there is a need for expertise in its implementation.

Future of ERP

The ERP system is becoming a popular cost containment policy in both HICs and LMICs because of its relative simplicity and its consequent assurance to the general public that they are paying the same prices for drugs as people in other countries (Persson and Jönsson, 2016). A huge benefit of using this model is its potential to bring down the prices of drugs, especially those that are protected by patents and other intellectual property rights, which can lead to obvious cost savings at least in the short run (Espin et al., 2011). Although the main aim of ERP is to reduce drug prices, it must also align with the objectives of health policy. For many countries, especially high-income countries, the goal of health policy is not only to reduce pharmaceutical expenditure but also to bring about improvement in research and new drug development (Rémuzat et al., 2015). In that case, the ERP system might play a negative role by decreasing drug prices and hence profits to the companies, ultimately causing reduced investment in the development of new drugs (Geng and Saggi, 2017).

ERP is also seen as a threat to market competition and price discrimination. If LMICs keep taking high-income countries into their reference basket (may be due to lack of pricing data from other LMICs), one price will be seen in all the markets and companies will not be able to discriminate according to the buying capacity of countries at different levels of economy. This will also decrease revenue to manufacturers that could have been more by discriminating (selling products at high prices to the high-income countries and at low prices to low-income countries). Manufacturers can respond to such a situation in two ways: first, by selling high priced drugs to high- and middle-income countries and ignoring low-income countries and, second, by launching new drugs in two waves, that is, first in high- and middle-income countries at high prices (thereby accumulating profit for some years) and then launching the drug in low-income countries. In the first case, high- and middle-income countries will have to pay high prices (Geng and Saggi, 2017; Persson and Jönsson, 2016). In both cases, low-income countries will either have no or delayed access to new drugs. This places a big question mark on the existence of the ERP system.

In view of the potential benefits and harms of the ERP system, it becomes very important to evaluate the true impact of ERP on medicines prices (especially in the LMICs). Besides this, the LMICs should focus on strengthening their legislative work and databases for medicines pricing to make comparisons at the same level of economy possible and to get the best out of the ERP system.

Abbreviations

ERP external reference pricing
LMIC lower- and middle-income country
HIC high-income country
EU European Union
OECD organization for economic co-operation and development

PPRS pharmaceutical price regulation scheme
VAT value added tax.
WHO World Health Organization
MDGs millennium development goals

Glossary

External Reference Pricing The World Health Organization (WHO) defines ERP as "the practice of using the price of a pharmaceutical product (generally ex-manufacturer price, or other common point within the distribution chain) in one or several countries to derive a benchmark or reference price for the purpose of setting or negotiating the price of the product in a given country". It is also indicated that "Reference may be made to single-source or multisource supply products" (WHO, 2015).
Cost Plus Pricing A negotiated additional cost besides the costs for drug manufacture and research & development is decided with the manufacturer using the "cost plus" pricing method. The fixed mark-up usually includes this added cost (e.g., cost for drug promotion, stability testing, and workers' profit, etc.) (Nguyen et al., 2014).
Profit Ceiling This usually involves periodic negotiations with the pharmaceutical manufacturing companies to set the profit, which they can achieve by selling their products. The profitability of the company as a whole is taken into account as compared to setting margins for individual drug products (Rietveld and Haaijer-Ruskamp, 2003).
Price Negotiations This system includes negotiations, usually between government's price regulatory bodies and the manufacturers, over setting fair drug prices.

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Pharmacy Workforce Development: A Global Pathway to Gender and Health Equity

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Pharmacy Workforce Development: A Global Imperative

The intersection of health, access, and equity lies at the heart of global health and the collective to achieve universal health coverage (UHC). Social pharmacy provides a lens through which the development of the pharmacy workforce can directly improve health, expand access to services, and advance equity (both in terms of [1] health equity and access to services and [2] equity within the workforce itself). This paper presents the global Pharmaceutical Workforce Development Goals (PWDGs) as a means to achieving UHC and the global health agenda and examines, in particular, the 10th Goal on gender equity and diversity balances as a priority area for development, and catalyst for better health everywhere.

Developing the Pharmacy Workforce for Universal Health Coverage

Access to quality essential health services and safe and effective medicines and vaccines is fundamental to achieving UHC by 2030, as part of the United Nations (UN) Sustainable Development Goals (SDGs)—especially SDG 3: "Ensure healthy lives and promote well-being for all at all ages" (United Nations, 2015). Health service delivery, health workforce, and access to essential medicines are three of six World Health Organization (WHO) health system building blocks (World Health Organization, 2010). As medicines experts, the pharmacy or the pharmaceutical workforce plays a key role in improving health outcomes through responsible use of medicines and in optimizing effective choice and use. Pharmacy workforce refers to the whole of the pharmacy-related workforce (e.g., registered pharmacist practitioners, pharmaceutical scientists, pharmacy technicians, and other pharmacy support workforce cadres, preservice students/trainees) working in diverse settings (e.g., community, hospital, general practice, research and development, industry, military, regulatory, academia, and other sectors) with diverse scope of practice. Investing in the development of an adaptable, flexible, competent, and well-distributed pharmacy workforce contributes toward achieving UHC, SDGs, and strengthening health systems.

Medicines are vital in the prevention, diagnosis, treatment, and cure of disease. Access to effective and safe medicines is an essential human right and a central foundation of any healthcare system. Medicines and drug development, medicines management, and the responsible use of medicines are vital components in improving the health of nations. As medicines experts, the pharmacy workforce is an integral part of the healthcare team that plays a key role in bettering health outcomes through optimizing patients' use and understanding of medicines (Nkansah et al., 2010). In many countries, pharmacists are the most accessible of all healthcare workers and as such are at the forefront of healthcare service delivery (Anderson et al., 2010). However, the capacity to meet these expectations, including delivering these pharmacy services, depends on having an assured, competent workforce and an integrated academic workforce to train sufficient numbers of new pharmacists and other support staff at both foundation and advanced levels. This, in part, explains why pharmacists have been recognized in the UN indicator for the achievement of the health target 3.c focusing on health workforce:

> 3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing states.

The measurement will include the density of pharmacists per population (in addition to physicians, nursing personnel, midwifery personnel, and dentists) (United Nations, 2017).

Despite pharmacists being at the forefront of healthcare delivery, the global pharmacy workforce faces many challenges. The 2012 Global Pharmacy Workforce Report by the International Pharmaceutical Federation (FIP) described a number of problems

facing pharmacy human resources around the world, mirroring the challenges faced by the wider global health workforce (International Pharmaceutical Federation, 2012). Access to pharmacy services in developing countries and regions, such as Africa, is hindered by the insufficient supply of well-trained pharmacists. This carries implications for global inequalities in access to medicines and medicines expertise. The 2015 Global Pharmacy Workforce Intelligence Trends Report illustrates that, while the past decade witnessed a general increase in workforce numbers around the world, some low-income regions and countries still have a disproportionately low number of pharmacists and a low capacity for delivering pharmacy services (International Pharmaceutical Federation, 2015).

The Pharmaceutical Workforce Development Goals

Transforming the global pharmacy workforce requires a global vision with clear and consensus-based objectives consistent with global health strategies. The FIP is the global professional leadership body representing over 4 million pharmacists and pharmaceutical scientists around the world. FIP has developed a transformative workforce road map adopted at the Global Conference on Pharmacy and Pharmaceutical Sciences Education held in Nanjing, China, on November 7–8, 2016. The workforce road map sets out the desired milestones for education and workforce development of pharmacists and pharmaceutical scientists, clearly linked with a global vision for transforming pharmacy and pharmaceutical sciences education (International Pharmaceutical Federation, 2017). After an extensive consensus-based consultation process, the following three milestone documents were presented and adopted at the Global Conference:

1. A Global Vision for Education and Workforce that provides a description of the future directions of pharmacy profession and how education can support the progression of medicines science and practice.
2. A set of PWDGs that aim to facilitate national implementation of the global vision and road map through a series of measurable, feasible, and tangible goals.
3. A set of Statements on Pharmacy and Pharmaceutical Sciences Education (the Nanjing Statements) that describe an envisioned future for progressive professional education to enable further enhancement of pharmaceutical education standards worldwide.

The PWDGs (Fig. 1 and Table 1) have been developed as a measurable, feasible, and tangible means to activate and give purpose to the Global Vision. These 13 goals were the product of extensive external and internal consultation processes and adopted by consensus. The goals will provide action-oriented workforce planning and ways of monitoring progress toward global achievement

Figure 1 The FIP pharmaceutical workforce development goals.

Table 1 The pharmaceutical workforce development goals: description, rationale, drivers, and potential indicators

Cluster	*PWDG*	*PWDG general description. Countries/territories and member organizations should have:*	*Rationale, drivers, and potential indicators*
Academy Focus on schools, universities, and education providers	 1. **Academic capacity**	Engagement with pharmaceutical higher education development policies and ready access to leaders in pharmaceutical science and clinical practice in order to support supply-side workforce development agendas	• Increase the capacity to provide a competent pharmaceutical workforce by developing initial education and training programs that are fit for the purpose, according to national health resource needs (clinical practice, pharmaceutical science areas, and stakeholders across all cadres) • Develop new and innovative ways to attract young pharmacists into all areas of pharmaceutical practice and science (e.g., encourage young pharmacists to consider careers in clinical academia, as preceptors/trainers, in industrial pharmacy, regulatory sciences, nuclear and veterinary pharmacy, among others) • Capacity building should include the ability to meet minimum national standards of facilities, educators, and student support in order to ensure access to quality education for all students • Enhance interprofessional education and collaboration with key stakeholders, including governments, national and international pharmacy/pharmaceutical organizations, and patient advocacy groups to achieve sustainable solutions for capacity development • The clinical academic educator workforce needs more attention to training, career development, and capacity building, which must, importantly, include research capacity enhancement
	 2. **Foundation training and early career development**	Foundation training infrastructures in place for the early post-registration (post-licensing) years of the pharmaceutical workforce as a basis for consolidating initial education and training and progressing the novice workforce toward advanced practice	• Create clear and purposeful education and training pathways/programs to support post-registration (postgraduation) foundation training (clinical practice and pharmaceutical science areas) • Develop early career maps and frameworks to support a seamless transition into early career practice and toward advanced practice • Develop structured approaches to early career mentoring systems to support novice practitioners to engage with peers and preceptors (in clinical practice and pharmaceutical science areas across the pharmaceutical workforce)
	 3. **Quality assurance**	Transparent, contemporary, and innovative processes for the quality assurance of needs-based education and training systems	• Ensure the quality of the workforce by quality assuring the continuous development and the delivery of adequate and appropriate education and training; quality assurance needs to address academic and institutional infrastructure in order to deliver the required needs and competency-based education and training • Establish standards-based global guidance for quality assurance of pharmacy and pharmaceutical science education in the context of local needs and practice • Implement fair, effective, and transparent policies and procedures for quality assurance of pharmacy and pharmaceutical science education and training • Define critical stakeholder input on development of adequate education and training and fair and effective policies, including necessary student input

(*Continued*)

Table 1 The pharmaceutical workforce development goals: description, rationale, drivers, and potential indicators (*cont.*)

Cluster	*PWDG*	*PWDG general description. Countries/territories and member organizations should have:*	*Rationale, drivers, and potential indicators*
Professional development Focus on the pharmaceutical workforce	 4. **Advanced and specialist expert development**	Education and training infrastructures in place for the recognized advancement of the pharmaceutical workforce as a basis for enhancing patient care and health system deliverables	• Need for a common and shared understanding of what is meant by "specialization" and "advanced practice" in the context of scope of practice and the responsible use of medicines • Ensure competency and capability of an advanced and expert pharmacist in all sectors (including specializations extending into industry and administration settings) for greater optimization of complex pharmaceutical patient care. This may now include prescribing roles within a recognized scope of practice • Systematic use of professional recognition programs/systems as markers for advancement and specialization across the workforce, including advanced pharmaceutical scientists
	 5. **Competency development**	Clear and accessible developmental frameworks describing competencies and scope of practice for all stages of professional careers. This should include leadership development frameworks for the pharmaceutical workforce	• Use of evidence-based developmental frameworks to support the translation of pharmaceutical science within scope of practice, across all settings and according to local/national needs • Support professional career development by using tools such as competency frameworks, describing competencies, and behaviors across all settings • Evidence of clear policy that links leadership development (from early years) with competence attainment for the advancement of practice activities
	 6. **Leadership development**	Strategies and programs in place that develop professional leadership skills (including clinical and executive leadership) for all stages of career development, including pharmaceutical sciences and initial education and training	• Creation of programs/strategies for the development of leadership skills (including tools and mentoring systems), to support pharmacists and pharmaceutical scientists through their careers • Advocacy for leadership development in healthcare teams, linked to collaborative working activities (e.g., promotion of team-based approaches to healthcare service delivery) • Ideally, this should be linked with competency and foundation and early year career development activities
	 7. **Service provision and workforce education and training**	A patient-centered and integrated health services foundation for workforce development, relevant to social determinants of health and needs-based approaches to workforce development	• Systematic development of education and training activities based on local healthcare systems, their capacity, and funding • Evidence of systematic development policies and strategies for the strengthening and transforming pharmaceutical workforce education and the systematic training of trainers/educators • Education providers must ensure, by the provision of evidence-based approaches, that lecturers/teachers/trainers are themselves appropriately trained for capability and competency • Enable the pharmaceutical workforce and key stakeholders to promote health equity through actions related to social determinants of health
	 8. **Working with others in the healthcare team**	Clearly identifiable elements of collaborative working and interprofessional education and training which should be a feature of all workforce development programs and policies	• Evidence of policy formation to demonstrate how healthcare professionals can develop and engage in partnerships to achieve better health outcomes • Develop education and training strategies/programs to ensure collaboration within the pharmaceutical workforce and training on medicines for other healthcare professionals • Ideally, this should be linked with formal professional development activities

Table 1 The pharmaceutical workforce development goals: description, rationale, drivers, and potential indicators (*cont.*)

Cluster	*PWDG*	*PWDG general description. Countries/territories and member organizations should have:*	*Rationale, drivers, and potential indicators*
Systems Focus on policy development, governmental strategy and planning, and monitoring systems	 9. **Continuing professional development strategies**	All professional development activity clearly linked with needs-based health policy initiatives and pharmaceutical career development pathways	• Evidence of an effective continuing professional development strategy according to national and local needs • Development of programs to support professional development across all settings of practice and all stages of a pharmacist's career • Ideally, this should be linked with all professional development activities across the workforce • Education in continuing professional development strategies and self-directed behaviors should be initiated at the student level
	 10. **Pharmaceutical workforce gender and diversity balances**	Clear strategies for addressing gender and diversity inequalities in pharmaceutical workforce development, continued education and training, and career progression opportunities	• Demonstration of strategies to address the gender and diversity inequalities across all pharmaceutical workforce and career development opportunities • Ensure full and effective participation and equal opportunities for leadership at all levels of decision-making in pharmaceutical environments; avoidable barriers to participation for all social categories are identified and addressed • Engagement and adoption of workforce development policies and enforceable legislation for the promotion of gender and diversity equality, policies and cultures for the empowerment of all without bias • This should be applicable to academic capacity and leadership development activities
	 11. **Workforce impact and effect on health improvement**	Evidence of the impact of the pharmaceutical workforce within health systems and health improvement	• Engagement with systems to measure the impact of the pharmaceutical workforce on health improvement and healthcare outcomes. Links with needs-based education, training, and workforce planning • Gather continuous data points to monitor the performance of the pharmaceutical workforce • Ideally, this should be linked with strategies to enhance workforce intelligence
	 12. **Workforce intelligence**	A national strategy and corresponding actions to collate and share workforce data and workforce planning activities (skill mixes, advanced and specialist practice, and capacity). Without workforce intelligence data there can be no strategic workforce development	• FIP should aim to have a global workforce compendium of case studies developed by 2019 • Develop monitoring systems to identify workforce trends to enable decision-making on deployment and supply of pharmaceutical workforce, noting that time lags are often present in these activities • Ideally, this should be linked with stewardship and leadership for professional leadership bodies
	 13. **Workforce policy formation**	Clear and manageable strategies to implement comprehensive needs-based development of the pharmaceutical workforce from initial education and training through to advanced practice	• Adopt and strengthen sound policies and enforceable legislation for holistic needs-based approaches to professional development across all settings and stages • Develop strategies where pharmaceutical science and professional services are the driving forces for this activity

of the workforce vision. Crucially, they will provide a consistent structure for coherent and comprehensive national workforce development actions.

The 13 PWDGs are gathered into three groups:

- Academy: Focus on schools, universities, and education providers
- Professional development: Focus on the pharmacy workforce
- Systems: Focus on policy development, governmental strategy and planning, and monitoring systems

Progressing the Goals to Progress Gender and Health Equity

Gender and Diversity Balances in the Workforce

PWDG 10: "Gender and diversity balances in the workforce" calls for countries around the world to develop clear strategies for addressing gender and diversity inequalities in pharmacy development, continued education and training, and career progression opportunities. Progress toward this goal can be measured through the demonstration of strategies to address the gender and diversity inequalities across all pharmacy workforce and career development opportunities. It includes ensuring full and effective participation and equal opportunities for leadership at all levels of decision-making in pharmaceutical environments; avoidable barriers to participation for all social categories are identified and addressed. The engagement and adoption of workforce development policies and enforceable legislation for the promotion of gender and diversity equality, as well as policies and cultures for the empowerment of all without bias, are needed to progress PWDG 10. These policies and strategies should be implemented across all sectors and at all levels of the workforce starting from education.

PWDG 10 links directly not only to the UN SDG 3 on health but also particularly on SDG 5: "Achieve gender equality and empower all women and girls" and its targets with an emphasis on Target 5.1: End all forms of discrimination against all women and girls everywhere and Target 5.5: Ensure women's full and effective participation and equal opportunities for leadership at all levels of decision-making in political, economic, and public life.

Gender equity is the process of being fair to men and women. To ensure fairness, measures must often be put in place to compensate for the historical and social disadvantages that prevent women and men from operating on a level playing field. Equity is a means. Equality is the result. Gender inequity has contributed to unemployment and underemployment, low education and health achievements, and overall poverty. Sustainable development will depend on better gender equality. Yet, while in the developed world progress has been made, the International Labour Organization (ILO) states that African women continue to face persistent challenges to get decent jobs (International Labour Organization, 2016). Any change requires a continental effort and proactive action. The UN Development Programme's flagship 2016 report on development in Africa focuses on gender equality and women's empowerment (United Nations Development Programme, 2016). The report describes a continent limited in its potential by serious problems; it finds that gender discrimination leads to a loss of an average of $95 billion every year. The UN High-Level Commission on Health Employment and Economic Growth acknowledges that the health sector can greatly contribute to gender equality by being one of the biggest and fastest growing employment sectors for women (International Labour Organization, 2017) recommended to "Maximize women's economic participation and foster their empowerment through institutionalizing their leadership, addressing gender biases and inequities in education and the health labour market, and tackling gender concerns in health reform processes" (World Health Organization, 2016).

Science, technology, and innovation have been identified as the key driver of economic progress and sustainable development, which, for Africa, will depend largely on the use of its human and natural resources. All recent African declarations agree on this question. UNESCO's vision for sustainable socioeconomic development in Africa has translated this into action in four key projects, making science education accessible to women involving women in science. UNESCO also has had a number of projects promoting science, technology, engineering, and maths (STEM) careers to girls at school (United Nations Educational, Scientific and Cultural Organization, 2017). If we take Kenya as an example, two in five students in higher education are women and one-third of the students studying STEM subjects are women. The gender gap is narrowing in pharmacy education; there are 822 male and 690 female students.

A recent *Lancet* editorial promotes gender equity in science as both a moral and necessary imperative (The Lancet, 2018). A US national survey has identified STEM workplaces as "deeply misogynistic" (Parker and Funk, 2018). In the United Kingdom and Australia, schemes, such as Athena SWAN, show that STEM workplaces cannot be gender inclusive without institutional commitment to removing unconscious bias. Gender balance is not reflected at the leadership level, too.

Paving the Pathway to Equity

Seven out of ten health and social workers are women, and unpaid care work represents half of women's contribution to global wealth. Women health workers deliver care to around 5 billion people. WHO predicts a shortage of health workers (18 million), especially in low- and middle-income countries (LMICs) to achieve UHC. Resilient health systems and UHC cannot be progressed without consideration of the gendered aspects of the workforce.

Without this consideration, we will not be able to achieve the SDGs. Addressing gender biases and inequities in the health and social workforce is not only essential to achieving SDG 3 (health and well-being), but also SDG 4 (quality education), SDG 5 (gender equality), and SDG 8 (decent work and inclusive economic growth).

The ILO–OECD–WHO five-year action plan on health identified the (1) development of gender-transformative global policy guidance and (2) support to build implementation capacity to overcome gender biases and inequities in the education and health labor market as two key deliverables to maximize women's economic participation and empowerment.

Global Pharmacy Workforce

The recent 2018 FIP report on workforce intelligence trends describes the global capacity trends observed in the pharmaceutical workforce from 2006 to 2016, including gender distribution (International Pharmaceutical Federation, 2018). The proportion of women in the pharmacy workforce between 2009 and 2016 shows a steady increase at a percentage rate of around 7.5% every decade. The Southeast Asia region showed the highest proportional increase in the sample period. The results indicate that the average female proportion of the total global pharmacy workforce will continue to increase to around 72% by 2030, mirroring the proportions of the global health workforce.

Countries across each WHO region and income level category are experiencing an increase in the proportion of female pharmacists in the last decade as identified by the FIP report. This acceleration of female participation in the pharmacy workforce indicates a strong and positive attraction among females for entering the profession globally. Similar trends are found in medicine; all economic national categories have experienced increases in female participation in education, training, and entry to the medical workforce. In higher-income countries such as the United States, females now represent 50% of medical school graduates—an increase of 7% in the last 50 years (Pelley et al., 2016). In Canada, this increase is more marked with only 8.5% of female medical students in the 1970s increasing to 50% in the 1990s and currently sitting at around 57% of all medical students (Weizblit et al., 2009). The current UK proportion is approximately 60% (Moberly, 2018).

One major impact of having a high percentage of female pharmacists is the decrease in the overall contribution to the workforce. Various studies have highlighted that globally female pharmacists are more likely to take career breaks and work part time in comparison to male pharmacists, most commonly associated with child and family care (Carvajal, 2018).

Current research on gender equity in the health and social care workforce is focused on quantitative analysis of data (World Health Organization, 2018). While sex-disaggregation data shed light on the realities of gender equity such as the wage gap, quantitative research alone does not provide insight into the barriers and facilitators identified through the lived experiences of women in the workforce. Qualitative research is needed to ensure policy changes are attuned to the contextual realities of gender challenges. A high proportion of the literature identified in the recent WHO review (International Pharmaceutical Federation, 2017) points to inequities in the health workforce. The link between gender-transformative policies at the academic level and their positive impact on gender equities in the health workforce affecting both students and faculty improves the distribution, extent, and skill mix of the workforce. For example, segregation often starts at enrolment and more evidence examining this link and its impact on gender-based outcomes in the workforce is needed to influence higher education policy.

Job and Career Satisfaction as an Equity Issue

Female pharmacists in higher-income countries have consistently reported higher levels of job satisfaction than male colleagues, while the latter indicate greater intentions to leave the profession. In the United States, female pharmacists reported higher overall satisfaction levels including a higher satisfaction with pay, even though average statistics indicate reduced remuneration rates of up to $11,000 less than males (Carvajal et al., 2018). In Taiwan (a high-income country), one study indicated that more male pharmacists wanted to leave the profession (across all sectors) compared with female colleagues, which was reported as due to insufficient professional challenge (Lin et al., 2007). In Lebanon (an upper-middle-income country), female pharmacists reported greater satisfaction with the profession than male pharmacists (Salameh and Hamdan, 2007). Similar results have been reported in the United Kingdom, with females being more satisfied, in particular with career aspects such as working hours, social engagement, and patient interaction (Seston et al., 2009).

That these reports consistently suggest greater job satisfaction in the profession seems a generalizable trend and clearly linked with social roles. With association between satisfaction, gender, and the social interactivity of modern pharmaceutical roles, this would seem to suggest that the quantitative forward projections of an increasingly female-majority workforce have an underlying basis in gender identity. The global challenge is in ensuring that pharmaceutical workplace environments and pharmaceutical employment policies are contemporary and flexible enough to support this global trend.

Conclusion

This paper has shown how social pharmacy provides a lens, focusing on gender and diversity equality and health equity, through which the development of the pharmacy workforce can directly improve health, access to services, and advance equity (both in terms of [1] health equity and access to services and [2] equity within the workforce itself). We have presented the global PWDGs as a means to achieving UHC and the global health agenda and examined, in particular, the 10th Goal on gender equity and diversity

balances as a priority area for development, and catalyst for better health everywhere. Further research is needed to provide insight into the barriers and facilitators and the lived experience of women in the workforce.

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Role of Pharmacists in Responding to Humanitarian Crisis

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Learning Objectives

- Introduction to the concepts of humanitarian aid and types of humanitarian crisis.
- Identification of the role of the pharmacists in responding to humanitarian crisis.
- Understanding responsibilities of pharmacists toward handling of medicines during crisis.
- Learning from good and bad cases of donation of medicines.
- Understanding the role of technology in the development of pharmacist's role in provision of professional services in emergency condition.

Take Home Lessons/What Needs to be Done

1. Pharmacist is an essential component of the humanitarian aid team and must be involved in all segments of its planning and execution.
2. The donation supply and management needs to be an ongoing process of learning and need to be evidence based.
3. Supply chain management is an integral part of the pharmacist's role during health emergencies.
4. Rationality and ensuring responsible use of medicine must be at the core of the planning of pharmacy services.
5. Awareness and training regarding disaster management is needed for health-care professionals.

Background

Medical and pharmaceutical responses are crucial for saving precious lives during any humanitarian crisis. These responses include provision of both supplies as well as skilled human resource. Increasing number of humanitarian crisis situations are happening due to natural (owing to global warming, climatic change, and natural geographic processes) as well as global sociopolitical scenario with rising number of unresolved conflicts, economic turmoils, and international disputes (The World Economic Forum, 2019). Hence, health professional's response to humanitarian crisis have evolved as a permanent feature of the global health-care scene.

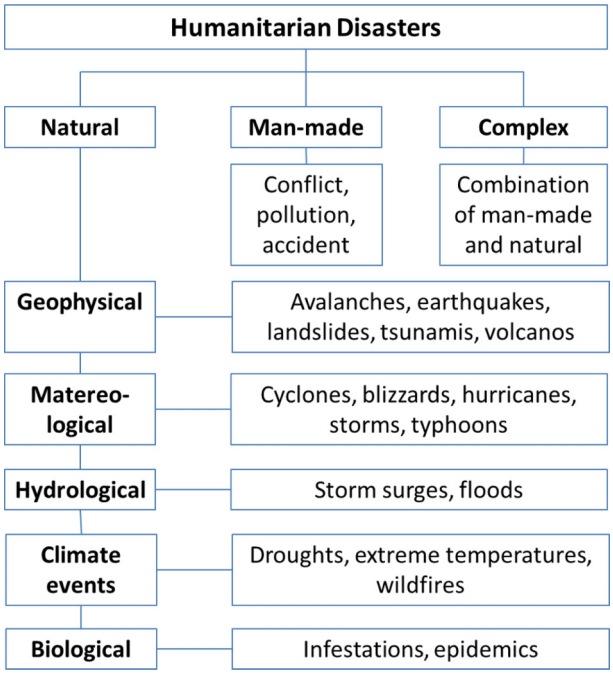

Figure 1 Classes of human disasters.

Pharmacists as the essential member of health-care team, are incorporated in the health system network globally, also including their presence in the emergency conditions. The role of pharmacist is transforming globally to patient-centered approach. Similarly, in emergency medicine, pharmacists have not only struggled to advance their role in the logistic management but also focussed on rationality and safety, in accordance with the needs of the population.

Types of Humanitarian Crisis

The events that result in threatening situations toward safety, health, and well-being of single person or community are identified as humanitarian crisis. Such events influence the community's capacity to cope with physical, environmental, or economic damages that arise due to these events.

Centre for research on the epidemiology of disasters (CRED) and the international disaster database (EM-DAT) have categorized the human disasters as in Fig. 1.

These crises can also be classified on the basis of resource needs, operational challenges, and overall requirements (1). This includes

1. Small-scale injury/illness events: tornado, small level disease breakout, bus crash.
2. Large-scale natural disasters: tsunamis, hurricanes, flooding, moderate earthquake.
3. Complex events: terrorism activity (multiple shooting of bombing), mass burn events, limited outbreak of infectious disease such as severe acute respiratory syndrome (SARS), and Avian Influenza.
4. Catastrophic health events: major earthquake, bioterrorism, pandemic, or nuclear detonation.

Health-Care System During Crisis Conditions

Implementation of emergency response emphasizes the importance of sustaining the resources of primary health-care system and reflecting these services into primary health-care strategies, policies, and services (Swathi et al., 2017). For instance, a number of health policies have been implemented by the United Nations and International Federation of Red Cross (with Non-Governmental Organizations) in collaboration with the local governments. The essential components of primary health-care system have been adopted to devise these policies. Reduction in events of disaster associated chances of morbidities and mortalities have also augmented the importance of implementing these policies. Moreover, standalone emergency response (trauma care, management of chronic situations, immunization, psychological support) has been recognized as an essential component of primary health-care system (Swathi et al., 2017).

The need of a design and implementation of an integrated health-care system for humanitarian crisis management framework was felt due to the lack of framework, competency in disaster management, and appropriate skills. Despite understanding of levels of disasters and their types (Fig. 1), meager efforts have been made to invest on strategies to cope and treat the aftermaths of such threatening events. The available policies do not train health-care professional students (physicians, pharmacists, nurses, and so on) to directly excel in disaster management competencies. Disaster management has classically not been part of the core curricula in health systems and mostly opted as an additional course delivered by the international or regional humanitarian aid organizations. The limited web-based programs and conferences only target the professional health-care workers and not the students.

An iconic disaster management system is envisioned of preparedness and rescue, which is regionalized, tiered, adaptive, and resilient. It can cope with all the different types and levels of humanitarian crisis. This system should be based upon networks of disaster management health-care centers and community-based resilience. Long-lasting success of this system is based on the alliance of three major components, that is, a resilient community, specialized disaster management hospitals/centers, and network of skillful health-care professionals (Toner et al., 2018).

The Phases of Response to Humanitarian Crisis and the Health-Care Professionals

The phases of crisis have been studied under prevention, incident preparation, response generation, and recovery efforts. A more comprehensive scheme includes six stages including warning, risk assessment, response, management, resolution, and recovery. The nature and severity and type of needs may vary tremendously in the initial phase of the emergency. The initial acute phase of 24 h needs can be further split into the immediate needs (0–2 h) and the extended phase (12–24 h) (Hurd and Mount, 2008).

Preparedness

Crisis is declared when the health-care needs exceed the capacity of the available infrastructure. The scale, intensity, and the short time in which these demands arise warrant the need of prior preparedness of the health system to deal with any emergency. Following key components of the emergency preparedness are identified in the literature (Hurd and Mount, 2008)

Planning

Anticipation of the role of health-care providers and identifying the types of disasters needed to be covered in planning are of important national and organizational concerns. The key health-care providers identified for responding to crisis are also called first responders. In the United States, pharmacists have been identified as part of the planning team for the crisis management since 1960s. Disaster preparedness is part of the requirement for accreditation of hospitals by the Joint Commission on Accreditation of Health Organization. According to a national survey in the United States, all hospitals have plans for responding to natural disasters, whereas most hospitals also have plans for chemical, biological, explosive, or nuclear/radiological events.

A diverse range of professionals are involved in response to the disasters. The personnel coming in first contact are termed first responders and include police, security, or other law enforcement personnel, firefighters, rescue personnel and paramedics, and ambulance attendants. Evacuation helpers, drivers, air lifters, and divers may also be engaged in depending upon the nature of emergency. Professional health-care personnel are mostly involved at second level, in the health-care facility or clinic whether permanent or in a make shift capacity. A good number of volunteers and public works personnel are also involved (Hurd and Mount, 2008).

Emergency department (ED) pharmacist has a key role in planning and responding to intentional (man-made) or unintentional (natural) disastrous events. ED pharmacist should be connected to regional and national emergency networks and should be involved in planning and policy-making decisions. Selection of pharmaceuticals and associated provisions for emergency inventories can be decided by involving ED pharmacist in disaster planning committees. The competence of ED pharmacist can help developing the guidelines for the treatment of disaster victims, postexposure symptoms, prophylaxis, patient isolation, and the provision of antidote in all emergency-related health-care centers. Another important role for ED pharmacist is to rationalize the procedures to obtain antidote from national stock in case of insufficient supplies available in the local emergency centers. ED pharmacist can provide antidote in case of bioterrorism event and can effectively participate in actions concerned with prophylaxis, treatment, and counseling. The pharmacist can also help in the provision of mass supply of appropriate medications and advise to physicians for rational prescribing.

Rescue

Search and rescue (SAR) is one of the most important and dynamic operation in disaster management. To do so, there are some principle methods, which can be applied. Security and safety should be always fully considered for both staff and victims. Generally, the initial SAR phase could last for hours or days after the crisis. However, a prompt response is required to save the lives from imminent danger. This phase usually passes in few days and actions turn toward providing support to the affected people.

The personnel engaged should be familiar with the role of rescue services in work on-scene, incident command structure, and international standards for rescue missions. In the crisis of Hurricane Katrina in 2005, SAR phase extended to 4 weeks. People remained trapped in their houses with limited food availability. Houses were surrounded by flood and most shared the emergency

supplied foods with neighbors until disaster teams rescued them. It was only possible with the collaborative effort of health-care professionals and local authorities. Immediate rescue concerns in emergencies that are more focused on health issues may warrant the need of arrangement of immediate medical supplies, which may be followed by setting up a temporary structure for pharmacy (bus or trailer or mobile van) rather than establishing a permanent structure.

Rehabilitation

The rescue and respond activities are followed by recovery, reconstruction, and rehabilitation. This is the most challenging phase of the disaster cycle and covers a wide range of actions. Perhaps the most demanding element is to review and evaluate the disaster management process to see whether it could have been managed better in preparation for possible future disasters. This phase may include spatial planning, developing infrastructure, communication, water, hygiene, and sanitation, housing, livelihoods, social security, transport, agriculture, and evaluation. This transition phase from the temporary and ad hoc structures to permanent ones may call for exceptional service designs from the health-care professionals. Like temporary relaxation of pharmacy dispensing procedures to ensure that health coverage is not compromised among masses following the crisis situation (Hurd and Mount, 2008).

Role of Pharmacists

Pharmacy professionals can deliver various roles in disasters, emergency situations, conflicts, wars, and disease out breaks as a part of the humanitarian aid organizations or being a part of the health facilities of the affected region. These include

1. Planning and purchasing of pharmaceuticals and related supplies
2. Monitoring and evaluation of the stocks received
3. Establishing drug supply system
4. Carrying out pharmacovigilance activities and monitoring the supply chain for any infiltration of substandard and falsified medicines
5. Ensuring rational use of medicines
6. Preventing antimicrobial resistance
7. Counseling and ensuring medication adherence
8. Preventing wastage of medicine
9. Controlling and preventing misuse and abuse of medicines
10. Minimizing communication barrier between affected community and pharmacy professionals to ensure proper counseling and understanding of the social and cultural preferences.

Policy and legal framework, drug supply management, and management support are three main levels of pharmacist's role in health facilities (WHO Regional Office for Africa, 2004).

Pharmacists can play the role of a health-care volunteer, a regulator, a team member. He can help development of indigenous guidelines drug donations to cater the needs of the local population specially in settings that are particularly vulnerable to disaster or crisis. Once donations are received at the relief camps pharmacy professionals are responsible to ensure that the supply is utilized in a rational and safe manner.

Delivering Pharmacy Services According to the Sociobehavioral and Cultural Needs of People

Health-care services of societies are closely aligned with the cultural, social, and religious beliefs of the people. It is important for the pharmacists to ensure this in its planning, procurement, and service design activities. The sensitive scenario of humanitarian crisis where many lives are at stake and people are already facing trauma, loss, and insecurity careful analysis of their social needs enable the pharmacist to implement its role in an effective manner.

The humanistic needs of the aid provision are important component. Pharmacists in humanitarian aid organizations can also be involved in managing advocacy campaigns or working. To understand the actual needs of the community, it is important for some of the professional members to work in field projects. Understanding patients' behavior and psychology is inevitable to ensure the proper delivery of pharmaceutical services to the population.

Preventing Antimicrobial Resistance and Disease Outbreaks

Epidemics and infectious diseases are an identified threat during any manmade or natural disaster situation. Scarcity of clean water and proper toilets pose problems of water borne diseases such as diarrhea, cholera, and gastroenteritis. The situation can become an urgent threat to the lives of population, which may be practically cutoff from the regular supplies or food and medicine. Cholera outbreaks were reported in the past in many natural and man-made disasters including the civil war in Sierra Leone (Dyer, 1995), floods (Tordrup et al., 2013), and post-earthquake (Bukhari et al., 2010) in Pakistan.

Apart from cholera malaria, tuberculosis and skin infections including scabies were also reported in such situations, due to people living in confined settings where they have poor sanitation, poor ventilation, and no sunlight. Apart from drug supply shortages, poor quality of pharmaceuticals has also been identified as the one of the problems encountered. Substandard antimalarial was found to be the cause of poor prognosis and emergence of multidrug-resistant malaria in an Afghan refugee camp in Pakistan (Leslie et al., 2009). Hence, adoption of a concrete policy for the quality assurance of the supplies is warranted in the disaster management programs. WHO prequalification system has been used as an effective tool in this regard (Bukhari et al., 2010). Rational use of medicines and efficient inventory management ensure the availability of antimicrobials as well as their safe and effective use. The shortage of trained staff in such situations are compensated using predesigned and standardized dosing protocols as used by relief and rescue organizations such as Medicines Sans Francis.

In order to develop a cautious approach to the public health issues regarding infectious diseases and their outbreaks, pharmacists must be equipped with the skills to understand and effectively use the epidemiological tools such as World Health Organization's (WHO) Disease Early Warning System (DEWS) for estimation and planning of pharmaceutical supplies in need. WHO established DEWS for early detection of diseases in the war-stricken regions of Iraq, Sudan, Serbia, and Afghanistan in early 2000s (World Health Organization, 2019). The key components of this system include infectious disease monitoring, outbreak investigation, disease control coordination, logistical support, and quality control (U.S. Agency for Internatioanl Development, 2013).

Irrational supplies, poor-quality medicines, absence of trained health professionals, and lack of prescribing protocols for safe and rational use of antimicrobials need to be preoactively addressed to prevent emergence of resistant pathogens in the resource constraints environment such as refugee camps.

A specialized logistic system needs to be established that entails the responsibility of safe use of pharmaceutical in the circumstances where affected people are more vulnerable to damage than in normal circumstances.

Antibiotic needs of the population are likely to be different in emergency situation than during peacetime (World Health Organization, 2011). AMR guidelines (antibiotic choices, doses, duration of treatment) for emergency situations must be evaluated. It is challenging to decide on a single appropriate guideline in such situation due to difference in nature of each type of hazard (i.e., trauma, flooding, earthquake, blasts, or volcanic eruptions) as each produce different medical problems and infections. Hence, no single approach can be adopted as a guiding principle.

Absence of laboratory support is also an important area that demands an alternate strategy for supporting diagnosis for use during the crisis situations. However, adopting AMR as a priority in the response planning may present a difficult task due to different priorities of the crisis management settings (World Health Organization, 2011).

Good Donation Practices

Initially introduced in 1996 (World Health Organization, 1999), the guidelines for medicines donation by WHO were revised in 2010 to interagency guidelines (World Health Organization, 2010). The document incorporates experiences of major international humanitarian agencies. It provides lessons from medicines donations carried out around the globe during the last decade. These Interagency Guidelines for Drug Donations are developed and endorsed by Caritas Internationalis, Churches Action for Health of the World Council of Churches, International Committee of the Red Cross, International Federation of Red Cross and Red Crescent Societies, International Pharmaceutical Federation, Medicines Sans Frontieres (MSF), Oxfam, Pharmaciens Sans Frontieres, The Joint United Nations Commission on HIV and AIDS (UNAIDS), United Nations Development Programme (UNDP), United Nations Population Fund (UNFPA), the United Nations High Commission for Refugees (UNHCR), United Nations International Children's Emergency Fund (UNICEF), World Bank, and WHO.

The guidelines describe medicine donation problems by using the examples from the earthquake in Gujarat, India (2001), the Tsunami in Srilanka (2004), and the inconsistent and insufficient supply of medicines in Tanzania.

Administration of veterinary eyedrops to women in Lithuania (1993) causing temporary eyesight loss, supply of large quantities of useless items (contact lenses) in Sudan (1990), donations of thousands of tonnes of poor-quality pharmaceuticals to Bosnia and Herzegovina during 1992–96, and inappropriate quantities of unsorted items delivered to Armenia (1998) are the historical examples quoted in the guidelines documents to enable the understanding of the recipient countries to be aware of rationalizing the donation process (World Health Organization, 1999, 2010).

In addition to the type, packaging, labeling, and quality issues, several other ethical issues are also identified regarding medicines donations. These include donation of returned, expired, or short expiry drugs, and so on. Hence, not being able to foresee the hazards of receiving uncontrolled donations may result in a bigger financial and ethical liability then controlling the damage caused by medicine shortage (World Health Organization, 2010).

Core principles of guidelines for drug donations according to interagency guidelines issued by WHO (World Health Organization, 1999, 2010).

1. Donations should be aimed at the benefit of the recipient
2. Recipient has the right to exercise its authority and wish in choosing the nature and quantities of the donations
3. Care should be taken to watch against double standards in quality (supply of medicines not registered in the donating country or banned in donor country, near expiry, or expired drugs donation, compromised or damaged stock or returned or controversial, doubtful stocks)
4. Effective communication between donor and recipients is needed

Examples of Bad Medicines Donation

Banda Aceh province in Indonesia was hit by Tsunami in December 2004. WHO has funded a study to evaluate the drug donation situation and its handling following the disaster. Pharmaciens Sans Frontières Comité International carried out this comprehensive study that provides the factual analysis of the situation.

The report is an excellent source to help humanitarian aid workers, organizations, and governmental organizations, who have a stern stance on donation policies during humanitarian crisis. The report states that nearly 60% of donated medicines were not listed in the national List of Essential Drugs and 10% had expired before reaching the destination. Thirty percent of donated medicines had just 6 months or less shelf life, also they had missing expiry dates. This was a result of accepting the unasked donations of 4000 tonnes for a population of 2 million people (Pharmaciens Sans Frontières Comité International, 2005).

Similarly, in 2004, during the Tsunami crisis in Srilanka, a large bulk of medicines was donated by 278 donors, including 150 International organizations and 30 foreign governments. Medicines were labeled in more than 16 foreign languages. In 2005, the use of poorly stored spinal anesthesia from these stocks led to the growth of Aspergillus sp., resulting in meningitis in three pregnant women. It also resulted in Health Ministry in Srilanka paying for the huge costs not only for the storage, shipment, and handling of donations but also for the cost of the medicine disposal (Benaragamama and Fernandopulle, 2007).

Case Stories Pharmacists Serving in Humanitarian Crisis Globally

FIP and Capacity Building of Pharmacist Working in Humanitarian Crisis

The International Federation of Pharmaceuticals combines the role of emergency pharmacist and the military services under the umbrella of military and emergency pharmacists (MEPS) since 1994 (International Pharmaceutical Federation (FIP), 2019). The organization provides extensive framework of activities including the meeting of the MEPS colleagues during annual congress of FIP, webinars, newsletters, and special projects including the FIP pictogram project and development of guidelines for emergency preparedness of pharmacists during disaster situation.

In Chronic Disease Management

As global political conflicts continue to increase, more and more refugees are facing urgent challenges such as the unavailability of proper medical care. Many of the Syrian refugees now living in Jordan (the entire group accounts for one-tenth of that country's population) are struggling with at least one chronic disease, placing tremendous strain on existing health and humanitarian resources as a result.

A 3-month long-single blinded randomized study was carried out in three cities of Jordan with the majority Syrian refugee population. The total number of patients recruited was 109. Treatment-related problems (TRPs) were identified and resolved using the pharmacist-delivered Home Medication Management Review (HMMR) service based on the Australian HMMR protocol. Significant differences were observed between the intervention and control groups with the percentage of TRPs resolved/improved in the intervention group being 66.8% in comparison to 1.5% in the control group. The postintervention evaluation showed that only 19.7% of the TRPs remained unresolved in the group receiving medication review by the pharmacists (**Fig. 2**). The study demonstrates that pharmacists can play a vital role in closing treatment gaps for managing chronic health conditions among this underserved population. The interventions were received positively by the physicians as well as by the patients, and the authors recommend that this service can be of vital significance in designing effective refugee health programs (Al Alawneh et al., 2018).

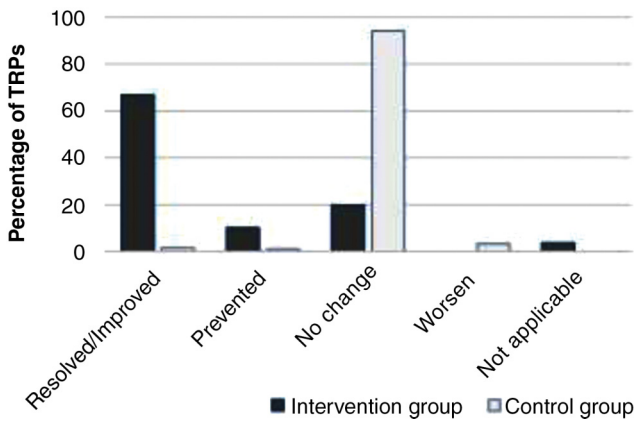

Figure 2 Outcome on TRPs observed in the Syrian refugee population undertaking pharmacist led Home Medication Management Review in Jordanian cities.

Ensuring the Adequate Supply of Quality Essential Medicines in a Country with Poor Access to Essential Medicines (2005–2013)

In 2005, earthquakes hit the northern regions of Pakistan, and the federal capital and the task of essential medicines availability were closely managed by a team of pharmacists that grew from few pharmacists to an expanded team working in nation-wide disaster management offices under World Health Organization (Bukhari et al., 2010).

For a country where pharmacist was still to be recognized as an essential health-care team member, the pharmacists managed to provide essential medicines to the far flung regions in the country. WHO acted as a hub for receiving and rationalizing the donations for many donor agencies, and this centralized framework was the main reason for a low pharmaceutical waste documented during this humanitarian operation.

Emergency pharmacists were trained along with the establishment of central warehouse and satellite facilities. Apart from logistic supplies, it was ensured that the medicines were provided with the training of paramedics delivering the services of catering the remote facilities. Storage, dispensing, and prescribing protocols were developed, and the huge number of pharmacists and paramedics were trained to work in close collaboration with the public health experts and epidemiologist to enhance the effectiveness of emergency response.

The concept of health-care kit supplies was used to ensure rational and complete provision of the treatment needs. The whole process was aided with the development of an ungraded software (LSS upgradation to Pharmacy Information System (PIMS)) that linked the central warehouse with the regional units. Two types of customized kits were designed to cater different types of health-care needs and speed up the delivery and demand process (Bukhari et al., 2010).

Advances in Management of Humanitarian Crisis—Use of Technology and Involvement of Multidisciplinary Approach

The use of information technology can aid the pharmaceutical need in humanitarian crisis by making the processes more efficient and cost-effective by minimizing the wastage. Along with the classical use of logistic software such as Logistic Support Service by WHO, use of online access to dosing protocols, the of use of pictogram-based software has also been used to promote health literacy and to improve patient counseling.

In 2004, the International Pharmaceutical! Federation (FIP) in collaboration with its Military and Emergency Pharmacy Section (MEPS) with the Children Hospital of East Ontario (CHEO) started the Pictograms Project. The project is designed to provide easy to understand pictograms to provide information on the proper and safe use of medicines for use in illiterate patients or patients with language barriers as seen with immigrants and during the humanitarian aid projects. The project has wide application and was tested for its use during the Syrian refugee crisis when a number of immigrants who were non-English speaking women, children, and elderly reached Europe. The software is called PictoRx and the Arabic version was added to the software in 2015 to help the refugees. The previously available languages included English, French, Spanish, Dutch, Maori, German, Chinese, and Polish. PictoRx software is used to aid local pharmacists in routine dispensing by ensuring that patients receiving the medicines are provided with the proper counseling using pictograms and printed labels. It has been tested in several communities across the globe, including Germany, the recipient of largest number of Syrian refugees. The project has been granted WHO Grant on Patient Safety in 2010 and the 2009 Canada Post Community Literacy Award. An improved version of the software is developed by Applied Research and Innovation at the Algonquin College, O Ottawa, Canada. The software is available as online or offline version from the home page (www.fip.org/pictograms, https://www.fip.org/pictogramsoftware). The software provides printable material and labels for use as the counseling aids to the patient. Various modalities are provided in the software to provide comprehensive medicine information to the patient in the form of an information sheet as well as prescription calendar, which incorporates several medicines for a patient at one place (Vaillancourt et al., 2012).

Technological advances and their usage in humanitarian crises have led to the transformation of the aid process and added a greater diversity to its needs and resources attached. The modern plan of aiding in humanitarian crisis shifts from giving aid in kind to cash, collecting data for development purposes, private sector partnerships, use of blockchain, keeping the recipients right as priority, use of unmanned aerial vehicles, tracking and identifying aids including 2D-bar code, and Radio Frequency Identification tags and labels.

Simple and cost-effective aids are also in use along with the universal adoption of Track and Trace systems for tracking and identification of authenticity of pharmaceutical supplies in order to prevent the influx of substandard and falsified medicines in the supply chain (Rasheed et al., 2018).

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Strengthening Health Systems in Low and Middle-Income Countries Through Evaluating Cancer Medicine Prices, Availability and Affordability: A Case Study and Proposal

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Background

Nearly 1 in 6 deaths globally is due to cancer and almost 70% of these deaths occur are in low- and middle-income countries (LMICs) (World Health Organization Facts Sheet, 2018). The median survivals have improved as a result of chemotherapy (NIH, 2015). Among patients with metastatic breast cancer, the average life expectancy has increased over time by 13.2 months, however the lifetime medical costs have increased by USD 72,200/person (Howard et al., 2016). Given that low and middle-income countries (LMICs) account for the largest proportion of cancer deaths (Kanavos, 2006), the ever-increasing cost of cancer medicines is an important field to explore (Farmer et al., 2010). Cancer-related treatment services are available in more than 90% of high-income countries compared to less than 30% of low-income countries (World Health Organization Facts Sheet, 2018). In LMICs, only less than a third who develops cancer survive whereas in high-income countries the cancer survival rate is high (Gelband et al., 2016).

High priced chemotherapeutic agents are one of the major reasons leading to differences in survival rates in LMICs (Gelband et al., 2016). High prices of new cancer medicines impact on patients' access to medicines, however, the prices of the same medicines vary greatly between high-income countries (Howard et al., 2016). Vogler et al. (2016) surveyed the prices of 31 cancer medicines in 18 high-income countries. The results showed that the prices of cancer medicines varied, from 388 for high priced country to 28% for a low priced country (Vogler et al., 2016). Goldstein et al. (2017) systematically measured the differences in prices of eight cancer medicines between high-income countries (Australia, Israel, the United Kingdom, and the United States) and LMICs (China, India, and South Africa). The prices showed great variations and were lower in high-income countries than in LMICs (Goldstein et al., 2017). For instance, the 4-weekly prices of bevacizumab ranged from USD 543 to 6827 among high-income countries and USD 4364 to 19006 among LMICs.

Preliminary research in LMICs suggests that there are variations in cancer medicine prices impacting on affordability and medicine-buying capacity of patients and funders. However, these studies have methodological challenges, they have obtained pricing data from published resources and the empirical data is scarce on the issue (Salmasi et al., 2017; Goldstein et al., 2017; Sarwar et al., 2018). Also, no consideration of discounts and rebate or add-ons like taxes and distribution fees were taken into account. In this context, the prices reported in these studies may not reflect what actually patients and governments were paying for these medicines. The WHO/HAI methodology differs to the extent that it collects actual patient prices through a tested and validated methodology. The methodology has been used to collect data on other non-communicable (Mendis et al., 2007) and infectious diseases (Cameron et al., 2009), however, very little data has been collected on cancer medicine prices.

The growing number of expensive innovative cancer drugs impact on cancer care budget and patient access to innovative cancer drugs has become challenging. The economic impact of cancer is increasing as total annual economic costs of cancer in 2010 were estimated at USD 1.16 trillion (World Cancer Report, 2014). After including the long-term costs to patients and their families, the annual global cost of cancer is around USD 2.5 trillion (World Cancer Report, 2014). Generally, cancer treatment is expensive and is

either paid by the patients themselves, insurers or the government reimbursement and funding agencies (Howard et al., 2016). Due to absence of any special access schemes and government reimbursements in LMICs, many patients, have to bear the cost of the treatment. Naturally, with poor socio-economic condition most of the newer cancer drugs are out of reach for large vulnerable and neglected populations in LMICs and even the older cytotoxic agents remain only affordable to a minority of patients.

Measuring cancer medicines prices fits into the global agenda of making cancer drugs accessible and affordable. This is directly in line with the United Nations' Sustainable Development Goal of ensuring healthy lives and promoting well-being (UN, 2018). World Health Organization has also highlighted the need to measure cancer drugs pricing and affordability and this has been considered as a key priority area to explore. This proposal can advance knowledge regarding pricing and availability of medicines across a spectrum of LMICs. Availability of more accurate data on cancer prices would improve affordability and quality of life of the cancer patients. The project can aid in policy and decision-making related to drug affordability and accessibility, funding, and reimbursement of medicines.

Aims and Objectives of the Proposal

According to Global Initiative for Cancer Registries (GICR), only one in five LMICs have the necessary data to drive cancer policy (GICR, 2018). People living with cancer are often frail and vulnerable and their survival depends on factors including availability, affordability, and accessibility to treatment (WHO, 2018). The proposed study aims to gather data on prices, availability, and affordability data of cancer medicines using WHO/HAI methods (WHO/HAI, 2008). The long-term aim of this project is to form a global database on cancer drug prices. A model or tool would be developed by using test data from one country.

Proposed Research Design and Methods

Stage 1: Piloting of Study Methods

Sampling Plan

The proposed study methods are planned to be tested in one of the LMICs. The World Health Organization/Health Action International (WHO/HAI) methodology will be used to collect data on medicine prices, availability, and affordability (WHO/HAI, 2008). A systematic sampling method will be used to collect data across two sectors (public and private sectors) in at least six geographical regions of the country. The Area 1 will be a federal territory. Areas 2–6 will be within 400 km (one-day traveling) from the federal territory (including other major cities). These regions will be fairly representative of the whole country. In each area, one major city and four peripheral cities will be chosen. Data will be collected from public hospitals, and private specialist cancer clinics. In each area, the main government hospital in the major city and four other government hospitals in peripheral cities will be included. A private hospital and a private specialty clinic will be randomly chosen within a 5 km radius of the indexed government hospital. A list of public, private hospitals, and cancer clinics will be obtained from central authority.

Prices of Cancer Medicines

A sample of at least 40 cancer medicines will be evaluated. For each medicine, pricing and availability data will be collected on originator brand (sold by the company originally holding the original intellectual property) and lowest price generic (LPG, locally or internationally produced generic version) medicines. Public sector procurement prices will be collected centrally and from public facilities, while availability will be assessed only at the facility level. The medicines will be selected based on the following criteria: (1) medicines with high consumption rate in LMICs, (2) availability of international reference price (IRPs) for the selected medicine, and (3) authorized for oncology indications by relevant agency.

For each selected medicine, one presentation of the medicine will be determined (defined as a medicine in a specific pharmaceutical form, strength, and pack size (example—name: Cisplatin; brand: Cisplasol (Pfizer); strength: 50 mg; pack size: 1; dosage form: injection). A prerequisite for the inclusion will be availability of selected presentation in the same pharmaceutical form and the same strength in the selected LMICs. Either monthly or total treatment cost and daily dose of a tablet, or monthly vial for injection (or weight-based 2–4 weekly injections) will be used to compare results in this study. The total medicine dose required for 2–4 weeks of treatment will be calculated using average weight and a body surface area based on average height and weight in selected countries. The Workbook software calculated the median price ratio (MPR) for each medicine type in each sector only if the medicine will be available in at least six facilities. The MPR is the comparison of the local median unit price of the medicine with the median unit price in the Management Sciences for Health Price Indicator Guide (International Drug Price Indicator Guide, 2014).

Affordability of Cancer Medicines

The data on affordability of 40 cancer medicines will be collected. In this study, affordability will be assessed using both the impoverishing payment method and WHO/HAI methods (WHO/HAI, 2008; Niens et al., 2010). The impoverishing effect of a medicine is defined in terms of the percentage of the population that would be pushed below an income level of poverty lines when having to purchase the medicine. The most recent and widely recognized poverty indicator of USD1.90 per day by the World Bank will be used (WBG, 2018). This suggests that if the pre-payment income is above the USD1.90 poverty line and the post-payment

income falls below these lines, then purchasing the medicine impoverishes people. The impoverishment rates denote the percentage of the population that would become impoverished (Niens et al., 2010). The affordability of a medicine then refers to the percentage of the population that either already is or would remain above the poverty line when having to procure the medicine (Niens et al., 2010).

Qualitative Study

The qualitative interviews (the occurrence of saturation will dictate the final number) will be conducted with the key stakeholders (e.g., healthcare providers, policy makers, etc.) and the people living with cancer based on several visits. The point indicates the occurrence of saturation where the new information obtained from any further interview does not provide further insight into the issue. Semi-structured interview guide will be developed with a variety of open-ended questions. Theoretical sampling, which is a process of sampling individuals that can contribute to build the open and axial coding of the theory, will be used to select participants of the qualitative study.

Suitability of the Approaches and Methodologies

The WHO/HAI methodology on measuring medicines pricing, availability and affordability has been tested in over 50 countries (WHO/HAI, 2008). This methodology became a validated and internationally accepted means of collecting reliable evidence on medicine prices and availability and the work is published in *Lancet*, *PLoS Medicine*, and in the *Bulletin of World Health Organization*. The strength of qualitative research is its ability to provide complex textual descriptions of how people experience a given research issue (QRM, 2018). In-depth interview is one of the three most commonly used qualitative methods. In-depth interviews are optimal for collecting data on individuals' personal histories, perspectives, and experiences, particularly when sensitive topics are being explored. Pricing strategies and interventions are sensitive issues particularly in LMICs. Thus, qualitative approach (interviews) is a suitable method to achieve above objective. The proposed research will provide a strong foundation for the health systems in the target LMICs to build upon in their effort to ensure access to cancer medicines for all patients in a fair and equitable way.

Stage 2: Developing Global Pricing Database

In long term, the data collection tool developed will be used to collect data from over 100 LMICs. These countries will be selected based on the Global, Regional, and National Cancer Incidence, Mortality report (1990–2015) (GBDCC, 2017), as well as on the basis of cancer incidence and inclusion in the OECD Development Assistance Committee (DAC) list. The collection of large medicine prices and affordability data on yearly basis from LMICs would allow tracking the changes in pricing strategies and to plan interventions to promote availability and affordability of cancer medicines. Besides medical and health sciences, the project would attract researchers from public health, health economics, and social sciences with multidisciplinary approaches. There is a scope of involving data scientist and/or data analyst to extract and interpret the data, which requires both tools and methods from statistics and machine learning. This would help investigators and partners in LMICs to make better decisions about data sharing and technology enhanced models for capacity building in LMICs.

Research Impact

The proposed project has very high significance to create real change in LMICs. The project will have impact at several levels. The actual data on medicine prices in LMICs will help governments and funders negotiate better prices with drug companies to improve the affordability of cancer medicines. It will also support the decision makers and reimbursement and funding bodies to formulate policies to promote access, affordability, availability, and to ensure the transparent and efficient distribution of funds. Cancer medicines pricing is complex and using WHO/HAI methods would initiate and pave the way for larger and bigger cancer medicines pricing studies in this area. The project will improve the quality as well as the quantity of the LMICs data related to cancer medicine prices. Performing interviews with stakeholders as well as information from cancer pricing data will be helpful to build a data collection tool to capture information, which is otherwise not available just alone with pricing data. Academic papers, technical reports, evidence summaries, conference posters, and papers will be produced. Successful completion of this project will provide the basis for expanding the research work to over 100 LMICs. The open access database developed will be a valuable resource for LMICs, making available much-needed information for these countries, which suffer from inherent lack of accurate data relating to cancer treatment. This research will strengthen LMICs' health systems' ability to plan and deliver cancer treatment in an affordable and equitable way. It will also strengthen health systems negotiating strategies, thus, ensuring fair pricing and, consequently, improving access to affordable cancer medicines for patients in LMICs.

This research will strengthen the exiting collaboration with partners in the LMICs involved, through close working and exchange of ideas. LMIC partners will be included based on their expertise and relevant research work in the area of pharmaceutical pricing and policy. Ideally, co-applicants representing LMICs should be experienced researchers and the ones who understand the issues surrounding cancer medicine prices and affordability in LMICs.

List of Abbreviations

HAI Health Action International
GICR Global Initiative for Cancer Registries
LMICs Low- and middle-income countries
MPR Median Price Ratio
USD United State Dollar
WHO World Health Organization

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Definitions, Principles, and Concepts of Pharmacoepidemiology and Pharmacovigilance

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Introduction

Prescription Drugs

Prescription drugs are used to treat, maintain, or prevent symptoms of a medical disease or condition. All drugs available for use in humans have been deemed as "safe"; however, safety is a relative term. A safe drug is not one that is without risks, rather the known risks associated with that drug are deemed acceptable (Strom, 2013b). The likelihood of harm increases if a prescription drug is taken against clinical advice such as failing to complete the prescribed drug regimen; excessive use, that is, taking the medication at a higher dose, more frequently or for a longer duration than prescribed; medication error; taking a drug prescribed for another person; or, concomitant use with other prescription drugs, over-the-counter (OTC) products, illicit drugs, or alcohol.

At the time of prescribing, the health professional must consider the risk/benefit profile of any prescribed drug, according to the patient's unique clinical profile, including their likelihood of benefiting from prescription drug therapy. The prescriber must inform each patient of the potential risks associated with prescription drug use so the patient can make an informed decision about their health care. The evidence regarding the risk/benefit profile of a drug is generated from clinical trials, pharmacovigilance/pharmacoepidemiology activities or reporting systems once the drug is approved for prescription (or use as an over-the-counter drug) to the general public by a regulatory agency [e.g., US Food and Drug Administration (FDA) or the European Medicines Agency (EMA)].

In order for a drug to be approved for use in the general population, the drug developer must demonstrate the drug is both safe and effective in humans via clinical trials. Clinical trials enroll participants according to strict criteria to ensure the population is similar (homogenous) and to test the drug's safety and efficacy in a controlled environment to ensure consistency, including drug dose, patient adherence, and all effects the drug has on the patient. This is important as the human response to a prescription drug varies based on multiple factors which include (but are not limited to): age, sex, weight, genetic profile, ethnicity, diet and exercise. Consequently, enrolling a sample of homogeneous people will reduce the variability of the drug response to determine safety and efficacy. However, if the drug is approved for use in the community, the general population is likely to be diverse according to these factors in addition to their clinical profile, comorbid conditions, other prescription or illicit drug use, and alcohol consumption. Due to these diverse patient populations other side effects or adverse events may occur that were absent during the clinical trials (Box 1). The disciplines of pharmacovigilance and pharmacoepidemiology focus on identifying the risks, and potential benefits, associated with prescription drug use during clinical trial phases and in the real-world setting.

Box 1 Importance of patient population

Example demonstrating variation in patient response

A clinical trial demonstrated the response of 215 patients to a statin. The majority had a reduction in LDL cholesterol levels, which is the expected affect a statin should have on cholesterol. However, a small proportion of patients had an increase in their LDL levels. This example demonstrates the need for pharmacovigilance and pharmacoepidemiology surveillance, as we need to be aware of the range of responses a drug can elicit and recognize patient factors that may lead to a poor response to reduce, and ideally prevent, future ADEs.

What is the Process for a Prescription Drug to be Approved for Use in Humans?

In order for a drug to be prescribed to humans, its safety and efficacy needs to be proven for the symptom/condition of interest in preclinical phases such as testing in a laboratory through drug discovery and using animal models (Fig. 1). The preclinical phases may take several years to complete. If the drug progresses past the preclinical phase, it will be assessed in three clinical trial phases (Australian Government National Health and Medical Research Council Department of Industry Innovation and Science, 2015). Currently, the cost of developing a drug from preclinical phase to market is estimated between $1.3 and $1.7 billion (Strom, 2013a). Consequently, there needs to be strong evidence from preclinical phases that the drug has the potential to go to market and be profitable for the drug company.

There is ample evidence that describes and critiques the methodology, strengths and limitations of clinical trial phases. This section briefly summarizes the purpose, population size and duration of each clinical trial phase to demonstrate how pharmacovigilance and pharmacoepidemiology methods can complement clinical trial data. The population size and duration of each phase described in this chapter are a guide only, these factors will vary between trials based on the drug and population size of the disease/condition of interest.

Phase I—Determine Safety

Purpose: test the safety of a drug by documenting the frequency of adverse effects or adverse drug events (ADEs) occurring during the trial period (Box 2). Drug dose may be varied to determine whether higher doses are associated with adverse effects.

Population size: 20–80 healthy controls (persons that do not have the symptom/condition of interest).

Duration: few weeks.

Box 2

What about patient safety in clinical trials?

Clinical trials are often double-blinded to reduce the possibility of biasing the results. To ensure a drug is safe, and the patients in the intervention group are not harmed by a drug, a safety monitoring committee, (members are not involved in the clinical trial), will review any reported adverse event as they emerge to determine if the ADE occurs more frequently in the intervention group. Clinical trials may be abandoned early due to drug safety concerns.

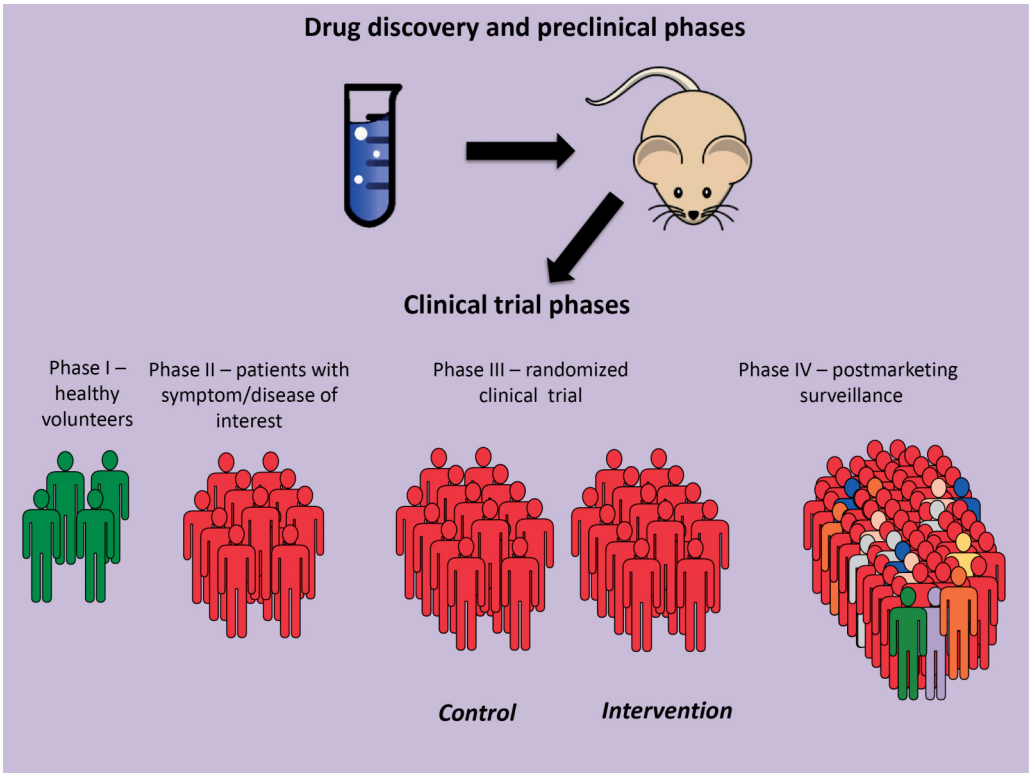

Figure 1 Summary of the process for a drug to be approved for use in the community.

Of note, some drugs (e.g., cytotoxic drugs) are not tested in healthy individuals as they may cause long term adverse health outcomes. Consequently, these drugs are tested directly on patients who require these drugs (e.g., cancer patients).

Phase II—Determine Efficacy

Purpose: test the efficacy of the drug, that is, whether the drug achieves its intended purpose in a clinical trial setting. For example, does an opioid analgesic reduce pain severity or symptoms? This phase continues to evaluate the drug's safety in patients with the symptom/condition of interest. Doses may vary to examine the therapeutic range and determine efficacy at higher and lower dosages.

Population: ≥100 people with the symptom/condition of interest.

Duration: few months.

Phase III—Demonstrate Drugs Superiority to Standard Care/Control Condition

Purpose: to demonstrate the superiority of the new drug or regimen (intervention) against standard care (control). Patients with the condition of interest are randomly allocated to the intervention or control group. The randomised allocation of patients to the different clinial trial conditions (intervention or control), is the primary strength of clinical trial methodology as it ensures both patient groups are similar, and any confounders, either known or unknown, will be comparable between the two groups. Clinical trials are generally double-blinded meaning neither the researchers nor the patients know whom is receiving the intervention versus the control, to minimize the risk of bias when recording results (Box 2). This phase continues to build upon evidence (from Phases I and II) regarding the frequency of adverse events and benefits. In order for a drug to be approved for use in humans (in the community, not only in a clinical trial) a drug must have five positive clinical trial results (a positive

result is when patients in the intervention group have a superior outcome compared to patients in the control condition). Although clinical trial evidence is regarded as compelling due their strict methodology, there have been instances where clinical trial findings have been misrepresented which was discovered after a drug was approved for use in the community. As a deterrent for this potentially fraudulent practice, drug companies have paid large fines and may be required to withdraw the drug from the market (Box 3).

Box 3

Clinical trial evidence controversy

There have been multiple controversies surrounding clinical trial evidence, A well-known example is from the UK in 2012 where GlaxoSmithKline was ordered to pay £1.9 billion in fines because they knowingly deceived the public to prescribe an antidepressant (Paxil; paroxetine] to children, despite their clinical trial data clearly showing paroxetine was ineffective for adolescent depression and increased suicidal ideation. An investigation was launched after a number of completed suicides were associated with paroxetine use. To ensure drug companies do not only report favourable outcome measures, all clinical trials must be registered prior to enrolling patients. During the clinical trial registration process, researchers must define all outcomes of interest including how each outcome will be defined and the time period of assessment. This increases the transparency of clinical trial findings, and ensures the outcome measures are objective, and not determined after data collection or analysis.

Population: ≥1000 people with the medical condition/symptom of interest.
Duration: few years.

Phase IV—Postmarketing Surveillance Studies

Purpose: to continue monitoring drug safety in the community after the drug is available for use (via prescription or over-the-counter). It is increasingly common for regulatory agencies to mandate additional drug safety data be collected during routine use in the community. This practice may eventually be part of the drug approval process across jurisdictions.

Population: general population with the symptom/condition of interest; size ranges from hundreds to millions of patients.
Duration: indefinite; potentially the life of the drug on the market.

What is the Point of Pharmacovigilance and Pharmacoepidemiology?

The utility of pharmacovigilance and pharmacoepidemiology have been demonstrated on a number of occasions where prescription drug use was associated with adverse drug events (ADEs) after it was approved for community use. The most infamous example is thalidomide. Thalidomide was developed in the 1950s by a West German pharmaceutical company, it was marketed as an anticonvulsive drug. It also made people feel tired and relaxed. In Germany in 1956, thalidomide was available as an over-the-counter drug (not requiring a health care professional to write a prescription) to reduce morning sickness in pregnant women. In the 1960s, doctors were concerned about the possible side effects of thalidomide including nerve damage in limbs associated with long-term use. There was also an increase in children born with phocomelia (a rare medical condition characterized by malformation of the limbs) and other effects included deformed eyes, heart, alimentary, and urinary tract; blindness; and deafness. The link between thalidomide and phocomelia was discovered, and thalidomide was withdrawn from the market.

Interestingly, in 1964, a health professional noticed thalidomide reduced leprosy symptoms. This association was proven in 1967 in a clinical trial conducted by the World Health Organization. Today, thalidomide is used to reduce the symptoms of leprosy, AIDS, and some cancers.

The thalidomide example demonstrates the dual nature of pharmacovigilance and pharmacoepidemiology, to examine the negative, and potentially positive, impact of prescription drug use for patients.

What is Pharmacovigilance?

Pharmacovigilance Definition

There is no one accepted definition of pharmacovigilance. The World Health Organization defines pharmacovigilance as:

> "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. . .. The aims of pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmers by providing reliable, balanced information for the effective assessment of the risk-benefits profile of medicines." (World Health Organization, 2017)

In short, pharmacovigilance monitors the frequency of adverse events that may be a consequence of prescription drug use. If the number of cases (patients) experiencing a common adverse event after using the same prescription drug is higher than expected, the relationship between drug use and the adverse outcome will be examined. Pharmacovigilance also includes the collection,

reporting, analysis, and dissemination of information regarding ADEs including off-label use, abuse, misuse, occupational exposure, or medication errors (Van Puijenbroek and Harmark, 2017).

The primary challenge of pharmacovigilance is the under-reporting of adverse drug events (ADEs). This underreporting occurs when a health professional suspects an adverse event is connected to prescription drug use, but does not report it to a pharmacovigilance monitoring system. In fact, under-reporting may be as high as 94%, meaning only 6% of ADEs are reported, which makes it difficult to examine the strength of the relationship between an ADE and prescription drug use (Hazell and Shakir, 2005).

Furthermore, there is considerable variation in the quality and detail of the reports made by health professionals (Carleton, 2017). Reports may be duplicates, where multiple health professionals report the same ADE or overreported where the frequency of a known ADE is more commonly reported than unknown adverse events, particularly if an adverse event has been reported in the media.

Another challenge of pharmacovigilance is knowing how to effectively communicate the risk of prescription drug use once an ADE has been discovered to both the general population and health professionals. For example, a clinician reads a letter stating there is an incidence of 0.09% of a particular adverse outcome occurring in patients taking that drug (Carleton, 2017). This is not meaningful to the clinician as there is a very small chance any of their patients will actually experience this outcome (9/10,000 people taking the drug). Clinicians are more interested in the individual patient's risk rather than the population risk. If the letter provided patient-specific risk information, such as an increased risk in the elderly, the clinician may alter their prescribing patterns or alert the patient to the risk of harm. It is believed that if clinicians benefit from the clinical impact of reporting ADEs then both the number and quality of reports would increase.

What is Pharmacoepidemiology?

There is no consensus on the definition of pharmacoepidemiology, it applies the methods of epidemiology to the content area of clinical pharmacology (study of prescription drug use in humans) (Strom, 2013a). The World Health Organization defines *epidemiology* as:

> "the study of the distribution and determinants of health-related states and events in the population, and the application of this study to control health problems." (World Health Organization, 2003)

Pharmacoepidemiology is a specific branch of epidemiology. The World Health Organization defines *pharmacoepidemiology* as:

> "applying epidemiological methods to studies of the clinical use of drugs in populations. A modern definition .... is the study of the use and (side) effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes." (World Health Organization, 2003)

The case of thalidomide discussed previously is only one example of a prescription drug causing harm once it has been released on the market. Recently, multiple studies investigated the number of drugs withdrawn from the marketplace due to safety concerns (Food and Drug Administration; La Rochelle et al., 2016; McNaughton et al., 2014; Onakpoya et al., 2016; Procon.Org, 2014; Siramshetty et al., 2016). The frequency of prescription drug use and their associated harms led to the development of the discipline of pharmacoepidemiology (Strom, 2013a).

Adverse Drug Events: The Burden to Patients and Society

From the definitions of pharmacovigilance and pharmacoepidemiology, it is clear that these disciplines focus on prescription drug safety, and frequency of potential harms for patients. This section will focus on the impact of the harms called ADEs, from patient and health care system perspectives.

An ADE is a "harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future [use] and warrants prevention of specific treatment, alteration of the dosage regimen, or withdrawal of the product" (Edwards and Aronson, 2000). There are six types of ADEs:

1. **Dose-related:** the event occurs from a particular dose threshold.
2. **Nondose related:** the event occurs regardless of the drug dosage.
3. **Time-related:** the event occurs after taking the prescription drug for a specific time period.
4. **Dose-related and time-related:** the event occurs after taking the drug at a particular dosage for a specific time period.
5. **Withdrawal:** the event occurs after a patient has stopped taking the prescription drug.
6. **Failure of therapy:** the event occurs but does not effect the medical condition or symptom it was intended to treat.

Historically, drug companies and clinicians have reported ADEs. In practice, clinicians rarely believe ADE reporting is one of their primary duties (Carleton, 2017), consequently many ADEs are underreported, despite patients presenting to a health professional as a consequence of an ADE. It is mandatory for drug companies to report all ADEs.

Burden of Adverse Drug Events

ADEs are recognized as a leading cause of morbidity and mortality globally. The incidence of ADEs range from 0.2% to 65% depending on the population and jurisdiction of interest. ADEs cost the health care system $77 billion annually (Johnson and Bootman, 1995). The drugs most commonly associated with ADEs include: anticoagulants, systemically administered antibiotics, diabetes agents, opioid analgesics, antiplatelets, renin-angiotensin system inhibitors, antineoplastic agents, and sedative/hypnotic agents (Shehab et al., 2016).

Despite the frequency of ADEs, it is estimated 20%–70% may be preventable (Strom, 2013a), that is the drug dose/administration route was inappropriate for the medical condition/symptom; standard laboratory tests were not performed; medication error; excessive amount taken; or known drug–drug interaction or allergy (Classen et al., 1997). The action required to treat an ADE varies from no intervention (ADE will resolve spontaneously) through to requiring other medication(s), emergency department presentation or hospitalization; however, some ADEs are fatal.

Few studies have quantified the burden of ADEs in the outpatient setting (Bouvy et al., 2015). However, it is reasonable to assume that because ADEs are the most common form of iatrogenic harm, the cost to the outpatient system would be considerable.

The frequency of ADEs resulting in an emergency department presentation is increasing. Over 8 years, the number of presentations increased 87% (5.2–9.7/1000 persons); of these, 27% resulted in a hospitalization (Meier et al., 2015). Of note, 62% of emergency department presentations for ADEs were preventable (Meier et al., 2015).

Of the $77 billion ADEs cost the health care system annually, $2.6–$47.4 billion are due to hospitalizations (Bates et al., 1995, 1997; Hafner et al., 2002; Johnson and Bootman, 1995). Annually, up to 3.5% of hospitalizations are due to ADEs and 10% of hospital inpatients experience an ADE (Bouvy et al., 2015). An ADE hospitalization is associated with a significantly prolonged length of in-hospital stay, increased economic burden and increased risk of death (Classen et al., 1997). Annually in Europe, 84 million patients are hospitalized due to an ADE. In the US, ADEs account for >32 million hospital visits annually (Classen et al., 1997).

The potential savings to the health care system in reducing the number of preventable ADEs was recently demonstrated in Germany. The cost of ADE-related hospitalizations was €2.3 billion annually (Meier et al., 2015). However, this cost could be reduced by €1.3 billion if preventable admissions were avoided.

It is difficult to quantify the number of deaths which may be attributed to ADEs. In relation to inhospital deaths due to ADEs, in Europe, the rate ranges from 0.05% to 0.5%; equating to 42,000–419,000 deaths annually (Bouvy et al., 2015). The crude mortality rate for ADEs during a hospitalization is 3.5% (Classen et al., 1997). Patients who develop an ADE inhospital are almost twice as likely to die compared to patients who do not develop an ADE (Classen et al., 1997).

This section has demonstrated the frequency and burden of ADEs on patients and the health care system. Consequently, a better understanding of the relationship between prescription drug use and adverse drug reactions is now an urgent goal of the public health system.

Common Pharmacovigilance and Pharmacoepidemiology Data, Methods and Study Design

The most important stage of any research study is the planning stage, where you develop the research question, identify the appropriate data, (and its limitations), study design, outcome measure(s) of interest, define outcome measures, consider the impact of any explanatory or confounding variables (especially if they are not measured in the data source), determine how to interpret the results accurately and the potential limitations of study findings. The methods for pharmacovigilance and pharmacoepidemiology overlap considerably, so the data, methods, and study designs for both disciplines will be presented together.

Data

Preclinical Study Data

Data from preclinical studies investigate whether a drug has major organ toxicity, chronic toxicity, carcinogenicity, mutagenicity (capable of inducing genetic mutations), and teratogenicity (capable of producing physical defects in an embryo) (Waller, 2010). These data generally determine whether the drug will have extreme adverse events in humans, they do not necessarily demonstrate safety. Generally, for a drug to progress to use in humans, they will not induce any of these outcomes. In rare circumstances, some adverse outcomes may be acceptable based on the intended patient population. For example, a drug with teratogenicity properties may be deemed safe for use if the prescription drug is intended for use exclusively in men.

Clinical Trial Data

Clinical trial data may be analyzed to examine the frequency of particular adverse events. Data from Phase III clinical trials may be used to determine whether adverse events occur more frequently for the new intervention drug against its comparators. However, these data will not detect adverse events that: are rare, develop after prolonged use of the drug, occur in particular populations (e.g., elderly and pregnant women) or the consequence of inappropriate use of the medication, such as drug nonadherence or taking greater than anticipated doses, or combining use with other prescription or illicit drugs, or alcohol. **Table 1** describes summary of the strengths and limitations of the clinical trial methodology.

Table 1 Clinical trials methodology: strengths and limitations

Strengths	*Limitations*
Randomized patient allocation	Short-time period of assessment
Specific predefined outcome measures	Artificial conditions (i.e., increased patient monitoring and adherence) which may bias results
Strict inclusion criteria	Homogenous patient sample reduces generalizability of results
Double-blinded	Drug may not be tested against other available drug treatments
Multiple phases to examine safety, efficacy, and/or superiority to standard care	

Postmarketing Surveillance Data

Postmarketing surveillance data focus on prescription drug use after it is available for use in the community. The cornerstone of pharmacovigilance and pharmacoepidemiological research are postmarketing surveillance data as they demonstrate whether a patient has been exposed to the drug, and adverse health effects that required a health care interaction. These data are generally de-identified which means they contain basic patient information such as date of birth, sex, limited socioeconomic information; and content data for drug databases including drug name, quantity dispensed, and prescribed daily dose (i.e. the amount of the prescribed per day by the clinician). However, content data for each health dataset varies between jurisdictions and health care systems.

The ability to examine a drug's safety profile depends on the rate of uptake. If a drug has a slow uptake then it may take years to examine the safety profile and potential adverse events. Alternatively, if there is rapid uptake, and the drug induces an adverse effect, then many people may experience ADEs while the safety of the drug is being investigated. These data may include: prescription data, pharmaceutical claims data, or electronic health records.

Prescription data are generated by general practitioner clinics, where patients present with a symptom/condition and a health care professional prescribes a drug to resolve the issue. However, these data generally overestimate the number of people taking prescription drugs as not all patients prescribed a drug will get the prescription filled at a pharmacy. A patient may decide not to take the drug or symptoms may resolve without taking the drug.

Pharmaceutical claims data are generated by pharmacies, where patients have filled their prescription. These data are more accurate than prescription data; a filled prescription is commonly used as a proxy for drug exposure, as it is assumed if a person pays for a prescription to be filled they are likely to take the drug.

Electronic health care records are data that combine health records from multiple sources, which may include prescription, pharmaceutical claims, disease registries, and outcomes data (discussed below), depending on the jurisdiction (Black et al., 2015). These data are increasingly used to detect adverse drug reactions (Black et al., 2015).

Outcomes Data

Outcomes research may be defined as the "study of the end results of health services. . .intended to provide scientific evidence relating to decisions made by all who participate in health care" (Roger, 2011). Examples of outcomes data include hospitalization, emergency department, health practitioner consultations, mortality data, or disease/drug registry. Apart from registry data, all other datasets are routinely collected meaning they are collected for a purpose other than research such as for reimbursement. These data include limited patient demographics and content data relevant to reimbursement arrangements. For example, hospitalization data include all diagnoses for which a patient is treated for during their episode of care as the hospital is only reimbursed for provided treatment. The record will not contain a diagnosis for a medical condition if it was not treated during the hospitalization. Similar to pharmaceutical data, the particular variables contained in each dataset described in this chapter vary across jurisdictions.

Data Limitations

These datasets have varying degrees of completeness, based on the health care system and jurisdiction. For example, in the US health insurance is provided by employment and health insurance is generally required to receive in-hospital treatment. Consequently, hospitalization data are limited to persons who are employed or can afford health insurance and is not representative of the entire US population. In contrast, Australia has a universal health care system which means all residents/citizens have access to treatment, regardless of health insurance status.Prior to using any health dataset, it is important to familiarize yourself with the features of the health system and limitations.

Methods

Levels of Evidence

To determine the safety, or risk, of using a prescription drug, study findings (referred to as evidence) are reviewed by clinicians and researchers. However, different studies can present contradictory findings. For example, one study may find that drinking red wine

Figure 2 Levels of evidence.

reduces the risk of coronary disease, whereas another study may find any alcohol consumption increases the risk of cancer. In order to determine which study findings are more robust, we judge the study based on levels of evidence (Fig. 2).

The World Health Organization categorized the various methods and study designs for pharmacovigilance studies (World Health Organization, 2007). The themes and study designs included in this chapter are based on the WHO framework and include:

- Passive surveillance: spontaneous adverse reports, case reports, and case series.
- Active surveillance: sentinel sites, medicine event monitoring, and registries.
- Comparative observational studies: cross-sectional study, case–control study, and cohort study.
- Descriptive studies: natural history of disease and drug utilization study.

Passive Surveillance

Spontaneous Adverse Reports

The World Health Organization defines a spontaneous report as

> "an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization that describes one or more adverse drug reactions in a patient who was given one or more medicinal products which was not derived from a study or organized data collection scheme." (World Health Organization, 2007)

The purpose of this system is to generate a safety signal to determine whether there is a relationship between a drug and an adverse reaction, which was previously unknown or incompletely documented (Breckenridge, 2015). These reports can also provide information regarding at-risk groups, risk factors and clinical features of known serious ADEs (World Health Organization, 2007). The rate of which spontaneous reports are reported depend on multiple factors including time since the launch of the medicine, pharmacovigilance-related regulatory activity, media attention, and the indication for the drug (Group, 2001; Heimann, 1980; Sondheimer, 1988; Weaver et al., 1991).

Case Reports

A case report describes a series of events that happened to a single patient after being exposed to a particular prescription drug, and usually includes the patient's outcome(s) and any clinically relevant details.

The purpose of such reports are to increase the awareness of a potential ADE, including drug interactions, as well as describe the treatment a patient received and the outcome to guide other clinicians who encounter a similar case.

However, as these reports usually focus on a single patient, they should not be the sole source of information to make decisions about drug safety. Rather these reports can be the first piece of evidence for a specific ADE, which will then be tested in a rigorous study design with a larger number of patients. However, there are two scenarios in which more rigorous testing may not be required. Firstly, if the outcome is rare and consistent with the drug profile effect or known side effects of that prescription drug. Secondly, when the disease course is well established and the treatment causes an unexpected change in the disease trajectory, including if the patient returns to their previously treated state after the drug is withdrawn and treatment can be repeated without any side effects. For example, if a patient overdoses on methadone and naloxone is administered the patient will regain consciousness with no side effects, and if they overdose again, naloxone may be administered again.

Case Series

Case series either describe patients with the same drug exposure and their clinical outcomes are reported; or, the antecedent exposure will be described for a group of patients with the same clinical outcome. The evidence for a case series is stronger than case reports; however, any findings of case series should also be tested in a rigorously designed study with many patients.

Active Surveillance

Sentinel Sites

Surveillance at a sentinel site involves reviewing all medical records or interviewing patients and/or physicians at key sites to obtain data on any adverse event (World Health Organization, 2007).

The purpose of this methodology is to target key sites to ascertain complete information regarding patient prescription drug use, any adverse event or side effect, detailed patient demographics and the nature of prescription drug use at the time of the adverse event. These data are examined more systematically than spontaneous reports. The limitations of this approach are: it is based on patients who present to a key site (selection bias), includes a small number of patients and increased costs.

Medicine Event Monitoring

This method is cohort-based, prospective and observational. Patients are identified from any prescription data source including electronic or health insurance claims. A single prescription or series may be collected over the period of monitoring. A follow-up questionnaire is then sent to each prescribing physician and/or patient at predetermined time intervals to obtain outcome information. The information derived from the questionnaire complements the data obtained via the data source, such as indication for treatment, dosage regimen and duration, reasons for discontinuation, and medical history.

Registry

Registry data are organized around a specific drug, drug class, or medical condition (see Section "Outcomes Data" for information regarding registry data). Generally the drug or condition of interest is quite rare. These data are invaluable to determine whether an ADE occurs in one of these specific populations. Data are collected via standardized questionnaires prospectively. However, as these data are not routinely collected, data quality may vary across patients, particularly if there are multiple enrolment sites. Registries may opt-in and as a consequence may not be representative of the entire population. However, studies have demonstrated the representativeness of patient demographics and outcomes for a registry cohort may differ from the entire patient population diagnosed with that disease or using a prescription drug. If the two populations (registry and general community) characteristics are disparate, the generalizability of study findings is unclear (Catalano et al., 2013; Curtis et al., 2009; Gomez et al., 2015; Knapstad et al., 2016; Reeves et al., 2012; Zhang et al., 2017).

Comparative Observational Studies

Cross-sectional Study

A cross-sectional study involves collecting data on a group of people at a single time point (or a specified time period), regardless of exposure, or disease status. This is often referred to as a "snapshot" to see what is happening at a given moment of time. This method is predominantly used to gather data for surveys or ecological analyses to determine the prevalence of disease or examine trends over time. Studies are also used to examine crude associations between exposure and outcome in ecological analyses.

Ecological studies examine trends in an exposure and/or drug-related outcome. For example, I wrote an ecological paper examining Australian prescription opioid utilization and number of opioid-related hospitalizations and deaths (Blanch et al., 2014). This paper clearly demonstrated that as prescription opioid utilization increased, so too did the number of opioid-related hospitalizations and deaths. However, as these data are aggregated, it is unclear whether the patients prescribed opioid analgesics are those experiencing the opioid-related adverse outcome. These studies may provide evidence and generate questions that are then examined using person-level, linked, pharmaceutical drug and outcomes data. Secular trends can be compared across multiple regions within one jurisdiction; longitudinally; and/or across jurisdictions.

Case–Control Study

A case–control study includes persons who have been exposed to the drug (cases) and those who have not (controls). In general, the purpose of a case–control study is to compare the frequency of an outcome between these two groups to determine whether persons taking a prescription drug have a higher or lower chance of that outcome than persons not taking the drug, or taking a different drug in the same therapeutic drug class.

Cohort Study

A cohort study involves enrolling/identifying a group of people defined by a specific characteristic who are followed over time. Cohort studies generally compare exposed patients to unexposed patients, but they can also compare one exposure to another. An association is identified when the outcome occurs more frequently in the exposed than the unexposed group. Comparators can be persons not exposed to the drug, or taking a drug from the same therapeutic class. Yet, due to the nonrandom assignment of groups, increased attention must be given to the selection of appropriate comparators.

Routinely collected pharmaceutical data may be used to identify a cohort of persons all exposed to the same drug, who may then be observed for years to examine the long-term side effects of that prescription drug use. If these data include all drug dispensings, researchers use other prescription drug use as a proxy for comorbidities to calculate the risk of a specific outcome occurring based on the presence of disease.

Descriptive Studies

Descriptive studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of prescription drug use.

Natural History of Disease

Epidemiology originally focused on the natural history of disease, including characterizing the patient population for a specific disease; determining the distribution of disease in particular populations; and, population prevalence and incidence rates of outcomes of interest. These studies often include a description of adverse events which provide a context to interpret the occurrence of events described in spontaneous reports.

Drug Utilization Study

These studies describe how a drug is marketed, prescribed and used in a population and may also examine how these factors influence patients' clinical, social, and economic outcomes. These studies may stratify the cohort based on important characteristics such as age (elderly, children); presence of disease (diabetes, cardiovascular disease); sex, or concomitant drug use. These studies also consider the effect of drug policy changes, media attention, or regulatory action on utilization; adherence to guidelines; investigate potential for inappropriate use of drug; burden of disease; and economic analyses.

Limitations of Pharmacovigilance and Pharmacoepidemiological Studies

The primary concern of all pharmacovigilance or pharmacoepidemiological studies is identifying an association between prescription drug use and an adverse outcome, when no such relationship exists (Strom, 2013b). Another concern is providing false reassurances about a drug's safety. These risks are minimized by appropriate study designs based on the limitations of the original dataset, and appropriate and responsible interpretation of the results obtained (Strom, 2013b). The limitations of all study designs covered in this chapter are summarized in **Table 2**.

Challenges in Pharmacovigilance and Pharmacoepidemiology Studies

Signals

The primary challenge of pharmacovigilance and pharmacoepidemiology is to determine whether there is a clear signal demonstrating a previously unknown (beneficial or adverse) relationship between prescription drug use and an outcome.

A signal is defined as "information that arises from one or multiple sources which suggests a new potentially causal association or new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions" (Hauben and Aronson, 2009).

There are no clear guidelines on how to act once a signal has been established. A few factors contribute to deciding what action to take: the seriousness of the suspected ADE; condition being treated; and, alternative drugs available for treatment. Each jurisdiction may respond uniquely to signal information and enforce different outcomes. For example, one country may withdraw a drug from use, another country may issue a black box safety warning.

Future Directions for Pharmacovigilance and Pharmacoepidemiology

As described previously, pharmacovigilance and pharmacoepidemiology rely on data to make associations between drug use and outcomes, yet underreporting increases the challenge of making these associations. To overcome this issue, the utility of other data sources and datasets to complement more traditional methods are being explored.

Social Media

The Internet has proven to be an effective method for patients, and caregivers, to research medical conditions and adverse events associated with prescription drug use indications and side effects. It has also connected many patients and caregivers via health social networks. A recent survey by the Pew Research Centre indicated that 34% of caregivers and 20% of patients either read or watch someone else's commentary or experiences online. Also, 11% of caregivers and 6% of patients share their experiences and post questions online (Fox, 2011). Social media analyses are becoming more common to investigate ADEs, and has been used by popular pharmacovigilance resources including the FDAs adverse event reporting system (Sarker et al., 2015). In recent years, pharmacovigilance and pharmacoepidemiological research activity has focused on how to best utilize social media posts to better understand prescription drug use and ADEs.

There are many strengths associated with this emerging methodology. Firstly, posts are read in real-time, so may identify disease outbreaks quicker than more traditional surveillance methods (Sarker et al., 2015). Secondly, given the ease of Internet access,

Table 2 Pharmacoepidemiological and pharmacovigilance study methods (World Health Organization structure)

Study design	*Strength(s)*	*Limitation(s)*
Passive surveillance		
Spontaneous reports	• Establish a signal for a previously unknown association between prescription drug use and an adverse outcome.	• Limited information regarding patient demographics and nature of prescription drug use at time of event. • Extremely small sample size ($n = 1$).
Case series	• Patients are typical of those with the exposure or disease. • Quantifying incidence of an adverse reaction. • Increase awareness of ADEs that may not have been apparent during clinical trial phases.	• Difficult to determine if the description of the patients are unique to the exposure or outcome.
Active surveillance		
Sentinel sites	• Efficient for drugs used mainly in institutional settings such as hospitals and nursing homes. • Helpful in identifying risks among patients taking orphan drugs.	• Selection bias – only includes persons presenting for treatment at that site. • Small sample size. • High costs associated with employing staff to complete data abstraction or interviews.
Medicine event monitoring	• Potentially includes entire population in country or region. • Information from patient and prescriber perspectives. • Incidence rates available to allow for precise calculation of risk factors.	• Poor physician/patient response rates for questionnaire.
Registries	• Large sample size of patients with a rare disease or prescription drug use. • Questionnaires provide opportunity to collect detailed clinical and disease history.	• Quality of self-report data may vary by individual and enrolment site. • Opt-in registries may not be representative of the entire patient population.
Comparative observational studies		
Cross-sectional study	• Relatively quick study design to examine trends between the exposure and outcome(s) of interest.	• Temporal relationship between exposure and outcome cannot be assessed.
Case–control study	• Study multiple causes of a single disease, as the same cases and controls can be used to examine multiple exposures and potential risk factors. • Studying relatively rare diseases, as it requires a sufficient number of cases with the disease. • Study rare diseases with a smaller sample size than required for a cohort study.	• Information obtained retrospectively. • Past exposure information is self-report and generated by abstracting medical records, administering questionnaires or interviews. • Validity of self-report data are unclear. • Difficult to appropriately select controls and may lead to selection bias, which may lead to incorrect conclusions.
Cohort study	• Provide evidence when a randomized clinical trial is unethical or unfeasible. • Representative study population. • Relatively cheap and cost-effective compared to other study designs. • Examine multiple potential outcomes from a single exposure.	• May require large sample sizes to study uncommon outcomes. • Prospective cohort drug studies may include a prolonged time period to study delayed drug effects. • Unmeasured confounding may impact on results/interpretation.
Descriptive studies		
Natural history of disease	• Quantify the disease course, particularly important for rare diseases. • Examine the impact of therapy on patient population over time.	• Long observation period.
Drug utilization study	• Examine trends over an extended time period. • Determine prevalence of prescription drug use. • Examine frequency of adverse events (to accurately interpret spontaneous reports).	• Lack of clinical outcomes data for patients using drug.
Analyses of secular trends	• Provide evidence for or against a specific hypothesis.	• Studies use aggregated data, so minimal information on patients are provided. • Unable to control for confounding factors. • Unclear if patients took the medication as instructed. • Unclear if same patients who were prescribed the medication are the people experiencing adverse outcomes.

affordability and the prevalence of use, social media analyses may include data from people that are unable to access health care through formal channels (Velasco et al., 2014). Also, these data are global, not confined to a specific region. Further, it may include experiences of patients who are typically excluded from clinical trials such as those with rare diseases, pregnant/lactating women, geriatrics or patients with comorbidities (Stricker and Psaty, 2004). Thirdly, social media posts can be used to validate or reject signals that have arisen in other reporting systems (Sarker et al., 2015).

The limitations of social media include the issues of credibility, recency, uniqueness, frequency, preciseness, and salience of these data (Abbasi et al., 2014). For example, Twitter is one of the most utilized social media platforms, yet due to the 140-character text limit information regarding ADEs will be superficial and may be vague, so if someone says they are sleepless using a sedative, is it an ADE or the reason for the sedative use? (Nikfarjam et al., 2015; Sarker et al., 2015). In the fields of pharmacovigilance, natural language processing analyses free-text fields, generally created by health care professionals, to ask important health care questions. Challenges for this methodology include the source data being free-text and entered by multiple people, information varies between entries; misspellings; and, nonmedical, descriptive terms may be used to discuss health issues; these issues are exacerbated when the general public enter these data (Sarker et al., 2015). For example, current natural language processing techniques are less effective in identifying relevant concepts in shorter texts, such as tweets. Consequently, this method is being refined for the purpose of applying it to social media entries such as Twitter or Facebook (Owoputi et al., 2013). See a review by Luo for further information (Luo et al., 2017). A recent systematic review found many studies use data that are not publically available so attempting to compare methodologies to identify ADEs are not possible (Sarker et al., 2015). Also, evaluation and development of systems have progressed in different directions without the development of any standard evaluation criteria (Sarker et al., 2015).

Patient-Reported Adverse Drug Events

Historically, drug companies and health professionals report ADEs. Reporting is mandatory for drug companies and voluntary for health professionals (Sarker et al., 2015). However, patient reporting systems are becoming increasingly popular across jurisdictions and may assist in combatting under-reporting as it would take the onus away from health professionals. In the European Union, after introducing patient reporting systems the number of recorded ADEs increased 30% (Inácio et al., 2017).

Spontaneous reports from patients are more detailed than clinician reports and include temporal facts; reports about different drugs and system organ classes (such as the central nervous system, general disorders, and administration site conditions) (Alves et al., 2013; Avery et al., 2011; Harmark and Van Grootheest, 2008; Hazell et al., 2013; Pal et al., 2013; Silverman, 2009; Van Hunsel et al., 2011). The patient perspective also describes the impact and severity of ADEs on daily life, including quality of life (Inácio et al., 2017; Van Balveren-Slingerland et al., 2015). Despite the unique utility of this information it is an underused resource as patient reporting of ADEs is rare in most countries.

Of note, there were no qualitative differences in information provided by patients and health care providers (Inácio et al., 2017). As expected, media attention led to a spike in patient reports received by the pharmacovigilance authority (Inácio et al., 2017). The opportunity to report ADEs online also increased the reporting rate in patients (Inácio et al., 2017). However, the tolerability and seriousness of ADEs may vary based on the perspective of the reporter. For example, many ADEs would be regarded as nonserious according to internationally agreed professional criteria, while nevertheless being intolerable, considered serious and causing severe problems for patients (De Langen et al., 2008; Frankenfeld, 2004). The evidence from these studies demonstrate that allowing patients to report ADEs adds new information which complements existing data from pharmacovigilance systems. This information can contribute to improved decision-making processes in regulatory activities.

The main limitation to patient-reported ADEs is the lack of patient awareness that these pharmacovigilance systems exist and they can contribute valuable information. For example, a patient spontaneous reporting system has been in operation in the UK since 2005, yet only 9% of patients are aware they could report an adverse event (Inácio et al., 2017). The longer a system has been in place, the higher the level of patient awareness and engagement (Inácio et al., 2017). There could also be potential participation bias, meaning the patients that report ADEs may not be representative of the entire population taking that drug. There is also a limit to the ADEs a patient can report, that is patients cannot report ADEs that require a medical test to confirm. Similarly, patient reported ADEs are not confirmed medically, so the pharmacovigilance system may need to introduce an addition system to follow up these reports.

Conclusions

This chapter introduced the key components, definitions, and principles of the disciplines of pharmacovigilance and pharmacoepidemiology, which should be considered whether embarking on a new research study or reviewing previous studies in this field. The most important aspects of pharmacovigilance and pharmacoepidemiology is understanding the data used to assess the association between prescription drug use and an outcome, whether adverse or beneficial; and, understanding the limitations of the study design chosen to answer the research question. It is important to realize all prescription drug use is associated with harms, but an independent body has reviewed the evidence and deemed the known harms to be acceptable. It is important to investigate if any new harms emerge after the drug is approved for used in the community, to ensure we minimize the risk of avoidable adverse drug events.

Glossary[1]

Adverse drug event (ADE) an untoward outcome occurring during or following clinical use of a drug.
Case–cohort study a study design that compares cases (persons with the relevant medical condition/exposure of interest) to controls (persons without condition or exposure). These studies may examine different exposures to disease, or quantify the risk of a particular outcome.
Case report describes a patient's experience after prescription drug use. Case reports may be the first piece of evidence indicating an association between drug exposure and an ADE.
Cohort study a study design that identifies a defined population and follows them forward in time, examining their frequencies (e.g., incidence rate) of disease.
Confounding variable a variable, other than the risk factor and outcome measures, that is independently related to both the risk factor and the outcome and may create or mask an association.
Cross-sectional study examines exposure and outcomes in a population at one time point.
Descriptive studies describe drug utilization or outcomes in a population.
Drug any administered substance that originates outside the human body (exogenous) and exerts a physiologic effect.
Drug effectiveness a study examining whether, in a clinical setting, a drug has the intended effect upon prescribing it.
Drug efficacy a study examining whether, in a clinical trial setting, a drug has the intended effect upon administration.
Drug utilization examining the "marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (definition from World Health Organization).
Drug utilization (study) studies quantifying the use of a drug including current use, trends, and the time course of drug use at national, regional, local, or institutional levels.
Ecological study examine trends in prescription drug use or disease events over time and/or across jurisdictions and correlate them with an expected outcome.
Exposure use of a prescription drug.
Generalizability of results whether a study cohort is representative of the entire population; if so, then study findings can be used to describe use/outcome(s) for the entire population. Factors that impact on the generalizability of results may include patient sex, age range, socioeconomic status, other comorbid conditions, etc.
Incidence rate measure the frequency of how often a medical condition occurs. The formula to calculate the incidence rate is: number of new cases of disease in a particular time period and population, divided by the number of people in that population.
Observational studies researcher examines (observes) real world prescription drug treatment and outcomes using data that reflect actual treatment patterns.
Over-the-counter drug drug available from a pharmacy that does not require a prescription from a health professional.
Pharmacoepidemiology the study of drug use and its effects in the community.
Pharmacovigilance the identification and evaluation of drug effects in the clinical trial and community settings.
Population-based database or study an identifiable group of people whose medical care (e.g., prescription drug dispensings) are included in a database. This allows one to determine incidence rates of diseases and quantify health care interactions in a population. Population-based studies are a representative sample of all patients using a prescription drug in the real world, particularly compared to clinical trials.
Post-marketing surveillance study of drug use and effects after it is released onto the market (available for use in the general community).
Prospective study studies that enroll patients and examine an event of interest (e.g., prescription drug use or outcomes) that will occur in the future (i.e., event may not have occurred at time of study enrolment).
Retrospective study studies that enroll patients after the event of interest (prescription drug use or an outcome) has occurred.
Spontaneous reporting systems collect unsolicited clinical observations regarding prescription drug use and outcomes that originate outside of a formal research study.

[1] Please note: all glossary terms are defined in relation to the fields of pharmacovigilance and/or pharmacoepidemiology. However, many of these terms will describe terms that are used in other disciplines and may have a slightly different focus.

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Descriptive and Drug Utilization Studies

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Introduction

Medicines have a major role in the management of many conditions and illnesses. However, in order to achieve their desired outcomes, medicines must be used safely and appropriately in a manner that is consistent with best available evidence. In practice, there is often wide variation in medicine prescribing and use between prescribers, health services, practice settings, jurisdictions/provinces, countries, and regions. Although medicines can have many benefits, when used inappropriately, the negative outcomes associated with medicines use can have considerable health and economic consequences. This is a global issue of concern as worldwide, it is estimated that more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take them correctly (World Health Organization, 2002).

The World Health Organization (WHO) first defined the concept of rational medicines use in 1985 as "patients need to receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (World Health Organization, 1985). Many countries have subsequently adopted this principle in their own versions of policies on medicines use. For example, one of the central objectives of Australia's National Medicines Policy is Quality Use of Medicines (or QUM). This refers to the judicious, appropriate, safe, and efficacious use of all medicines (Department of Health and Aging, 1999) with appropriate use referring to use in a manner that avoids misuse, abuse, underuse, and overuse (Spinewine et al., 2007).

Medicine or drug utilization studies, as they most often referred, aim to increase our understanding of how medicines are being used in clinical practice, and ensuring that they are used safely and effectively, in a rational manner. Given the extent of medicines use in society, drug utilization research represents an extremely important and large research field. There are a number of approaches to undertaking drug utilization research studies, which have evolved in complexity. This chapter provides an introduction to the key concepts central to understanding drug utilization studies and highlights the scope of this field of research.

What are Drug Utilization Studies?

The importance of undertaking drug utilization studies was first highlighted in the mid–late 1960s following the pioneering work of researchers in Europe and the United Kingdom (World Health Organization, 2003a). Arthur Engel and Pieter Siderius' seminal work

Table 1 The medical, social and economic aspects of drug utilization research proposed by Baksaas and Lunde (Baksaas and Lunde, 1986; Wettermark et al., 2016)

Medical	• Benefits: efficacy/effectiveness of drugs in preventing, relieving and eliminating diseases or their symptoms and complications. • Risks: short-term and long-term adverse effects, special risk factors associated with genetics, disease and environment, nutrition, age, sex, pregnancy, lactation, etc. • Benefit/risk ratio: to which extent may inappropriate prescription (indication, choice, dosage, duration) and use (compliance) reduce benefits and increase risks?
Social	• Drug and health attitudes and their causes, current trends in the culture regarding pharmacotherapy use vs alternative therapies. • Drug misuse, abuse and dependence. • Disuse of drugs (noncompliance, nonjustified drugs for the purpose). • Discrimination and social injustice (unavailability of important drugs). • Effect of informative and regulatory measures or interventions.
Economic	• Drug/product price and cost, imports vs local production. • Drug cost-effectiveness and safety in relation to purpose and alternative measures. • Current and future allocation of national resources (money, human resources, and facilities) to the drug and health budget.

in this field demonstrated marked variations in the sales of antibiotics across six countries in Europe, prompting recognition of the need to assess and compare the use of medicines between different countries and regions (Engel and Siderius, 1968). The WHO subsequently held its first meeting in drug consumption in Oslo in 1969, resulting in the formation of the WHO European Drug Utilization Research Group (DURG) (World Health Organization, 1970). It was then acknowledged that in addition to assessing overall patterns of drug use, there was a need to understand factors related to the safe and effective use of medicines at an individual level. The scope of the field therefore needed to be extended to be able to answer the following types of questions (World Health Organization, 2003a):

- Why are medicines prescribed?
- Who are the prescribers?
- For whom do the prescribers prescribe?
- Are patients taking their medicines correctly?
- What the benefits and risks of these medicines?

In 1977, the WHO formally defined *drug utilization research* as the "marketing, distribution, prescription, and use of medicines in a society, with special emphasis on the resulting medical, social, and economic consequences" (World Health Organization, 2003a). The medical, social, and economic consequences of drug utilization are outlined in further detail in **Table 1**. In summary, medical consequences relate to establishing the benefits and risks of medicines use; the social consequences address aspects of inappropriate use and the overall culture of medicines; while the economic consequences concern the cost-effectiveness of medicines and the impact of drug costs and health budgets.

Although the main objective of drug utilization research is to provide insights into the patterns, quality, determinants, and outcomes of medicines use (World Health Organization, 2003a), over the years, there has been an increased emphasis on the methods used to undertake this work. Consequently, the definition of *drug utilization research* has evolved to be "an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes" (Lee and U, 2012).

As a field, drug utilization research intersects with many other disciplines, and is often considered to bridge the gap between health services research and pharmacoepidemiology (Wettermark et al., 2016). Although the terms pharmacoepidemiology and drug utilization research are sometimes used interchangeably, there are clear distinctions between the two disciplines. *Pharmacoepidemiology* is the "study of the use and effects of drugs in large numbers of people" (Strom, 2012a), with a key emphasis on undertaking population-based studies to examine the outcomes of medicine(s) use (Bergman, 2001). Although drug utilization studies often make use of population-based data sources on medicines sales or utilization, they are generally focused on the quantity and quality of medicines use and understanding the key drivers behind the patterns observed, rather than an emphasis on establishing an association between use and an outcome (Wettermark et al., 2016). Nonetheless, many core methodological principles of pharmacoepidemiology also apply to drug utilization research.

Descriptive vs. Analytical Studies of Medicines Use

Studies of medicines use are broadly divided into two categories—descriptive and analytical (World Health Organization, 2003a). *Descriptive studies* describe patterns of medicines use and identify issues for further investigation. In contrast, *analytical studies* investigate the link between medicines use and outcome measures. Data about medicines use can be *qualitative* or *quantitative*, and obtained at a number of levels including national, regional, local health facilities, households, or from an individual (World Health Organization, 2003a). In the context of research regarding patterns of medicines use, qualitative studies explore issues related

to the quality or rational use of medicines, often assessing the appropriateness of use (World Health Organization, 2003a). Meanwhile, quantitative studies aim to describe the current trends and patterns in medicines use, and also prescribing practices at various levels of the health care system (World Health Organization, 2003a). These data are often derived from prescription or registry data or from surveys (World Health Organization, 2003a). For example, national household surveys collecting data on self-reported use of a variety of prescription medicines and recreational drugs.

Types of Drug Utilization Studies

Drug utilization studies are often focused on examining one of the key stages in the medicines-use chain, such as (World Health Organization, 2003a):

- *the systems and structures regarding medicines use* (e.g., how medicines are ordered, delivered, and administered in a hospital or health care facility).
- *the processes of medicines use* (e.g., what medicines are used and the manner of use, including whether use is consistent with relevant criteria, guidelines, or restrictions).
- *the outcomes of medicines use* (e.g., determining the short-term and long-term effectiveness, benefits and harms of use, as well as utilization of resources such as pathology tests and health care utilization).

These studies can be either cross-sectional or longitudinal in nature. *Cross-sectional studies* provide a snapshot or representation of drug use at a particular point in time (e.g., on a specific day, or over a month or year) (World Health Organization, 2003a). They are especially useful for making comparisons of the patterns observed across other settings or regions, or to collect data before and after an intervention to examine the impact of a change in policy or intervention (World Health Organization, 2003a). *Longitudinal studies*, or cohort studies, consist of the collection of multiple measurements of a group of individuals over time (Greenland, 1998). These studies include cohort data from repeated cross-sectional surveys or continuous data derived from administrative datasets. Longitudinal studies are necessary for evaluating the long-term trends in medicines use and the impact on health outcomes.

Methodological Considerations When Designing Quantitative Drug Utilization Studies

Considerable planning is required prior to commencing a drug utilization study. Development of a detailed written plan for the drug utilization study, also referred to as a study protocol, with input from relevant stakeholders, is advised prior to study commencement (Gamble, 2014; Public Policy Committee International Society of Pharmacoepidemiology, 2016). Depending on the setting and data source that will be utilized, it may be necessary to obtain formal ethical approval from an independent human research ethics committee prior to study commencement. Factors such as identifying the aim of the drug utilization study and most appropriate study design, discerning between the use of a secondary data source or undertaking primary data collection, deciding how medicines use will be defined, and determining the most appropriate way to manage, analyze, and present the data are important steps in the planning and execution of quantitative drug utilization studies (**Table 2**).

Study Design

It is essential to formulate a clear research question and identify the exact exposure(s) and outcome(s) of interest prior to study commencement. In pharmacoepidemiological studies, the use of a certain medicine can be classified as either an exposure or an outcome, depending on the research question under study. Quantitative drug utilization and descriptive studies often report use of specific medicine(s) as the main outcome measure. Quantifying the exact reason for the study and the exposures and outcomes of interest will inform the study design and assist with selection of the most appropriate data (e.g., primary data collection or a secondary data source) in order to address the research question of interest.

Selecting a Data Source for the Drug Utilization Study

Data about medicines use can also be collected prospectively or retrospectively, and is largely dependent on the availability of sources of medicines use. Sources also differ between countries, dependent on the structure of individual health care systems, and requirements for the routine collection, analysis and reporting of data about medicines use. A range of different data sources may be suitable for conducting drug utilization studies. A data source which is valid and reliable, with complete capture of all medicine(s) of interest and medicines supplied across all necessary settings (e.g., hospital inpatient, community, residential aged care, or long-term care facilities) is desirable to avoid bias.

The most frequently used sources of information include manual collection of data about prescribing, dispensing or administration of medicines directly from individuals or their medical records, or accessing information from registries, administrative health claims datasets or electronic health records. It is important to be aware of the strengths and limitations of each potential

Table 2 Factors to consider when planning a quantitative drug utilization study (Bain et al., 1997; Birnbaum et al., 1999; Crystal et al., 2007; Gillum and Johnston, 2003; Kornegay and Segal, 2013; McGlynn et al., 1998; Mitchell et al., 1994; Motheral and Fairman, 1997; Petrie and Sabin, 2009; Sluggett, 2014; Sørensen et al., 1996)

Study design
- What is the research question and aims/objectives of the drug utilization study?
- What are the exposure(s) and outcome(s) of interest?
- What sample size is necessary for the proposed analyses?

Ethical considerations
- Have the necessary approvals been sought from data custodians?
- Is human research ethics approval required prior to study commencement?
- Where will the data be stored and who will have access to the data?
- What strategies will be used to maintain patient confidentiality?

Selecting a data source
- What data will used for the study (e.g., primary or secondary data source)?
- Is the data source valid and reliable?
- If an existing (secondary) data source is proposed for the drug utilization study, how representative is the population captured within the data source?
- Does the data source capture information about all medicines of interest and medicines use across all desired settings?
- If necessary, are there sufficient data available for follow-up?

Data management
- If data entry is necessary, how will data entry errors be minimized or identified?
- How complete are the data? Are there any missing data or outliers and if so, how will these be handled?

Defining and interpreting medicines exposure
- How will medicines of interest be identified and extracted from the data source?
- Is the indication for use, dose and duration of use for all medicines of interest available?
- What time period will be used to ascertain medicines use for the drug utilization study? Will incident and/or prevalent medicines use be assessed?
- Were there any changes in medicines subsidies, coding, patient eligibility, or relevant guideline recommendations during the study period?

Data analysis and presentation of results
- What software package will be used for statistical analyses?
- What is the best way to summarize the data?
- What is the best way to present the results?

data source, and whether there are aggregate or individual-level data available when determining between potential data sources for a drug utilization study.

Primary data collection involves the study investigator(s) collecting information about medicines use directly from subjects via interview or survey, or through auditing medical records (Kornegay and Segal, 2013). The term "medical record review" may be used to describe a drug utilization study that uses prerecorded, patient-focused data as the primary source of information (Worster and Haines, 2004). Primary data collection methods can elicit more comprehensive information about nonprescription medicines use than other data sources. In addition to information about medicines use, detailed demographic and clinical information can also be determined, enabling a more in-depth analysis at the individual level. However, primary data collection is often resource intensive and it can be difficult to obtain a sufficiently-sized sample. Self-reported medicine use may not reflect prescribed use, and there is potential for recall bias when medicines use data are self-reported (Hafferty et al., 2018). As with any data source, data collected must be both reproducible and valid (Boyd et al., 1979).

Aggregate data can be defined as "data that are tracked across time, across organizations, across patient populations, or across some other variable," but are not individual-level data (Ryan and Thompson, 2002). Aggregate data sources for drug utilization studies may include medicines procurement records, medicines sales and purchasing data, and summary records of medication errors or adverse drug events (World Health Organization, 2003a). These data are often used to compare the utilization of similar medicines for a specific indication in large populations, or compare utilization in different populations or countries (World Health Organization, 2003a).

Clinical registries are organized systems which collect prespecified data on a defined population for monitoring safety or for quality improvement purposes (Gliklich et al., 2010). Clinical registries may be developed to collect details of individuals with a specific medical condition or the use of specific treatments or medicines (Dreyer and Velentgas, 2012; Gliklich et al., 2010). Clinical registries often include comprehensive acute care data and reflect "real-life" practices and patient outcomes. It is important to discern how medicines information is captured (e.g., self-report, data linkage) when using clinical registry data to investigate drug utilization.

Administrative health claims datasets contain longitudinal records of medical and pharmaceutical claims submitted to a central body for payment (Sluggett, 2014), and often provide access to a large number of prescription records over many years. Population coverage, quality and completeness of data, and information about drug utilization may vary between databases (Schneeweiss and Avorn, 2005; Strom, 2012b). Administrative health claims datasets can be used to examine drug utilization among large populations

efficiently and cost-effectively. However, clinical data and information about nonprescription medicines are often not recorded in administrative health claims databases, and medicines dispensed in hospitals or long-term care facilities may not be captured (Furu et al., 2010; Stricker and Stijnen, 2010).

Medical record databases and electronic health systems are used by health professionals to record information such as health conditions, prescribed medicines, pathology results, and other clinical information for their patients (Ogdie et al., 2012). De-identified datasets extracted from medical record databases or electronic health systems are sometimes made available for research purposes (Ogdie et al., 2012). Information about the indication, dose and intended duration of a prescribed medicine is often available from these data sources; however, it may not be possible to determine if the medicine was dispensed or administered. There may be variation in the quality of data entry and quantity of free text entries, and loss to follow-up can occur if a patient switches to a different health care provider (Sluggett, 2014).

Linked health databases are commonly used to conduct drug utilization studies. Availability of unique personal identifiers may enable linkage between national administrative health claims datasets and registries. Data linkage, the process of connecting records for the same person across datasets to obtain longitudinal records for each individual and improve the utility of individual datasets (Kornegay and Segal, 2013), may also be undertaken by study investigators. Records can be linked based on the exact match of one or more unique identifiers available from each dataset (deterministic matching), or by using specific software to match records based on pattern recognition and probabilities (probabilistic methods) (Clark, 2004).

When using a secondary data source, it is essential to understand the coverage of the data source and the underlying rules and regulations that underpin the prescribing, purchasing or administration of medicines in the particular setting or health care system involved. These factors will impact decision rules and the analysis plan for the study.

Medicines Exposure in Drug Utilization Studies

Because drug utilization studies generally focus on the prescribing, purchasing, or administration of certain medicines, defining medicine exposure in an accurate manner is essential to ensure the validity of the study (ENCePP, 2013).

Incident and Prevalent Medicines Use

The concept of prevalent or incident medicines use is important to consider when planning or interpreting findings from a drug utilization study. Prevalent use considers all users of the medicine of interest, regardless of when the medicine was started. Drug utilization studies which consider incident (or "new-user") use of a medicine consider only those individuals who commenced use of a medicine within a defined period (Ray, 2003).

Incident user definitions of medicine exposure can reduce certain types of bias. This is because prevalent users of a medicine are essentially "survivors" of the early period of medicines use, meaning they have tolerated the medicine and not experienced significant adverse events, and may have had a positive response to treatment (Ray, 2003). However, incident user definitions are not without biases and it is still common for some drug utilization studies to define medicine exposure based on prevalent use (World Health Organization, 2003a).

It is possible to define an incident medicine user from a secondary data source such as administrative health claims data or electronic medical records using a "washout" period or window without any evidence of medicine use. However, there is no consensus on the most appropriate definition or duration of the washout window when undertaking a pharmacoepidemiological study (Johnson et al., 2012). It is important to minimize the risk of the *prevalent pool effect*, which can occur when prevalent users are misclassified as incident users, leading to an overestimation of the true number of incident medicine users during the first few years of a dataset (Brameld et al., 2003).

It is important to consider both the research question and the strengths and limitations associated with each strategy when deciding whether a prevalent or incident user study design is necessary. Certain research questions will not require incident use; for example, it may not be necessary to restrict to new medicine users when undertaking a drug utilization study to determine the percentage of patients treated with an antiplatelet after hospitalization for acute myocardial infarction. However, for a study investigating the likelihood of an adverse event when taking a medicine of interest, and the adverse event may occur soon after the medicine is initiated, then restricting the study population to incident users is advised.

International Classification Systems used in Drug Utilization Research

To ensure consistency and standardization in the presentation of data on drug utilization, and to enable cross-national comparisons in medicine use statistics, it is important to have a universal medicine classification system and unit of measurement to represent utilization. The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) metric were originally developed in Norway in the early 1970s, and are now the gold standard for international drug utilization monitoring and statistics (WHO, 2018a). The WHO Collaborating Centre for Drug Statistics Methodology is responsible for maintaining and updating the system, which can be found online at: https://www.whocc.no/atc_ddd_index/.

Structure of the Anatomical Therapeutic Chemical Classification System

Each medicine included in the ATC classification system is classified within a hierarchy consisting of five levels (WHO, 2018b). The 1st level comprises of 14 main anatomical/pharmacological groups. Each ATC main group is then divided into 2nd levels which are either pharmacological or therapeutic groups. The 3rd and 4th levels are chemical, pharmacological, or therapeutic subgroups and

the 5th level is the medicine/chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. The structure of the ATC classification system is illustrated below using metformin (ATC code A10BA02) as an example (WHO, 2018b):

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excluding insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	Metformin (5th level, chemical substance)

There is one seven-digit ATC code for each medicine/chemical substance, which usually represents its main therapeutic use (WHO, 2018b). However, there are exceptions when a medicines/substance can have multiple indications (WHO, 2018b). For example, calcium channel blockers are classified according to the pharmacological group C08 Calcium Channel Blockers, avoiding specifying whether the main indication is coronary heart disease or hypertension (WHO, 2018b). Similarly, a medicine may be assigned multiple ATC codes depending on the indication for use. For example, the ATC codes for aspirin (acetylsalicylic acid) are A01AD05 (agents for local oral treatment), B01AC06 (platelet aggregation inhibitors excl. heparin) and N02BA01 (salicylic acid and derivatives, under the 3rd level subgroup other analgesics and antipyretics). It is important to note that combination products are generally assigned separate ATC codes to the individual medicines.

Defined Daily Doses

The DDD metric provides a fixed unit of measurement independent of price, currencies, pack size and strength, enabling trends in drug utilization to be assessed and compared between population group (WHO, 2018a). A DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO, 2018a). Only one DDD is assigned per ATC code and route of administration (e.g., oral, transdermal, parenteral formulations). As the DDD is a unit of measurement to allow data from drug utilization studies to be standardized across countries and settings, the DDD for a given medicine does not always align with the doses recommended in clinical practice, nor does it take into account variations in dose recommendations for different clinical indications or treatment purposes (e.g., acute, maintenance, or prophylactic therapies) (WHO, 2018a). Moreover, DDDs also do not take into account individual characteristics or factors that can influence treatment responses such as age, weight, ethnic differences, type, and severity of disease (WHO, 2018a). Consequently, when interpreting drug utilization data that are presented in DDDs, it is important to be aware that these data provide an overall estimate of utilization, and may not represent actual trends in use.

Oral Morphine Equivalents

The potential limitations of DDDs to overestimate or underestimate drug utilization has been most recently highlighted in the context of undertaking studies of opioid analgesic utilization (Nielsen et al., 2016; Svendsen et al., 2011). Opioids generally require highly individualized dosing which is titrated to pain responses, rather than having standard therapeutic dose ranges, and there is significant variation in the opioid doses used to treat acute and chronic pain. Among a representative cohort of people prescribed strong opioids for the treatment of chronic pain in Australia, DDDs were found to be 0.6–7.1 times the median opioid doses used by the cohort (Nielsen et al., 2017). Given that there are significant differences in the actual doses used in clinical practice and the DDDs proposed by the WHO, researchers have proposed an alternative metric to quantify opioid utilization: oral morphine equivalents (OMEs) (Nielsen et al., 2017; Svendsen et al., 2011). OMEs are based on the idea that different doses of different opioids (with varying potency) may produce a similar analgesic effect. This metric has the added advantage of being able to take into account the use of multiple opioids, as is common in contemporary clinical practice. The use of OMEs is becoming increasingly common across a range of various research studies (Degenhardt et al., 2016; Karanges et al., 2018; Lalic et al., 2018).

Defining and Interpreting Medicines Exposure

Exposure to a medicine of interest can be defined in a number of different ways. Medicines exposure is often classified as a binary variable (e.g., yes/no) when undertaking a drug utilization study (Gamble, 2014). Exposure can also be classified according to the number of medicines of interest an individual is exposed to (e.g., 0, 1, ≥2 medicines) or the dose received (e.g., in mg, DDDs or OMEs (Nielsen et al., 2016)). The drug utilization studies described in **Table 3** have used a range of different approaches to define medicines exposure. The time period to determine whether an individual is exposed to a medicine of interest, or to ascertain the duration of medicines exposure or the cumulative dose an individual receives, must be considered carefully and may vary depending on the research question and data source.

Table 3 Examples of approaches used to assess medicines exposure in drug utilization studies

Reference	*Country*	*Summary*	*Approach used to report exposure to medicine(s) of interest*
Sluggett et al. (2015)	Australia	Administrative health claims data were used to determine prevalence of use of medicines to reduce secondary stroke risk after hospitalization for transient ischemic attack or stroke.	Medicine use was stratified by diagnosis, medicine class and age group. The number of participants receiving 0, 1, 2, and 3 guideline-recommended medicines, and clinical and demographic factors associated with use of all three recommended medicine classes were reported.
Nishtala and Soo (2015)	New Zealand	A repeated cross-sectional study was undertaken to assess utilization of proton pump inhibitors (PPIs) between 2005 and 2013 among people aged ≥65 years using a national population-level prescription claims dataset.	The number of defined daily doses (DDDs) of PPIs per 1000 people per day were determined. Utilization trends were further stratified by PPI type, age group, sex, ethnicity, and region of residence.
Degenhardt et al. (2016)	Australia	This study assessed utilization of strong prescription opioids, other prescription opioids or over-the-counter opioids in Australia in 2013 using national sales data.	Opioid utilization was estimated in three different ways: (1) the number of packs of opioids sold, (2) the number of milligrams of each opioid sold, and (3) the total oral morphine equivalent milligrams (OME mg). Utilization was mapped according to geographical location of supply for comparison.
Bell et al. (2010)	Finland	Medicines data collected by nurses for 2052 residents of long-term care wards over a 2-week period were assessed to determine exposure to sedative and psychotropic medicines as part of this cross-sectional study.	Exposure to individual medicines and medicine classes of interest were reported. Sedative load was calculated for each participant to determine cumulative exposure.
Gnjidic et al. (2012)	Finland	A cross-sectional study which assessed exposure to anticholinergic and sedative medicines and functional outcomes among 700 community-dwelling older people.	Exposure to anticholinergic and sedative medicines was determined using the Drug Burden Index.

An understanding of local medicine supply policies, coding of pharmaceutical claims, and changes to the availability of subsidized medicines is important when conducting a drug utilization study using pharmaceutical claims data, particularly when comparing medicines use across countries or examining changes in medicines use over time (Sluggett, 2014). There may have been changes to the ATC codes or the DDD assigned to the medicine of interest (WHOCCDSM, 2018), or release of new combination formulations with different ATC codes. Other factors, such as changes to treatment recommendations in clinical guidelines, medicines shortages and product withdrawals may also contribute to variation in the utilization of the medicine(s) of interest. Seasonality may also be important when interpreting the results of drug utilization studies assessing use of medicines such as vaccines or antibiotics indicated for respiratory infections (Antonova et al., 2014; Suda et al., 2014). Careful inspection of medicines use at regular intervals during the data analysis process is advised to identify unanticipated variability in medicines exposure.

Data Analysis and Presentation of Results

Statistical software packages are commonly used to analyze data for drug utilization studies. Descriptive statistics, such as percentages, rates, and measures of location (e.g., mean, median) and spread (e.g., standard deviation, interquartile range) are commonly used to summarize findings. Statistical tests may be used to determine any differences in demographic, clinical and health provider factors for those who received the medicine(s) of interest in comparison to those who were not exposed to the medicine(s) of interest during the study period. For example, statistical tests such as *t*-tests or Wilcoxon rank sum tests are sometimes used to compare continuous measures (e.g., age in years) depending on the distribution of the two populations. Statistical tests such as chi-square tests and Fisher's exact tests are commonly used to compare dichotomous variables (e.g., sex) in a contingency table, with selection of the most appropriate test depending on factors such as sample sizes within the cells of contingency tables. Outcome measures are often further stratified by demographic and clinical variables of interest such as patient age, geographical area, year, medicine/drug class or treatment indication. Multivariable regression models are often used to estimate measures of associations (e.g., odds ratios, relative risk) between demographic, clinical, and health provider factors and the prescribing, dispensing or utilization of the medicine(s) of interest in a drug utilization study.

Results of drug utilization studies are generally summarized within the text and presented within tables or diagrams. For example, for a drug utilization study examining the frequency of use of "pro re nata" (PRN or when required) medicines by residents of aged care services, the frequency of prescribing and administration of all PRN medicines were stratified according to the WHO ATC classification system and results were presented graphically (Stasinopoulos et al., 2018). Backward stepwise multivariate logistic regression was undertaken to determine resident characteristics associated with administration of PRN medicines among residents who were charted at least one PRN medicine and the unadjusted and adjusted odds ratios, 95% confidence intervals and *P*-values were presented in a table (Stasinopoulos et al., 2018).

As with any research study, it is important to follow good practices in the presentation and reporting of results and findings. There are several published standards and guidelines that are useful for reporting drug utilization studies, including: American Society of Health-System Pharmacists (ASHP) Guidelines on Medication Use Evaluation (American Society of Health-System Pharmacists, 1996); the International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practice (GPP) (Public Policy Committee International Society of Pharmacoepidemiology, 2016); the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2010); the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (von Elm et al., 2008); and REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement (Benchimol et al., 2015).

Applications of Drug Utilization Studies

As described throughout this chapter, drug utilization studies can address many different aspects of medicines use. There are an endless number of applications and examples of drug utilization studies in the literature, ranging from cross-sectional drug utilization evaluations to more complex longitudinal evaluations of health and policy interventions. Some selected examples of applications of drug utilization studies are presented below.

Evaluating the Rational Use of Medicines

One of the primary purposes for undertaking drug utilization research is to ensure that medicines are used rationally with an emphasis on maximizing benefits while reducing harm (World Health Organization, 1985). As such, a simple search of any literature database using the terms "rational medicines use" or "inappropriate medication use" will return many examples of studies and methods for assessing the rational use of medicines. By far, one of the most common applications of drug utilization studies is the conduct of *drug use evaluations (DUEs)*, *drug utilization reviews (DURs) or medication-use evaluations (MUEs)*. Undertaking DUEs is an essential process in order to evaluate the rational use of medicines and to optimize pharmacotherapy, even in low- and middle-income countries where resources for more sophisticated studies are limited.

Although drug utilization studies using aggregated data can identify whether medicines are being over- or underused, individual-level data is needed to determine whether medicines are used appropriately, and to identify the nature of any irrational use (e.g., incorrect medicine choice, incorrect dose, contraindications and any drug–drug interactions) (World Health Organization, 2003b). Therefore, DUEs provide a system for an ongoing, systematic and criteria-based evaluation of drug use to ensure that medicines are used appropriately at the individual patient level (World Health Organization, 2003b). A DUE can be drug or disease specific and be structured to assess any of the processes related to the prescribing, dispensing or administration of a drug (World Health Organization, 2003b). The term DUE is often used synonymously with the term drug utilization review (DUR). In addition to the overall goal of DUEs to optimize medicines use, MUEs also aim to improve patient outcomes and quality of life (American Society of Health-System Pharmacists, 1996; World Health Organization, 2003b). As such, MUEs also measure clinical outcomes, for example, number of infections cured, and whether blood pressure or lipid level targets have been met.

A systematic review of drug utilization studies in the WHO South-East Asia region identified that DUEs are the most common type of drug utilization study conducted, and that most studies used hospital-based patient records to assess the rational use of medicines (Bachhav and Kshirsagar, 2015). However, this is not reflective of the extent of drug utilization studies in more developed parts of the world where studies are often conducted across a range of settings (including the general community and in residential aged care facilities) and for many other purposes, including the evaluation of policy and health interventions.

Many countries have organizations or formal committees (often referred to as Drug and Therapeutics Committees) to coordinate ongoing programs of work to evaluate the manner in which medicines are being used in different settings, such as in individual hospitals or in the general community. For example, one of the core roles of Australia's Drug Utilization Sub-Committee is to advise the Pharmaceutical Benefits Advisory Committee on changes in national drug utilization patterns that have occurred as a consequence of changes in drug availability or restrictions on drug use, and to review the utilization of drugs or general therapeutic classes (Australian Institute of Health and Welfare, unknown). More information and past reports can be found online: http://www.pbs.gov.au/info/industry/listing/participants/drug-utilisation-subcommittee.

Cross-national Studies of Drug Utilization

As summarized earlier, a major factor contributing to the development of the ATC/DDD classification systems was to enable cross-country comparisons in drug use statistics. The increasing availability of administrative datasets, including dispensing registers and other pharmaceutical claims databases, have been instrumental in facilitating cross-national drug utilization studies, and more recently, in the development of multinational cohort studies, particularly in the Nordic region (comprising Denmark, Finland, Iceland, Norway, and Sweden) (Furu et al., 2010). To date, many of these studies have focused on various aspects of psychotropic medicines use including: population-based cohorts of Nordic residents examining the use of medicines to treat attention-deficit/hyperactivity disorder in children (Furu et al., 2017) and adults (Karlstad et al., 2016), and cross-national comparative studies assessing patterns of antipsychotic medicines use across 16–17 counties worldwide (Bachmann et al., 2017;

Hálfdánarson et al., 2017). Other examples include global studies of the use of and barriers to access opioid analgesics (Berterame et al., 2016) and an evaluation of the impact of *WHO Essential Medicines* policies on inappropriate use of antibiotics (Holloway et al., 2016).

Informing Pharmacovigilance

Drug utilization studies are often incorporated into post-marketing surveillance of newly registered medicines and in assessing the long-term benefits and risks of medicines. Traditional approaches to pharmacovigilance (defined as the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO, 2018c)) have focused on detecting safety signals from spontaneous adverse drug reaction (ADR) reporting systems (Coste, 2017). However, this method is limited by extensive under-reporting and limited generalizability, warranting the need for alternative pharmacovigilance approaches. One example is the use of prescription sequence symmetry analysis (PSSA) to detect ADRs using pharmaceutical claims data (Hallas, 1996; Pratt et al., 2014; Wahab et al., 2013). This method has been validated against known ADRs reported in randomized controlled trials (Wahab et al., 2013), and has shown consistency in estimates for identifying ADRs across five countries in the Asia-Pacific region (Australia, Hong Kong, Japan, Korea, and Taiwan) (Pratt et al., 2015). Other examples where PSSA has been used to investigate potential ADRs include studies assessing potential relationships between: proton pump inhibitor use and the risk of dementia (Park et al., 2018), hypothyroidism induced by antiepileptic use (Lai et al., 2013), urinary tract infections and angiotensin-converting enzyme inhibitors (Pouwels et al., 2013), stroke and nonsteroidal anti-inflammatories (Caughey et al., 2011), and depression and cardiovascular drugs (Hallas, 1996).

Informing the Design and Evaluation of Health Policy and Educational Interventions to Optimize Medicines Use

When used appropriately, medicines can improve health and wellbeing; however, medicines are not always used as intended. Inappropriate medicine use can lead to considerable economic costs for health systems and consumers, along with poor health outcomes such as adverse drug events, hospitalizations and mortality (Chiatti et al., 2012; Hyttinen et al., 2016). Once a potential medicines-related problem has been identified, for example through a drug utilization study, strategies to optimize the use of that medicine may be deemed necessary. Furthermore, new medicines are increasingly costly and health funders may implement policies or procedures to support judicious use of high cost therapies (World Health Organization, 2015). Drug utilization studies play a key role in the planning, implementation and evaluation phases of interventions to optimize medicines use.

Interventions to support medicines to be used safely, efficaciously, and cost-effectively may be funded and/or implemented by individual health care providers or organizations, research organizations, health care payers, regulatory bodies, or policy makers (Grimshaw et al., 2012). The target population for interventions to improve medicines use may include consumers and carers, clinicians, health care organizations such as hospitals or aged care providers, and other stakeholders. Examples of interventions which are commonly used to optimize medicines use include changes to health policies, formulary or medicines reimbursement restrictions, audit and feedback, written educational materials, educational meetings and academic detailing (Grimshaw et al., 2012). Multifaceted interventions are those which utilize more than one strategy to promote behavior change leading to improved medicines use (Squires et al., 2014). Health policy and educational interventions to optimize medicines use require considerable planning, stakeholder engagement and a comprehensive understanding of factors which may impact on the uptake, delivery and sustainability of an intervention. Consideration of relevant behavior change theories throughout this process is advised to increase the likelihood of success and support sustained change leading to improved medicines use.

After implementing a change or strategy to optimize medicines use, those responsible will be interested in monitoring the impact of the intervention on medicines use and health outcomes, and determining if the initiative was effective or if changes are necessary. Interventions to optimize medicines use may be investigated as part of a controlled trial; however, policy changes are often unable to be trialed within a controlled trial environment and randomization may not be possible for health policy and educational interventions that are implemented across an entire population (Bärnighausen et al., 2017). Quasi experimental designs such as interrupted time series and regression discontinuity studies may be used to investigate the impact of interventions to optimize medicines use. Examples are discussed in **Table 4**. Interrupted times series studies are increasingly used in drug utilization research and, in the absence of a controlled trial, are the most robust design to investigate the effects of an intervention to optimize medicines use (Briesacher et al., 2013; Jandoc et al., 2015; Wagner et al., 2002). This method enables assessment of changes in the use of a medicine of interest after one or more interventions, meaning the cumulative effects on medicines use over time can be determined (Pratt et al., 2017; Wagner et al., 2002). Detailed information regarding the design and interpretation of interrupted time series studies using pharmaceutical claims data is available elsewhere (Kemp et al., 2011; Wagner et al., 2002).

Finally, it is important to note that quantitative drug utilization studies may be undertaken in as part of a wider evaluation which may incorporate qualitative approaches to understand factors which impacted on the implementation of a policy change or educational intervention, or cost effectiveness analyses.

Finally, it is important to note that quantitative drug utilization studies may be undertaken in as part of a wider evaluation which may incorporate qualitative approaches to understand factors which impacted on the implementation of a policy change or educational intervention, or cost effectiveness analyses.

Table 4 Examples of studies examining the effect of health policy and educational interventions to optimize medicines use

Reference	*Country*	*Summary*
Pratt et al. (2017)	Australia	The combined impact of five national multi-faceted quality improvement interventions targeting clinicians and consumers to improve the use of proton pump inhibitors was evaluated using interrupted time series.
Komen et al. (2017)	Sweden	Study using interrupted time series to assess the impact of national and international guideline recommendations, local drug and therapeutics committee recommendations, and medication reimbursement decisions on the initiation of direct-acting oral anticoagulants among people with atrial fibrillation.
Judge et al. (2015)	United Kingdom	Study using interrupted time series to assess the changes in the prescribing of disease modifying anti-rheumatic drugs within the first 12 months of diagnosis of rheumatoid arthritis following release of national rheumatology guidelines.
Zuckerman et al. (2006)	United States	The impact of an educational intervention targeting potentially inappropriate use of short acting β2 agonist inhalers among children who received Medicaid-subsidized health services was assessed. Study findings obtained from a regression-discontinuity analysis were compared to results of an uncontrolled before–after analysis.

Conclusion

As evidenced throughout this chapter, drug utilization studies are a necessary part of increasing our knowledge and understanding of the manner in which medicines are used in the community, with the ultimate goal of ensuring that medicines are used safely and appropriately. As with any field of research, there are many study approaches and methodological aspects to consider when designing robust drug utilization studies. Understanding and applying the fundamental principles underlying these studies is especially important as the field continues to evolve in scope and complexity.

Glossary

Anatomical Therapeutic Chemical (ATC) Classification System a standardized classification system used to assign drugs to pharmacological groups according to a five-level hierarchy.
Defined Daily Dose (DDD) a standardized metric used in drug utilization research. The DDD represents the assumed average daily maintenance dose of a medicine for its main indication in adults.

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Case-Control Studies

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Introduction

Evidence-based data guide shape pharmacists' clinical practice. Randomized clinical trials, for example, provide the foundation for rational choices of treatments, establishing the conditions for which a medication will provide the greatest benefits to individuals. Nonetheless, clinical trial data have limitations. Clinical trials are usually performed among groups of people with homogeneous characteristics that poorly reflect the diversity of individuals seen in clinical practice. Older adults, multimorbid individuals, and those with renal or hepatic failure, for example, are often excluded from clinical trials. Ethical considerations also limit inclusions of pregnant women and children in many clinical trials. Moreover, limited follow-up and the fact that clinical trials include small numbers of individuals make it difficult to identify rare side effects.

Observational data, generated in real-world practice, are therefore equally useful for the health professionals including pharmacists. These data can be employed in studies to evaluate the actual effectiveness of drugs, investigate common or rare adverse events associated with their use, or simply describe the quality of medication use according to different norms or standards. Pharmacists can thus exploit the information gathered in such observational studies to inform their own practice.

Case-control studies are useful observational studies to evaluate the impact of medications on different health outcomes. Because of their particular design, case-control studies are especially useful for examining rare events and multiple exposures at the same time. These situations pose a particular problem when conducting research: to ensure sufficient power (i.e., an appropriate number of cases), many individuals would have to be followed up over long term. Studies requiring large number of individuals and/or long follow-up are often not possible or feasible to perform. Case-control studies thus provide valuable help in dealing with such situations.

The chapter proposes a review of the fundamentals of case-control studies. Of note, many elements that are addressed in this chapter are similar to the ones pertaining to observational cohort studies. Moreover, case-control studies are increasingly embedded in cohort studies.

Defining and Designing Case-Control Studies

By definition, case-control studies are analytic studies where cases who experienced the outcome under investigation are compared to controls who did not. Controls are chosen to represent the population that gave rise to the cases. As for study outcomes, they may be of various natures, either diseases or events such as mortality, hospitalizations, or fractures, for example. The case-control study therefore addresses the following question: did the exposure differ between cases and controls? In other words, were the cases more likely to be exposed to a particular risk factor or drug than the controls (or vice-versa)?

Case-control studies can be seen as the opposite study design of cohort studies. In cohort studies, exposed and unexposed individuals are followed up over time until the disease or event is observed (e.g., until the person dies, is lost to follow-up, or until the end of the study). In case-control studies, the outcomes are already known: the individuals who have experienced the disease or event under study are identified as the cases. The controls are individuals who did not experience the outcome of interest. Contrary to the cohort studies, the researchers in case-control studies must identify if the cases and controls were exposed to the risk factors or drugs. Fig. 1 illustrates schematically the procedures in a case-control study. Starting from the population, cases and controls are identified by the presence or absence of the outcome of interest. The following step is to determine whether or not the individuals were exposed to the risk factor(s) or the drug(s) studied. Fig. 2 depicts the nested case-control study, a specific type of case-control design that is embedded in a cohort study, which helps understand the contrast with cohort studies.

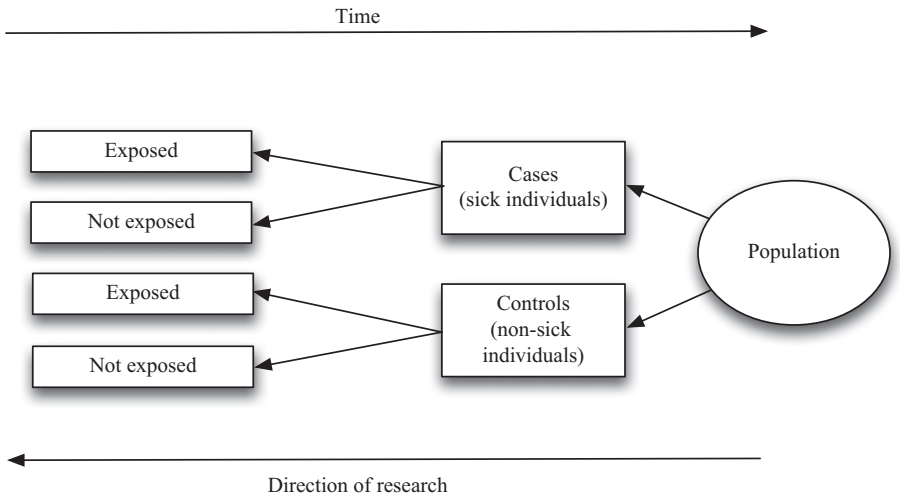

Figure 1 Design of case-control study.

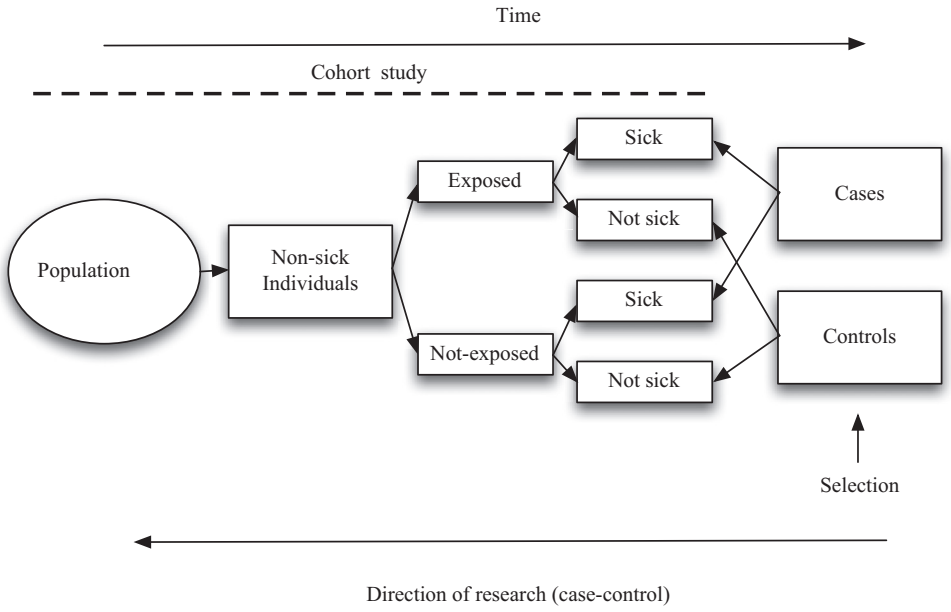

Figure 2 Design of nested case-control study.

As such, a case-control study can be viewed as an efficient cohort study because only a fragment of the total population is studied. The individuals who would have experienced the outcome under a cohort study are identified and compared only to a certain number of controls who would not have experienced the outcomes in a cohort study. The step of selecting cases and controls offers greater efficiency and less costly procedures.

Origin of Case-Control Studies and Examples of Case-Control Studies Studying Medications

The first case-control study in pharmacoepidemiology is believed to be one examining clear-cell adenocarcinoma of the vagina in young women: The hypotheses tested by the investigators were that exposure to either radiation or a drug caused the condition. They compared eight women with adenocarcinoma of the vagina (cases) to 32 controls, girls born at a similar date to the cases in the same hospital. Exposure to diethylstilbestrol (DES) was revealed to be associated with a great increase in risk: the odds for a baby girl exposed to DES in utero to suffer from a carcinoma was 132 times the odds of a baby not exposed. The strength of the association gave a clear indication that there was a strong link between the exposure to DES and cancer occurrence.

Other well-known examples of case-control studies involving drugs are those establishing the link between acetyl-salicylic acid (ASA) and Reye syndrome, and the relation between eosinophilia-myalgia syndrome with the food supplement L-tryptophan. In 1984, researchers in the United States conducted a case-control study with 30 patients with Reye's syndrome. After matching those cases with 145 controls for age, race, and type of antecedent illness, it appeared that the cases were significantly more exposed to ASA, with an odds ratio (OR) of 16.1. Similarly, a case-control study permitted to explicit that the origin of an outbreak of eosinophilia-myalgia syndrome in 1989 was associated with the manufacturing conditions of L-tryptophan by one specific company. The odds of developing the syndrome among individuals exposed to the contaminated product was 19.3 times the one of unexposed people. These case-control studies paved the way for dramatic changes in the way medications were used. But performing case-control studies entails following strict methodological founding principles; otherwise they are prone to bias and their conclusions may not be valid.

Selection of Cases and Controls

Appropriate selection of cases and, above all, controls, is fundamental in conducting case-control studies. Cases are selected according to inclusion and exclusion criteria and must be selected such that they are representative of the population, otherwise the results may be biased.

The major challenge of a case-control study is to select appropriate controls for the cases. As noted earlier, the controls must be representative of the population where the cases come from. Conceptually, this population is made up of all the individuals who would have been identified as a case if they had experienced the outcome. It is critical to select control by means of procedures that are independent of the exposure (i.e., of the studied medication in pharmacoepidemiology). The overarching goal of control selection is to determine the relative numbers of people exposed and not exposed to the medication in the source population. If controls are selected in a way that is related to the exposure, the estimate of the risk will thus be biased. This situation may lead to a selection bias that will confound the appropriate association between the use of the medication and the outcome. This problem will be further described in the section "Dealing With Bias".

Different techniques exist to select appropriate controls. In classical case-control studies, controls can be selected among the cases' neighbors (by applying systematic selection algorithms, for example). This allows for geographical representativeness and the control of socioeconomic status, which may be important confounding factors. Recruiting cases' friends is also an alternative sometimes used to identify potential controls. Yet, as friends often share similar interests—and hence exposures—care must be exerted to ensure that the exposure is truly representative of the source population. In hospital studies, cases may be individuals hospitalized in one or more departments or hospitals. Controls can thus be selected from among those hospitalized in the same hospitals. It is of utmost importance however to ensure that the reasons for hospitalization are not related to the studied exposure. Finally, when the outcome of interest is death (so cases are deceased persons), deceased controls can also be chosen to ensure better comparability of information. Regardless of the chosen technique, it is important to remember that it must be free of selection bias, which will be discussed later in this chapter.

Control selection methods may be somewhat different when studies are nested in larger cohorts. In pharmacoepidemiology, administrative data are often used to create large cohorts of individuals who may or may not be exposed to drugs. Individuals are defined as cases if they had an event during a specific period of time. Selection of controls can then be carried out retrospectively; the probability of being selected as a control will be proportional to the time the individual is at risk of becoming a case, which is known as incidence density sampling. An individual could therefore be chosen as a control and become a case later on in the follow-up.

Each case can be matched to one or more controls in the analysis. Matching provides the opportunity to control for potential confounding factors, that is, characteristics that both a case and his/her control(s) will share. For example, case X who is a women of 40 years of age, will be compared to a control Y who is also a women of 40 years of age. Matching a case to 3–4 controls will increase precision and power. Enhancing the ratio to greater than 4 will not result in much gain in precision and may increase study costs. Yet, nowadays the use of large administrative databases allows for the selection of many controls, without such restrictive monetary considerations; it is relatively common to see matching involving more than 4 controls, which will improve power.

Defining Exposure

Another challenge in case-control studies is to define the exposure appropriately. This is of particular issue in pharmacoepidemiological studies using the case-control design. In order to study the effect of a drug, it is fundamental to explore its pharmacology: its mechanism of action, the possible drug-drug interactions that may be involved, the way the product is eliminated. This information will help determine which elements are essential for defining exposure. It will also be necessary to question the effect of the dose, the duration of exposure, the frequency with which the individual receives the medication. In addition, exposure must be defined according to the event of interest. Does the individual need to be exposed immediately before the event? Should exposure be studied over a month, six months, one year, or ten years? The pathophysiology of the disease must also be taken into account when defining exposure. The hypothesis regarding the relationship between the exposure and the disease or event needs to be clarified before the start of the study. It will then be possible to determine the relevant exposure in terms of dose, duration, and temporal relationship regarding the occurrence of the outcome. For example, a myocardial infarction could not be attributed to taking a statin if an individual swallowed the first dose in the previous hour. Exposure may need to be maintained for a period of time for the individual to experience the effect of the drug. Therefore, the individual may not be considered exposed until a predefined length of exposure has been reached.

Several examples can be retrieved in the literature for defining exposure in case-control studies. For example, it can be categorized into classes, such as: current user of the medication at the date of the event (index date, for cases and similar date for the control), recent user, past user, or never user. Cumulative exposure can be described as a combination of length of exposure and mean dose received. Yet another consideration when assessing the effect of drug use on health outcomes, is to determine whether the effect of the drug will persist for a long time after the individual stops taking it. A drug that accumulates in the body, shows a long half-life, or causes irreversible effects on a tissue or organ could induce benefits or side effects well after the treatment is ceased. In this situation, it would be appropriate to consider the individual exposed to the drug even if, in fact, he or she did not use the product recently.

The conceptualization of exposure will also determine which data sources are the most appropriate. For example, it would be unrealistic to ask individuals to report their exposure to all the medications they have consumed in the last ten years. This measurement can, however, be done in large databases. On the other hand, one could easily recover the information by asking a person if the exposure was defined as use of a medication in the previous days. The data sources thus present strengths and limitations. Data reported by individuals may be prone to recall bias: it may be difficult to remember exactly what drug use was in a defined period of time. This bias may also be of a differential nature: a person who has experienced the event (a case) may better remember their exposure than the control. This can lead to problems in the interpretation of results, as will be discussed in the section "Dealing With Bias". In administrative data, the information available comes from purchased drugs. The actual use of the medication is not known, nor are the reasons for which the individual was or not prescribed the drug. This can lead to different issues, such as confounding by indication, as described again in the section "Dealing With Bias".

Calculating and Interpreting Odds Ratios

Odds ratios (ORs) are the measure of association in case-control studies. The odds ratios refer to the probability that an event will happen divided by the probability that it will not happen. To fully understand how this measure is calculated, one can construct a 2×2 table like the one presented in Table 1. The OR will compare the odds of being exposed between cases and controls. The proportion $a/(a + c)$ represents in a way the probability for a case of having been exposed and $c/(a + c)$ that of not having been exposed. The ratio $a/(a + c)/c/(a + c)$ reflects the relative chance of being exposed, which can be simplified by a/c. The ratio a/c measures the odds in favor of exposure vs. non-exposure. For example, if the odds is 2, the probability of being exposed is twice as high as that of not having been exposed.

Similarly, the odds for the controls are equal to b/d. The interpretation remains similar to the one previously stated for the cases.

Using the ratio $a/c \div b/d$, we can compare the odds of exposure between the cases and the controls. The OR can be written:

$$\mathrm{OR} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Table 1 2×2 table used to calculate odds ratio in an unmatched case-control study

	Case	*Control*	*Total*
Exposed	a	b	$a + b$
Not exposed	c	d	$c + d$
Total	$a + c$	$b + d$	$a + b + c + d$

Odd of exposure (cases) = Number of cases exposed/Number of cases not exposed = a/c
Odds of exposure (controls) = Number of controls exposed/Number of controls not exposed = b/d
Odds ratio = Odds of exposure (cases)/Odds of exposure (controls) = ad/bc

Table 2 Example of an odds ratio calculation in an unmatched case-control study

	Cases	*Controls*	*Total*
Exposed	15	7	22
Not exposed	30	38	68
Total	45	45	90

Odd of exposure (cases) = Number of cases exposed/Number of case not exposed = 15/30
Odds of exposure (controls) = Number of controls exposed/Number of controls not exposed = 7/38
Odds ratio = Odds of exposure (cases)/Odds of exposure (controls) = (15 × 38)/(7 × 30) = 2.71

The OR allows to estimate the relative risk between the exposure and the health outcome. If there is no association between the outcome and the exposure (e.g., drug) studied, the odds of the two groups will be similar, leading to an OR of 1. If there is a positive association between the exposure studied and the outcome, the odds will be higher in the cases than in the controls, so that the OR will be greater than 1. If the OR is <1, then the exposure to the drug under study prevents the health outcome. In Table 2, the OR is 2.7. The exposure is thus associated with the outcome. The odds of exposure among cases is 2.7 times the one seen in controls.

While it can be concluded that the OR estimates the relative risk between the exposure and the outcome, the estimate will be more or less close to the true relative risk depending on the type of case-control design and the prevalence of the outcome. In general, the OR overestimates the true relative risk. For example, if the OR = 2.3, the true relative risk may be 1.9. Similarly, if an OR demonstrates a protective effect, such as an OR of 0.6, the real relative risk will be less protective in reality, with a value of 0.8, for example. The rarer the event (prevalence <10%), the closer the OR will be to the relative risk. Some case-control designs allow for a more accurate estimation of the RRs. More information is available in the section presenting the different designs.

Interpreting an OR should also involve the evaluation of the confidence intervals (CI) surrounding this measure. The CI includes a range of values that may contain the true measure of association (the true OR in this case). For a 95% CI, if we were to repeat the same study a hundred times, 95 of the different CIs would contain the true value of the OR. The CI helps us examine two elements: the precision of the measurement and the fact that the observed association is more or less likely to be due to chance. A CI whose values are very widely spread will signify that the true OR could take a large range of possible values. The conclusion would be that the accuracy is low: it is possible that one or the other of the extreme values could be the real OR. The CI will also help establish the statistical significance of the result. A CI that includes a value of 1 means that there is a possibility that the exposure odds are the same for both cases and controls. In this event, there would be no association between the exposure and the occurrence of the event. Therefore, a CI that includes the value of 1 means that the difference observed in the study may be due to chance: the result will not be statistically significant.

Dealing With Bias

There are several biases that may affect the OR of a case-control study. As with other study designs, selection, information, and confounding bias can invalidate the measures of association in a case-control study. They must obviously be avoided so as not to affect the OR and the conclusions that will be drawn from the study.

Selection Bias

Selection bias relates to how individuals are recruited and how they are retained in a study. Selection bias occurs when a preferential selection of the individuals to be included in the study leads to a distortion of the results. In case-control studies, a selection bias will be present if the recruitment of cases or controls is related to the presence of exposure to the factor (e.g., drug) being studied.

To understand how this bias alters the results, we can analyze the distribution of case and control exposures from the total population and compare it with the study population (Table 3a). We should obtain a distribution of exposures in the study population that respects the same proportions as in the source population. Any imbalance in one portion of the table (e.g., a portion of individuals might have a lower probability of being included in the study) will lead to a potential bias. In the example of Table 3b, the OR in the population (the real OR) would be 2.7. However, the approach taken to recruit the controls was faulty, so that the estimated OR in the study is 1. There is therefore a significant disparity between the two results. The estimated OR from the study underestimates the true measure.

There are several types of selection biases that can influence the conclusions of case-control studies. Some of them are discussed below.

Survival Bias and Depletion of Individuals at Risk

If the selection of cases in a study rests upon the inclusion of prevalent cases, asymptomatic individuals and those with a fatal and short-lived episode are less likely to be included. For example, if individuals exposed to a drug are more likely to die than those who are not, the study of prevalent cases will lead to the inclusion of a group of individuals who will be more likely to not have been exposed to the drug. There will be overrepresentation of the cases that lived the longest, that is, the unexposed cases. This will bias OR estimates.

Table 3a From source population to studied sample

	Source population			*Studied sample*	
	Cases	*Controls*		*Cases*	*Controls*
Exposed	A	B	Exposed	a	b
Not-exposed	C	D	Not-exposed	c	d

In an unbiased study, the proportion of individuals included in each cell of the tables will be concordant between the source population and the studied sample. This is represented by the full line. When there is a disparity between one or more cells, as represented by the dotted line, the calculation of the odds ratio will be biased and thus spurious association will be found.

Table 3b Example of a selection bias due to improper selection of controls

	Source population			*Studied sample*	
	Cases	*Controls*		*Cases*	*Controls*
Exposed	100	1500	Exposed	10	80
Not-exposed	50	2000	Not-exposed	5	40

The selection of exposed controls was incorrect in the study, as it was not representative of the source population. This situation leads to an imbalance in the ratio of exposed/not-exposed controls: the ratio is 0.75 (1500/2000) in the source population and 2 (80/40) in the studied sample. Accordingly, the estimated odds ratio is incorrect. While the true odds ratio is 2.7 in the source population $[(100 \times 2000)/(1500 \times 50)]$, the estimated odds ratio is 1 in the study $[(10 \times 40)/(80 \times 5)]$. The true association is therefore underestimated: while there is no apparent association between exposure and the health outcome in the study, there is a 2.7 increased risk for those exposed to the drug in the source population.

For example, if a medication causes a gastro-intestinal intolerance shortly after individuals start the therapy, patients who do not withstand this effect will stop using the medication. This may result in a cohort of "survivors" who are much more likely to tolerate the product well and benefit from it. If the study includes only these "survivors," the results will be biased. Hence, the selection of prevalent cases rather than incident cases may cause problems in the evaluating the risk. Moride and Abenhaim highlighted the presence of this bias in a case-control study assessing the occurrence of gastrointestinal bleeding related to NSAID use. The relative risk estimate for individuals who had used an NSAID in the previous 3 years was 3.0 (95% CI 1.9–4.7), whereas for new users it was 22.7 (95% CI: 2.8–200.0). These results suggested a depletion of susceptible individuals; the individuals who continued the treatment were therefore those who could tolerate it better, while the others were excluded from the population at risk. To avoid such bias, it is preferable to include only incident users, that is, individuals starting the therapy.

Detection Bias

Detection bias occurs when the exposure to the medication of interest directly influences the detection of the disease or outcome under study (e.g., using the medication contributes to the diagnosis process). For example, if an oral contraceptive is known to increase the risk of venous thrombosis, more tests could be ordered in individuals using it. There is thus a higher probability of detection due to increased medical monitoring. Since more cases will be detected in users of the specific oral contraceptive, the association between oral contraceptive use and the outcome will be artificially inflated.

Admission Bias (Berkson's Bias)

This bias occurs when the comparison groups are hospitalized patients. The bias arises when the probability of being admitted to the hospital differs depending on whether or not the individual is exposed to the factor being studied. For example, exposed cases may be more likely to be admitted to the hospital or controls may be hospitalized because of the presence of the medication. The following hypothetical scenario illustrates this situation. The use of ACE inhibitors is believed to increase the risk of liver cancer. The researchers identify 200 cases of liver cancer recorded in a national registry. To calculate the risk associated with the use of ACE inhibitors, the researchers select 200 individuals admitted for any reason other than cancer to the hospital where they work. If there is no association between the exposure and the outcome, the distribution of ACE inhibitor users and non-users would be the same for cases and controls (and the OR would be 1). However, ACE inhibitors are used in a variety of conditions that may increase the risk of hospitalization, such as diabetes, coronary heart disease, or heart failure. Since diabetes and heart conditions represent very common causes of hospitalization, the sample of hospitalized controls will be more likely than the general population to be using ACE

inhibitors. Consequently, the ratio of exposed/not exposed among controls will be higher than expected, and the OR will be lower than 1. The observed protective effect will be spurious.

Information Bias

Information bias refers to the systematic errors related to how information about variables (exposure, outcomes, confounding, or modifying covariates) are measured during the study. For example, information bias could occur due to misclassification of exposure (unexposed individuals are considered exposed, and vice versa) or outcome (sick individuals are considered non-sick, and vice versa). This is called a misclassification bias. This type of error can occur in both cohort and case-control studies.

Recall Bias

Recall bias is particularly important to consider in case-control studies. Individuals who have experienced an outcome (cases) may be more prone to remember their behaviors and activities than those who did not experience it. A case-control study in which the cases know their status and the relationship being studied, and in which the exposure is of a socially sensitive nature could also be susceptible to information bias.

When using administrative databases, the definition of exposure will not be subject to recall bias. Information can be retrieved over a long period of time, even if exposure has been characterized by sporadic medication-taking. The use of administrative databases is therefore considered as one of the best methods for determining drug exposure. Nonetheless, data come from dispensed medications: patients may not have actually taken the medications, which may overestimate actual use and still lead to an information bias.

Protopathic Bias

In pharmacoepidemiology, it is possible to define the protopathic bias as a situation when a drug is prescribed for an early manifestation of a disease that has not yet been diagnosed, and that this drug appears to be the cause of the disease that is ultimately diagnosed. For example, an individual consulted a physician for exercise dyspnea. The physician prescribes a cardiovascular drug such as a nitrate. However, a pulmonary fibrosis is diagnosed a few months later. The cardiovascular drug may appear to have caused the fibrosis, but in fact, it was prescribed for the first symptoms of dyspnea associated with the fibrosis.

To decrease the possibility of spurious associations due to protopathic bias, it is suggested to use a lag period in the definition of exposure. This period includes a time interval, prior to the date of diagnosis, that is excluded from the definition of exposure. There is no pre-defined duration in the literature for the latency period. It must be defined according to the drug and the outcome studied. The control of protopathic bias, therefore, requires a good understanding of the pathophysiological mechanisms of the diseases studied and behaviors related to the use of drugs.

Confounding Bias

Confounding arises when the relationship between the exposure and the outcome can be explained in part or totally be the effect of another variable. This variable is related to both exposure and outcome, without being in the causal chain between the exposure and the outcome. Confounding variables may be responsible for some or all of the observed effect, may reverse the true effect or cancel it out.

As with other observational study design types, adjusting for potential confounding factors can be done using multivariate regression models. The effect of each variable included in the model is then taken into account. As stated previously, the case-control study design also provides another method for controlling potential confusion bias: matching. One can thus decide to compare each chosen case to controls who possess one or more characteristics similar to the case. These factors could be age, sex, and socioeconomic status, for example. Comparing the cases with controls who share these same characteristics allows for taking into account the potential influence of the selected confounding factors. Several confounding biases may occur in observational studies. Some biases that are relevant to medication exposure in particular are presented below.

Indication Bias

Indication bias is a true chameleon: it is also referred to as severity bias, channeling bias, confounding by severity, or treatment selection bias. An indication bias occurs when the medication is preferentially prescribed to individuals with a lower or higher risk of presenting the outcome of interest. There is always a reason that justifies a prescription, and this reason is often associated with the outcome being studied. If these relationships are overlooked, the association between treatment exposure and the outcome will be spurious.

A concrete example will help explain the importance and potential amplitude of indication bias. In a study performed in 1983, the use of warfarin was associated with an increased risk of thromboembolic events—the risk for those using warfarin was 27 times the one for those not using it. This result is quite inconsistent with the expected effect of warfarin, which prevents thromboembolic events. In fact, this paradoxical result is due to the indication bias: only patients at high risk of experiencing a thromboembolic event or those who already had the symptoms (potential protopathic bias!) were prescribed the therapy. Even after adjustment for several variables available in the records and related to the reason for the prescription, the bias persisted. (The adjusted risk remained 4 times higher in warfarin users.)

It is indeed very difficult to eliminate indication bias. There are many limits encountered in trying to avoid this bias, because the motives that lead a physician to prescribe a drug to one patient rather than another are often complex and beyond the scope of the pathology per se.

Adherence Bias

In 1980, the authors of the Coronary Drug Project in the United States were confronted with a surprising result: the individuals who had been assigned to placebo and who adhered to it experienced a 5-year mortality risk of 15%, whereas individuals who did not adhere to the assigned placebo had a risk of death of 28%. The hypothesis put forward to explain these facts was that the patients adhering to the treatment were also adhering to other interventions (e.g., other drugs, diet, physical activity). This example is not an isolated case. A meta-analysis of 21 randomized clinical trials has shown that people who adhere to placebo have lower mortality rates than non-adherents. Adherence to treatment could therefore be a marker of a healthy lifestyle. The tendency of healthier individuals to initiate and adhere to preventive therapies has led to the terms "healthy user effect," "health user adherent bias," "healthy adherence effect," "adherence bias," or "compliance bias."

When it is possible to measure health-related behavior or the use of health services, biases can be reduced or eliminated using statistical modeling. Other approaches can be used, notably with the assistance of designs themselves. For example, in case-control studies, the case-crossover and case-control-time designs could be appropriate alternatives for controlling such characteristics as the individuals are compared to themselves, as explained in the next section.

Types of Case-Control Designs

Other than the traditional case-control studies where prevalent cases are compared to selected controls, there is a variety of different designs that can be used to perform case-control analyses. Some of the designs are presented here with their strengths and limits. A summary of the different characteristics is also presented in Table 4.

Traditional Case-Control Design (Case/Non-Case)

In this type of case-control study, the controls are chosen from the unaffected or healthy individuals (non-cases) at the end of the follow-up. In this (formerly classical) study design, it must be assumed that the event is rare for the OR to be approximately equal to the relative risk.

Nested Case-Control Studies

Nested case-control studies are embedded in a cohort study. This study design is becoming more popular. Nested case-control studies are conducted both in administrative databases and in cohorts of patients from prospective studies and randomized clinical trials.

Table 4 Comparison of case-control study designs

Design	*Characteristics*
Traditional case-control (case-non case)	• Controls are chosen from the individuals who did not experience the outcome • Also known as epidemic or cumulative design • In this (formerly classic) study design, the event must be rare for the OR $\approx$ RR
Nested case-control studies	• Case-control study embedded in a defined cohort; Individuals who experience the outcomes are cases • Production of a risk set for each case, comprising individuals at risk of experiencing the event at the moment the case had the outcome • With incidence-density sampling and matching: OR $\approx$ HR • Efficient design: less demanding in terms of computer power than time-dependent definition of exposure, as would be required in a cohort study
Case-cohort	• Nested study in a cohort in which cases are compared to a representative sample of the cohort at the onset of follow-up (random selection of pre-defined number of individuals from the whole cohort) • In this study design, OR $\approx$ RR (if conditions are met) • The sub-cohort can form the control group for several types of cases • Simple situation if there are no losses to follow-up or competitive risks • Preferable to a comprehensive cohort study when additional information is required, because only a fraction of the cohort will have to be questioned • Can be seen either as a reduced cohort study where all the cases are added/a nested case-control study with non-matched controls
Case-crossover	• Built on the same paradigm that randomized clinical trials with cross-over for medication with short-term effect • Contains only cases; cases are their own controls; Individuals are exposed and non-exposed during certain periods • Appropriate design for the study of modifiable exposure with a temporary effect • Allows to control all the stable characteristics of the subject—not applicable if there are trends in medication exposure (use case-time-control design instead) • Conditions required: (1) Outcome must be the immediate consequence of medication use; (2) Drug effect period must be well-defined; (3) Exposure data must be valid and known for a long period of time

To perform a nested case-control study, one must identify a cohort of individuals that is followed up until they experience the outcome of interest (or the end of the study). Then, instead of analyzing the entire cohort, one chooses the cases that are matched to only a sample of selected controls. This design is much less complex than a regular cohort study when many thousands of individuals are followed for a long time and when they exhibit complex and changing drug exposure over time.

The following four steps must be followed to perform a nested case-control study:

1. Cohort definition: This step includes a good definition of the time of entry into the study ("time zero" or "index date") and inclusion and exclusion criteria as strict as in a usual cohort study.
2. Follow-up of individuals until outcome of interest (to select all cohort cases) or end of study (those are non-case individuals who have not experienced the outcome of interest).
3. Formation of a "risk set" for each case, comprising the case and his/her corresponding controls (controls are individuals without the outcome of interest who survived until the same moment as the case). One case could be a control of another case and an individual could be the control of more than one case.
4. Random selection of one or more controls for each case. Cases may be matched to controls according to different characteristics (e.g., age, sex, reference year).

Fig. 3 illustrates the creation of a case-control study, and particularly the formation of risk sets. All individuals are included in the cohort, and may enter at different points in time. The moment when an individual becomes a case is represented by the black circle. For each case, all possible controls must be identified. The risk sets of individuals 2 and 7 are shown in Fig. 3. Note that Individual 2 is a potential control of Case 7. In fact, the risk set for each case is formed by all members of the cohort who are at risk of undergoing the outcome of interest (i.e., did not suffer the outcome and are members of the cohort at that time). This risk set is defined at the moment the case undergoes his/her outcome. Thus, individual 3 cannot be a control for individuals 2 or 7 since he/she is not a member of the cohort at the moment when these individuals become cases. When the whole risk set is well identified, one can then choose randomly one or more controls. These controls can be matched according to other variables (age, sex, ...).

The method used to identify controls is called Incidence Density Sampling. If the sampling process and matching procedures are well conducted, the ORs obtained in such nested case-control study will be an unbiased estimate of the hazard ratio (HR) obtained in a standard cohort study. However, the OR will show a greater variability than the HR resulting from a full cohort analysis because there are fewer individuals included.

Exposure to the medication in a nested case-control study will be evaluated at the time the case became a case (index date). The exposure variable will therefore reflect the current use of the medication. Different options exist to define the exposure, depending on the agent involved and the outcome studied. For example, use could be defined as taking the drug in the last 60 days before the index date or the day before.

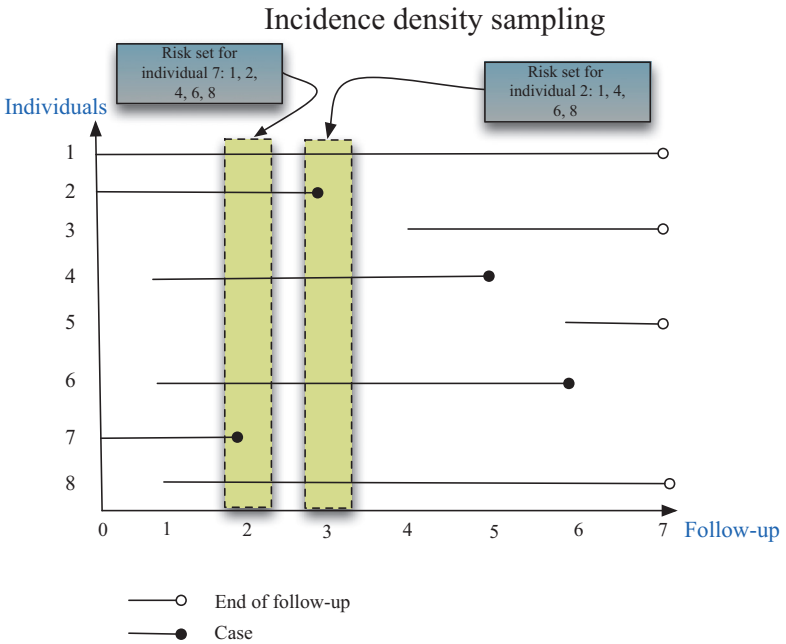

Figure 3 Incidence density sampling in a nested case-control study. In a nested case-control study, the incidence density sampling allows for the selection of a risk set for each case, from which controls can be randomly selected. For the individual 7 who became a case at time 2, five individuals are included in the risk set: 1, 2, 4, 6, and 8. Those individuals were at risk at the time individual 7 became a case. Of note, individual 2 himself/herself became a case at time 3. A case can therefore be a control before becoming a case.

Case-Cohort

In the case-cohort study, all cohort cases are identified (Step 1). Then, a random sample of predetermined size is selected from all individuals in the cohort (regardless of whether or not these individuals experienced the outcome of interest) (Step 2).

Among drawbacks of this design, one must cite that information-gathering on exposure and covariates must be carried out for the entire duration of the follow-up (whereas for the nested case-control study, this data collection may be carried out only during the period of the risk set). However, one of the interesting applications of case-cohort studies is the opportunity to assess the impact of potential confounding factors. In administrative databases, for example, several confounding factors are not available. It would be long, expensive, and difficult to investigate all the individuals included in a cohort. By collecting the required information from all the cases and a random sample of all the individuals included in the cohort, the problems are thus limited. Since the cohort sample is representative of the cohort, the distribution of confounders should be similar in the cohort.

Case-Crossover

The case-crossover design was developed in the late 1980s. As its name suggests, this is a study where cases will be their own controls. In some circumstances, it becomes imperative that a case be its own control since all other control groups would be too vulnerable to selection and information bias.

By definition, in this type of study, all individuals will experience the event of interest since there are only cases included. In pharmacoepidemiology studies, subjects will therefore be successively exposed and not exposed to the drug of interest for certain periods until the outcome occurs. It is then necessary to determine, when the case arises, whether the person was exposed to the drug in the pre-determined period before the occurrence of the outcome.

To carry out a crossover study in pharmacoepidemiology, three conditions must be fulfilled:

1. The outcome studied should be the result of a brief effect of the medication. (Medications that are characterized by chronic and stable use over time would not be good candidates for such studies.)
2. The period when the effect of the drug is expected (the window of the effect) must be precisely determined. (A poor definition of the window will greatly distort the risk estimate.)
3. Data on the use of the product must be valid and known over a long period of time.

Recall that, by definition, all individuals included in these studies undergo the outcome of interest (they are all cases). In addition, individuals will have varied exposure to the medication (they will be successively exposed and not exposed to the study medication until the outcome occurs). For the analysis, one can build a 2×2 table for each individual in the study. It will show whether the individual has been exposed to the drug at the time of the outcome of interest, and the number of times he/she has been exposed and unexposed without experiencing the outcome.

This type of analysis is particularly advantageous when it involves a transient effect of a medication used in a non-regular way. As each individual is matched to himself/herself, it allows for control of potential confounding biases that do not change over time. However, if certain confounding factors are time-dependent, they will not be taken into account. Time-dependent analyzes can be performed to correct time-varying confounding bias, but this complicates the analysis. Moreover, one of the limitations of this design is that it assumes that the prevalence of drug exposure does not follow a time-dependent trend. If this is the case, then the case-time-control study must be used.

In summary, the nested case-control and case-cohort studies answer the question: "Why them," i.e.: "Why did these individuals become cases when the other did not become cases?" (Although some controls will become cases, the designs assume that most controls will not.) The case-crossover answers the question: "Why now," i.e.: "Why did these individuals become cases this day rather than the days before."

Strengths and Limits of Case-Control Designs

The case-control design serves several uses in studying the relationships between drug exposure and health outcomes and can help identify rare side effects of drugs and risk factors for different health outcomes. Also, because case-control designs identify cases, that is individuals who have experienced the outcome, they do not require follow-up for the event of interest to occur, which may be useful in contexts where rapid responses are needed. In case of poisoning, for example, one might discover that a specific batch of a drug is of concern by conducting a case-control study. The impact of clinical practice itself could be evaluated by using case-control studies. For example, one could assess whether populations with higher influenza epidemics are those where pharmacists do not vaccinate. Hence, case-control studies are useful in many instances for research in pharmacy to inform clinical practice. Nonetheless, although the case-control design has several strengths, limitations must also be taken into account in interpreting the results. Table 5 summarizes these main elements.

Finally, an important point to stress is that, due to the observational design, case-control studies cannot be used to measure causal effects of drugs. The fact that there is an association does not imply that the relation is causal.

Table 5 Strengths and limitations of case-control designs

Strengths	*Limitations*
Provide power for rare outcomes (needs less data to measure the association between exposure and outcome than a cohort study would require)	Susceptibility to selection bias (cases or controls (especially) not representative of the source population)
Efficient in time and can be conducted with limited resources	Information bias possible in some circumstances (recall bias, which is not true with most pharmacoepidemiologic studies using large administrative databases)
Allow the study of multiple exposures	Inefficiency for studying rare exposures
Can study conditions with long latency periods	Inability to directly calculate incidence rates (although some designs allow the OR to approximate the HR)
Time-varying nature of drug exposures are more easily dealt with than with a cohort study	Complex design to understand for uninitiated people
Design allows for the control of confounding factors (e.g., matching, case-crossover)	Odds ratios can be difficult to interpret for uninitiated people
	Exposure definitions more limited than in cohort studies

Conclusion

Case-control studies can be very useful in determining the association between drug exposure and health outcomes. This study design is particularly efficient if the event being studied is rare, since only a portion of the study population will be included in the analysis. As with all observational studies, however, it must be ensured that the results are not affected by biases that invalidate the conclusions. The selection of controls in these studies is particularly sensitive to bias. It is necessary to ensure that the controls are representative of the population giving rise to the cases in order to respect the norms of conducting these studies. While case-control were long considered of lower methodological quality than cohort studies, the progresses in statistical and epidemiological methods have repositioned this design favorably in the hierarchy of studies. Moreover, they are often conducted within cohort and randomized control studies to inform on specific study questions that are best answered with the methodology of case-control designs. Hence, when performed according to stringent methodology, the case-control studies represent an important study design in pharmacoepidemiology.

Further Reading

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Cohort Studies—A Brief Overview

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Introduction

In this chapter, we will discuss the history of cohort studies and their use in pharmacoepidemiology, as well as their importance in clinical practice. Clinicians, including pharmacists need to understand cohort studies and other observational designs, their strengths and limitations, as well as the appropriate statistical analyses and the accurate interpretation of their results (Draugalis and Plaza, 2006; Lee et al., 2004).

We will review the details of cohort study designs and the various data sources that can be used. We will conclude with a discussion of best practices when conducting and evaluating cohort studies in pharmacoepidemiology.

A Brief History of Cohort Studies in Pharmacoepidemiology

The cohort design in research spans centuries. In the 18th century, James Lindt conducted what many consider to be the first (pharmaco)epidemiologic cohort study to analyze differences in scurvy development amongst sailors based on diet—ultimately determining that citrus fruits can effectively treat this serious ailment. Perhaps the earliest popularized use of cohort studies in North America came from the insurance industry. The actuarial Society of America published a report in 1903 detailing data derived from policyholders in the United States (US) and Canada from 1870 to 1899 (Actuarial Society of America, 1903). Using existing data, the authors could accurately determine premiums, and employers also attempted to project risk of death based on the data. Cohort studies were also used extensively during the tuberculosis epidemic at the turn-of-the-century, and saw advances in both methodology and analysis. By the late 1940s, large cohort study designs were being conducted throughout the world to address public health concerns. While larger cohort studies continued to be performed through the 1960s and 1970s, interest in improving drug safety and assessing adverse reactions was growing, and the first mention of "pharmaceutical epidemiology" was published in 1974 (Venulet, 1974). As a result, cohort studies investigating drug safety and adverse reactions were being conducted (Jick et al., 1979; Mann et al., 1975; Skegg and Doll, 1977). In 1968, the Medicines Act established the Committee on the Safety of

Medicines in the United Kingdom (UK), but by 1983 researchers continued to be dissatisfied with the available methods. A series of meetings held by the Centre for Medicines Research in 1984 led to the formal recognition of pharmacoepidemiology as a new discipline and set a goal to create an automated database in Britain linking all prescriptions filled with hospital diagnoses (Lawson, 1984). The National Institutes of Health in the United States (established in 1887) had a pivotal role throughout the years by funding large prospective cohort studies, such as the Framingham Heart Study and the Nurses' Health Study (NHS) (Brigham and Women's Hospital et al., 2016; National Heart, Lung, and Blood Institute and Boston University, 2018), and continues to conduct multi-center prospective cohort studies. In an era of "big data", the ability to link records from multiple sources has enhanced our ability to design and conduct pharmacoepidemiologic cohort studies.

Over the years, cohort study methodology and analysis has continued to evolve, enhancing our ability as researchers to use cohort studies to establish causal relationships and allowing observational designs to have broad impacts on both the clinical and regulatory landscape of drug therapy. For instance, the work by Ray et al. (2002) using existing data, related to Vioxx (rofecoxib) demonstrates the potential role of a well-design pharmacoepidemiologic cohort study in impacting the drug market. Approved in 1999 by the US Food and Drug Administration (FDA) for the treatment of arthritis, rofecoxib was touted as a safer alternative to other nonsteroidal anti-inflammatory drugs (NSAIDs) because of its decreased incidence of gastrointestinal adverse events. However, early postmarketing pharmacoepidemiologic studies began to highlight a possible concern for increased risk of acute myocardial infarction and other serious coronary heart diseases (CHD) among rofecoxib users. In fact, researchers from Vanderbilt University were able to use a retrospective cohort study design with data from the Tennessee Medicaid program (i.e., medical and pharmacy claims) to identify the increased risk of serious CHD in rofecoxib users more than 2 years before its official withdrawal from the market in the United States (Ray et al., 2002). By the time Vioxx was officially withdrawn from the market in 2004, an estimated 88,000 American Vioxx users experienced heart attacks, with nearly half of these patients dying (Resnik, 2007). Because signals of this increased risk were detected by researchers well before the results of any clinical trials could show them, it became evident that active postmarketing surveillance of approved drugs should include pharmacoepidemiologic studies. In 2007, the US Congress mandated the FDA to create an active surveillance system (Food and Drug Administration Amendments Act, 2007). Both the Sentinel Program and the Observational Medical Outcomes Partnership (OMOP) were results of this initiative (Platt et al., 2009; Stang et al., 2010). A similar project called the EU-ADR was established in Europe (Coloma et al., 2011).

Description: Defining and Designing Cohort Studies

In the case of the cohort study, groups are identified based on exposure status (Fig. 1). Designing a cohort study often starts with defining the population of interest. Subsequently, those without the outcome of interest (defined through inclusion and exclusion criteria) are selected, and exposure status is assessed. Exposed and unexposed individuals are followed over time to investigate whether any differences exist in the development of an outcome between groups. Exposure groups may be defined as exposed and unexposed, or groups composed of members with different exposures may be compared (e.g., comparative effectiveness studies).

In general, the purpose of a cohort study is to describe an exposure (or multiple exposures in the same population), and investigate the (causal) association with one or multiple outcomes of interest. In pharmacoepidemiology, the exposure is usually drug use, and the most common outcomes studied are effectiveness or safety of that drug therapy.

Study Design

Study Purpose

As with any research study design, the aim of a cohort study will vary based on the type of research question being investigated. Designs can aim to generate new hypotheses, test potential hypotheses, or strengthen the evidence on current hypotheses. The urgency of the answer to the research question can also impact the design of a cohort study.

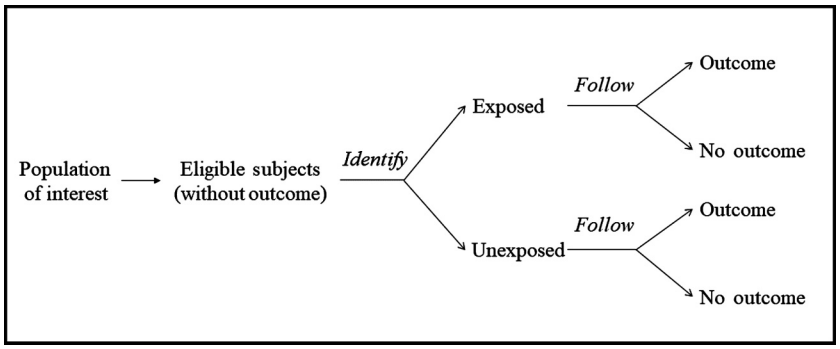

Figure 1 Cohort study design.

Depending on the study aim and context, cohort studies can be divided into two domains. The first domain includes studies whose goal is to assess prescribing trends and medication use in the general patient population, or in specific subpopulations; these studies are often known as drug utilization studies. They contain questions related to diagnosis or disease staging, comorbidities, other medications use, discontinuation of treatment, or other patient characteristics predicting treatment. Often, studies with these aims are more exploratory and hypothesis-generating in nature. For example, investigators in the United Kingdom conducted a population-based cohort study using a primary care database, the Clinical Practice Research Datalink (CPRD) to investigate the prescribing trends among centenarians between 1990 and 2013 (Hazra et al., 2016). They found that 73% of subjects had received at least one prescription, and the sample had a median of seven prescription items per subject. In another study, investigators used Medicaid data from a US state to quantify the use of antipsychotics and anticonvulsants during pregnancy (Epstein et al., 2013). Results such as these can be used to inform prescribing practices and highlight problems that would otherwise go undetected.

The second domain includes cohort studies addressing research questions about effectiveness, efficacy, safety, or studies investigating causal associations based on a priori stated hypothesis. These studies add important information to existing evidence resulting from clinical trials by accounting for patients' or providers' actual behavior under uncontrolled situations. Cohort studies attempting to establish causal associations must use adequate methodology to reduce confounding and the inherent bias threatening observational studies. These methods will be discussed in more depth later in this chapter. Some of these studies may be performed with the aim of investigating the potential for causal association (either a beneficial, or harmful) that is otherwise unfeasible or unethical to perform using an experimental design. For this reason, retrospective cohort studies can be useful to study drug effects during pregnancy, for instance. For example, statins are categorized as a pregnancy risk factor "X" in the United States, indicating that they are contraindicated in pregnancy. Despite this risk, however, some women do inadvertently take statins during the first trimester of pregnancy. To determine whether there was a difference in pregnancy loss between women taking statins shortly before pregnancy and those who did not take a statin, investigators conducted a retrospective cohort study using CPRD in the United Kingdom (McGrogan et al., 2017). Because the database includes medical records, investigators were able to identify the start and end dates of pregnancy and whether a statin prescription was recorded during or in the 3 months prior to the start of pregnancy. Those exposed to statins had a higher risk of spontaneous pregnancy loss. Using a cohort design to investigate these important clinical questions is critical because assigning anyone to use statins during pregnancy would be unethical.

Other cohort studies aim to evaluate whether a certain drug causes an adverse drug event (ADE), sometimes based on hypotheses raised by preclinical or small clinical studies. The occurrence of Reye Syndrome with the use of aspirin in pediatrics is one example of a rare, but serious, ADE that was identified using observational data long after the drug was initially marketed (Halpin et al., 1982).

While evidence about medications is often gathered for officially approved indications, studying the effects of off-label drug use is equally important. In addition to investigating whether a proposed hypothetical indication might be effective, cohort studies can also be used to examine current off-label prescribing trends. For instance, many drugs are not approved for use in children due to lack of evidence from clinical trials, but are used in this population nevertheless. A retrospective cohort study using administrative claims data from Medicaid programs in four US states reported on the off-label use of antidepressants in children and adolescents (Burcu et al., 2017). This study ultimately found an association between Type 2 diabetes mellitus (T2DM) and certain antidepressants, which is important to clinicians who are considering the off-label use of these agents in this population.

Recognizing the need for more research into the safety profiles of older drugs, the Agency for Healthcare Research and Quality (AHRQ) in the US funded the Centers for Education and Research in Therapeutics (CERTs) to improve how drugs are used in the general population. Because of this new initiative more safety concerns are being recognized. Studies suggest that over half of the existing drugs have a postmarketing label change due to major safety issues, and about 20% of drugs get black box warnings after initial marketing (Strom, 2006). Anywhere between 3% and 4% of drugs approved in the United States are ultimately withdrawn from the market for safety reasons—largely due to evidence gained from cohort and other pharmacoepidemiologic studies.

Cohort Study Classification

Cohort studies are classified by the timing of data collection relative to the time when the investigator designs the study (Grimes and Schulz, 2002), as seen in **Fig. 2**.

In prospective cohort studies, the investigator conducts the research by first identifying the population of interest and then classifying subjects as either exposed or unexposed. The investigator follows these subjects in time, recording the development of the outcome of interest. Because the investigator is following the subjects in real-time, these types of studies tend to take the longest to complete. A key element of defining a prospective cohort study is that, at the time the investigators begin enrolment and baseline data collection, study participants are disease-free (i.e., have not yet experienced the outcome(s) of interest). For example, the Framingham Heart Study (National Heart, Lung, and Blood Institute and Boston University, 2018) was designed as a prospective cohort study. Starting in 1948, investigators recruited about 5000 men and women from Framingham, Massachusetts to participate in the study with the objective of identifying risk factors for cardiovascular disease (CVD). Because CVD was their outcome of interest, only subjects without a history of cardiovascular disease were chosen to participate. Every 2 years, subjects' exposure to a variety of lifestyle and medical factors is assessed while investigators document the occurrence of any CVD. The study continues to this day.

In retrospective cohort studies, the investigator uses data that has already been collected to identify exposure groups and outcome occurrence. Because the data has already been collected, the investigators do not need to wait for outcomes to occur, and thus spend a relatively short amount of time identifying exposure and outcome status. A key element of defining a retrospective cohort study is that at the time the investigators design the study, the follow-up data is complete and (some) subjects already experienced the

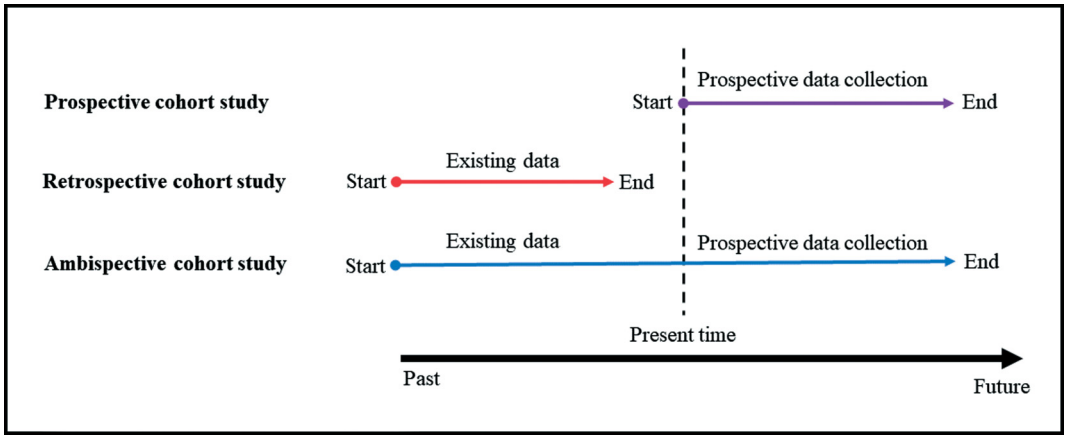

Figure 2 Cohort study classification. *Start*, Beginning of follow-up for study participants; *End*, Follow-up ends for study participants. *Source: Figure based on Grimes and Schulz, 2002.*

outcome(s) of interest. Even though information on exposure and outcome(s) is already available, study design procedures, in particular defining inclusion and exclusion criteria, should be planned without consideration of outcome(s) occurring during follow-up. A study conducted in 2015 utilized this design to investigate whether the risk of T2DM in children and adolescents was higher amongst users of atypical antipsychotics (Sohn et al., 2015). The investigators used data from health and pharmacy insurance claims between 2007 and 2009 to ascertain whether subjects were exposed to atypical antipsychotics. After defining the exposure date, they looked forward through the data and recorded any instance of the outcome, a diagnosis for T2DM. Because the subjects' exposures and outcomes occurred prior to the investigator's study onset, this is considered a retrospective cohort design. As a note, data collected prospectively in cohort studies or research-related longitudinal clinical evaluations can be used to later design retrospective cohort studies to address other research questions than those the original studies were designed to address. For example, a recent retrospective cohort study evaluated the association between bladder antimuscarinics and cognitive decline using data from the National Alzheimer's Coordinating Center (NACC) (Moga et al., 2017). NACC was established in 1999 to further research into Alzheimer's disease and related dementias and has since recruited nearly 40,000 subjects with and without dementia from centers around the United States (Beekly et al., 2004). Although NACC data collection was not designed to specifically investigate the association between bladder antimuscarinics and cognitive decline, the investigators could design the study with existing data from NACC.

Ambispective (or retrospective-prospective) cohort studies combine aspects of both retrospective and prospective study designs. In these studies, the investigator uses data that has been collected in the past to determine exposure status, but then continues to follow those subjects in real-time for outcome occurrence. One example is a study investigating the effectiveness of systemic chemotherapy (SC) alone versus SC plus a gastrectomy for patients with gastric cancer and liver metastasis (Liu et al., 2015). Investigators used retrospectively collected data on which treatment subjects received, and then beginning in 2012 followed subjects for synchronous metastases. Because investigators used data from the past to obtain exposure status, then followed subjects in real-time for outcome occurrence, this study qualifies as an ambispective design.

Defining Exposure and Outcome(s) in Cohort Studies

Depending on the study classification (see above), to quantify exposure(s), outcome(s), and other variables of interest (i.e., confounders, effect modifiers), the investigator has to either plan for data collection, or to rely on the existing data. Primary data collection as part of prospective cohorts gives researchers the ability to use validated definitions; exposures and outcomes, as well as other important variables are usually assessed through interviews, self-completed questionnaires, objective measurements, or laboratory tests. Retrospective studies rely on existing data collected from surveys, clinical records, or insurance claims; although the investigator has no control over the way data are collected, they still need to carefully consider how to effectively use existing information in defining variables of interest to minimize misclassification. Whenever available, investigators should consider validated definitions that compare the sensitivity, specificity, or predictive value of existing data to more accurate data sources (e.g., insurance claims compared to medical records).

Data Sources and Types of Data

In designing cohort studies, especially those retrospective in nature, important considerations should be given to selecting the data source. The choice of data can have important ramifications for the study design, data analysis, and generalizability of cohort studies. Thus, it is important that astute readers understand the nuances of different data sources available. Ideally, the data source of choice is large, stable, representative, and verifiable (Lao et al., 2016). When deciding between data sources, investigators need to consider the relative size, cost, and speed of accessing the data, in addition to generalizability.

While some data used in pharmacoepidemiologic cohort studies are available to the public (including some data provided by the Centers for Medicare and Medicaid Services [CMS] in the United States), other data sources are highly restricted. For instance, if protected health information exists in the data that can be traced back to individual subjects, the project requires review by an ethics committee, like the Institutional Review Board (IRB) or its equivalents. Furthermore, if data are the property of, or managed by an organization, investigators will be required to agree to specific terms specified in a Data Use Agreement (DUA) which clearly states the extent to which data can be used, the approved users, and the duration for use.

Datasets used in cohort studies may contain information on only a few hundred subjects, or may contain tens of millions of subjects. Small sample sizes may call into question the power of the study to detect a difference between exposure groups, while studies using large datasets (e.g., administrative data) may be "overpowered" and detect statistical differences that may not be clinically relevant.

It is also important to note that because the design of cohort studies involves selecting groups based on exposure (not outcome) status, investigating rare outcomes often requires substantially larger sample sizes than would be necessary for a case–control study. In order to detect a relative risk of an outcome that occurs in about 1% of the unexposed subjects, an investigator would need to include about 3000 subjects in each group to achieve 90% power. However, if the prevalence of the outcome was only 0.001%, over 300,000 subjects would be required in each group to achieve the same power.

Investigators should also consider the validity of both exposure and outcome identification. If either is incorrectly specified, any results and interpretation may not be generalizable to a population outside of the study sample. Specifically, misclassification of exposure and/or outcome can lead to spurious results. The goal specificity and sensitivity of measures for exposure and outcome depend on the purpose of the study. If one must choose between the two, maximizing the specificity of the outcome definition and maximizing the sensitivity of the exposure definition will help minimize bias (Brouwer et al., 2015a). When using claims data to define exposures and outcomes, the better algorithm to use can include a combination of diagnosis and medication codes to lower misclassification rates (Rector et al., 2004).

Investigators interested in conducting cohort studies have a plethora of options from which to select the best data. Available data sources for conducting cohort studies include databases of spontaneous ADE reporting or active surveillance, hospital records, health insurance enrollment data, medical claims data (either from outpatient or inpatient settings), or prescription claims data. While these data sources are described in detail in a different chapter, we will briefly discuss them as related to the design and conduct of cohort studies in pharmacoepidemiology.

Administrative Data

Administrative data sources have become more common in pharmacoepidemiology in recent years. Generally speaking, these data sources only contain medical information that would be relevant for billing purposes, which may limit the study questions that can be answered using them (Schneeweiss and Avorn, 2005). Because of their large size, these data sources often require investigators to have advanced computer programming and statistical knowledge as well (Brouwer et al., 2015b). Furthermore, while administrative data sources with pharmacy information contain records of each time a subject fills a prescription, few contain important clinical characteristics such as smoking status, alcohol use, and body mass index. Many different sources of administrative data exist in the United States and throughout the world. For example, in the Ontario province in Canada, administrative databases contain enrollment, pharmacy, outpatient, and inpatient data on all Canadians who utilize the health system in this province (Cadarette and Wong, 2015). In the US, large administrative databases are available from CMS, as well as from a variety of private insurance companies. The National Health Insurance Research Database in Taiwan contains insurance claims for 99.9% of Taiwan's population due to its single-payer system (Cheng et al., 2011).

Clinical Data

Cohort studies might also utilize data that were collected for routine clinical use and/or patient monitoring. Studies have shown that using automated health records collected for clinical purposes to conduct cohort studies can be an effective method of data collection (Hashikata et al., 2011).

In the United Kingdom, one of the largest sources of electronic health records used for research is the CPRD, which has been used in conducting several retrospective cohort studies. One example is a study that aimed to confirm whether corticosteroid treatment was associated with an increased fracture risk (van Staa et al., 2001). In fact, literature reviews have found that, among epidemiological studies, the most frequently used data source was the CPRD, formally known as General Practice Research Database, which accounts for about 20% of the studies using large existing data. Of these, 40% used a cohort design (Perrio et al., 2007).

Kaiser Permanente (founded in 1945) is one of the largest health plans in the US, serving approximately 11.7 million members (Kaiser Permanente, 2018). In addition to providing care, its Division of Research conducts and publishes health services and outcomes research (including pharmacoepidemiologic cohort studies). Using electronic health records obtained from Kaiser Permanente, investigators were able to determine that there was no increase in the risk of recurrent breast cancer in subjects taking paroxetine concurrently with tamoxifen, despite widespread controversy about this drug combination (Haque et al., 2016).

Studies using clinical data might also aim to answer questions about the effectiveness of emerging therapies for which guidelines have not yet been established. The Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (the only publicly funded health care provider in Hong Kong) provides electronic health records for research. When investigators were concerned about the growing trend of using gastro-protective agents to prevent gastrointestinal bleeds (GIB) in patients using the

anticoagulant dabigatran, they were able to construct a cohort study using data from CDARS to examine this relationship. With dabigatran dispensing records identifying exposure status and diagnosis records for GIB to determine outcomes, the investigators used Poisson regression controlling for baseline comorbidities and medication use to demonstrate that that patients who used gastro-protective agents with dabigatran had a 48% decrease in risk of GIB compared to those who used dabigatran alone (Chan et al., 2015).

Other Sources of Data

Spontaneous reporting systems were established after the public health disaster of thalidomide and the causal relationship between the drug and birth defects was determined. Between 1961 and 1965, 10 countries began their own reporting systems. In 1968, the World Health Organization (WHO) formed the WHO Programme for International Drug Monitoring (PIDM). As of January 2016, 123 countries report ADEs to the PIDM, which registered over 10 million reports in 2014 (World Health Organization, 2018). In the US, using the FDA's Adverse Event Reporting System (FAERS), health professionals, consumers, and pharmaceutical manufacturers are able to voluntarily submit reports of suspected ADEs. These systems are a cost-effective way to detect rare and serious ADEs that clinical trials do not discover. However, given the difficulties to determine the denominator for reporting rates of events (i.e., total number of individuals using a certain drug), their utility lies in generating hypotheses (also known as signals) of potential problems that require further investigation. Conducting cohort studies using data from spontaneous reporting systems can be fraught with concerns of validity, as nearly anyone can submit a report with very little evidence. In one study comparing the opinions of clinical pharmacists and physicians, the pharmacists agreed only 50% of the time as to whether a drug caused a hospitalization, and disagreed with physicians approximately one-third of the time (Karch et al., 1976). Whether an ADE is actually reported to the system is also a concern, as estimates suggest that less than 5% of nonserious reactions are reported to British and American spontaneous reporting systems (Rawlins, 1995; Scott et al., 1987).

Prescription event monitoring provides another source of data from which to conduct cohort studies. In the United Kingdom, the Drug Safety Research Unit (DSRU) receives individual-level longitudinal prescription information for every drug currently being monitored. After a few months, the DSRU sends prescribers a questionnaire seeking information about possible ADEs. Because the studies conducted by the DSRU (and by investigators using its data) are non-interventional and national, this data source is largely representative of current prescribing practices in the United Kingdom, though currently information is only collected on general practice prescribers.

Combining Data Sources

Considering the limitations of different data sources either in terms of the available information, as well as in terms of the specific population included, several initiatives are currently underway to develop methods to combine data from multiple sources. In the United States these include OMOP, the Sentinel Initiative, as well as the Health Maintenance Organizations Research Network, while Canada has the Canadian Network for Observational Drug Effect Studies (CNODES), Europe has the EU-ADR Alliance and the Innovative Medicines Initiative-Pharmacoepidemiological Research on Outcomes of Therapeutics (IMI-PROTECT), and in Asia the Asian Pharmacoepidemiology Network (AsPEN) has been established.

A 2015 literature review analyzed 22 pharmacoepidemiologic studies that used multiple databases, ranging from 2% to 17. 82% of these used a cohort study design, and claimed that the use of multiple data sources was motivated by improving power (Bazelier et al., 2015).

Data Analysis and Interpretation

The results of a cohort study give the investigator information on the relative risk and attributable risk of the outcome based on exposure status.

Estimates

The most commonly used estimates in cohort studies along with calculations for each of these can be found in Fig. 3.

The cumulative incidence, or risk, in either the exposed or unexposed group is the probability of the outcome occurring in that group. When a ratio of risks in the exposed and unexposed groups is constructed, this is known as a risk ratio or relative risk (RR). The attributable risk, also known as the excess risk, is the arithmetic difference between the incidence (either calculated as risk or rate) in the exposed and unexposed groups. Calculating the attributable risk implies an established causal association and it is important for considering the impact of that association in the exposed population (Walter, 2000).

The rate ratio is a ratio of the incidence rates of the outcome in the exposed and unexposed groups, or incidence density that takes into account follow-up for each group. A rate or risk ratio larger than one means that the exposed group is at a greater risk for the outcome than the unexposed group. A risk ratio less than one means that the exposure appears to protect against the disease (i.e., outcome). If the risk ratio is at or near one, it means that the exposed group is at a similar risk of the outcome as the unexposed group, and that there does not appear to be an association between the exposure and disease. Similarly, risk (rate) differences are interpreted in comparison to the null value of 0 (Fig. 4).

While the risk ratio does not consider the differences in follow-up for different participants, the rate ratio and the hazard provide instantaneous measurements at different time points.

	Outcome	No Outcome	Total	Total follow-up time
Exposed	a	b	a + b	PY_e
Unexposed	c	d	c + d	PY_0

Estimate	Calculation
Incidence density (Rate of disease)	Exposed: $ID_e = \frac{a}{PY_e}$; Unexposed: $ID_0 = \frac{c}{PY_0}$
Cumulative incidence (Risk of disease)	Exposed: $CI_e = \frac{a}{a+b}$; Unexposed: $CI_0 = \frac{c}{c+d}$
Incidence density (Rate) Ratio	$RR = \frac{ID_e}{ID_0} = \frac{a/PYe}{c/PY_0}$
Risk ratio (Relative Risk)	$RR = \frac{CI_e}{CI_0} = \frac{a/(a+b)}{c/(c+d)}$
Attributable risk	$\frac{a}{a+b} - \frac{c}{c+d}$ or $\frac{a}{PY_e} - \frac{c}{PY_0}$

Figure 3 Measures of disease frequency and association in cohort studies.

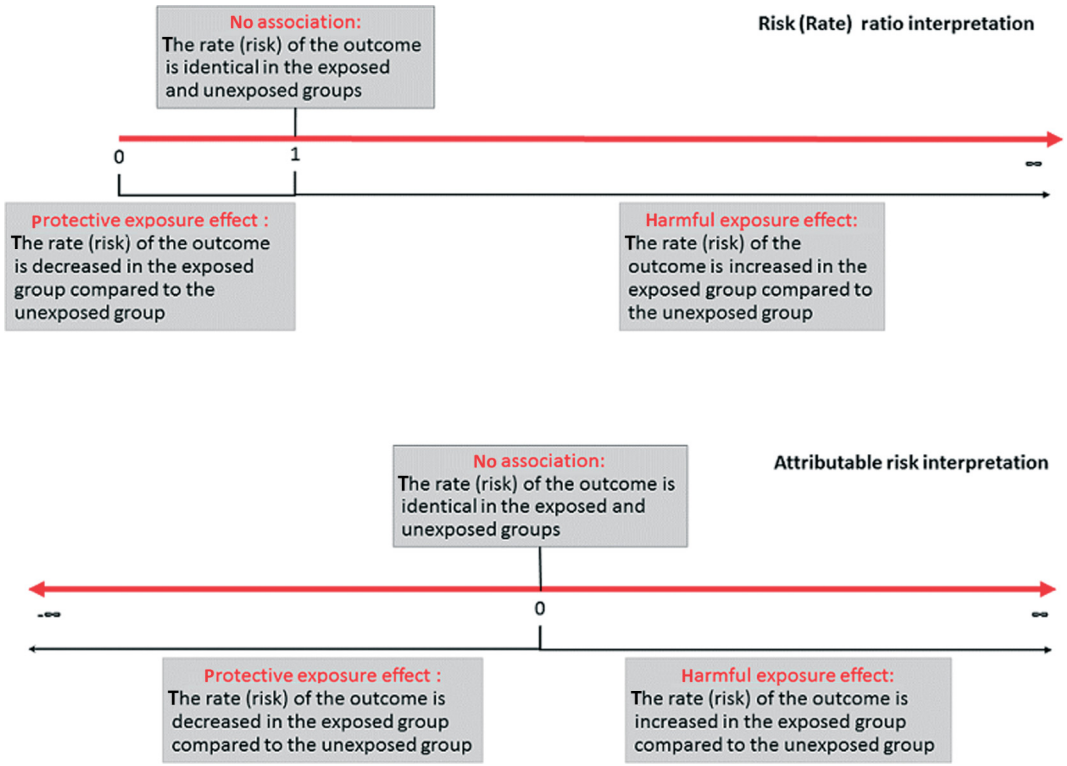

Figure 4 Interpretation of different measures of association in cohort studies.

Statistical Methods

While this section is not intended as a comprehensive description of statistical methods, we are presenting information that might be relevant and help the reader understand the available options for analysis in cohort studies.

Linear regression is used to analyze outcomes that are measured as continuous variables. Such examples include blood pressure measured in millimeters of mercury, adherence measures, and scores. One such example is a cohort study analyzing data from the population-based Norwegian Mother and Child Cohort Study (MoBa), which has collected questionnaire data as well as biological

material on approximately 110,000 women who gave birth between 1999 and 2010 in Norway (Magnus et al., 2006). Using MoBa data, researchers investigated whether prenatal antidepressant use is associated with behavioral problems in children (Brandlistuen et al., 2017). The outcome was measured as a score calculated from the mother-reported Child Behavior Checklist and multivariable linear regression adjusted for confounding factors was used to evaluate the association between prenatal antidepressant use and the behavior score measured in children.

More commonly, however, outcomes in cohort studies are measured as binary variables and analyzed using logistic regression (Levy and Stolte, 2000) that generates odds ratios (OR) (Bender, 2009). When the absolute risk of an outcome is small, the OR approximates the RR, but for more common outcomes the ORs are often larger than the risk ratio. In the earlier example of the cohort study evaluating the association between antimuscarinic use and cognitive decline using data from NACC, the outcome was measured as a binary variable: cognitive decline from baseline (yes/no). Exposure to antimuscarinics was determined based on the subject's responses during study visits. Using logistic regression adjusted for confounding factors, investigators reported an OR of 1.4: the odds of cognitive decline were 40% higher among bladder antimuscarinic users compared to nonusers (Moga et al., 2017) when measured using the Mini-Mental State Examination.

Cox proportional hazard regression (used in survival or time to event analysis) is commonly used in cohort studies and takes into account variable observation times, either because participants entered the study at different times, or because they left the study prior to study completion. In these analyses the outcome is measured as time until that outcome occurs. Cox proportional hazard regression models produce the hazard ratio (HR), which is interpreted in a very similar way to the other relative measures, like the risk ratio, but represents the instantaneous risk over a defined time instead of a cumulative risk over the entire study. In studies that utilize Cox models, descriptive results can be reported using Kaplan–Meier curves that allow one to determine the proportion of each exposure group that has experienced the outcome of interest at each point in time. Cox models were used in one cohort study that used data from the Framingham Heart Study. At the time of investigation, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) had just released their cholesterol management guidelines, which changed the eligibility criteria for statin therapy compared to the National Cholesterol Education Program's (NCEP) 2004 Guideline (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Stone et al., 2014). Investigators set out to determine whether the ACC/AHA guidelines improved the identification of subjects at risk for cardiovascular events compared to the NCEP guidelines (Pursnani et al., 2015). In this study, exposed subjects were those whose statin eligibility was determined by the ACC/AHA guidelines, whereas the unexposed subjects' statin eligibility was determined by NCEP guidelines. The main outcome of interest was time to CVD. Investigators found that subjects whose statin eligibility was determined by ACC/AHA (exposed subjects) had a hazard ratio for cardiovascular disease of 6.8. Interpreting this HR, one can say that at any time, 6.8 times as many subjects in the ACC/AHA eligibility group experienced an event compared to subjects in the NECP eligibility group. This meant that the ACC/AHA guidelines more accurately identified high-risk subjects. This cohort study was important in validating the use of these new guidelines in clinical practice.

In contrast, if the investigator is instead interested in the number of outcomes (frequency or rate) of a rare event in a set period, Poisson regression would be the more appropriate statistical technique. Both Poisson regression and Cox regression are often used in time to event analysis, but when the outcome of interest is a frequency or rate of an event per unit time, the appropriate model would be Poisson regression. The ability to identify the correct model use in the data analysis section of a cohort study is important and can determine the validity of that study's results.

Cohort Studies and Causal Inference

The discordance in results among observational studies, and between observational studies and randomized experiments has led to an undermining and devaluing of pharmacoepidemiologic studies by many clinical practitioners and researchers. To surmount this growing problem, guidelines such the **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology (STROBE) or the **RE**porting of studies **C**onducted using **O**bservational **R**outinely-collected health **D**ata in **P**harmaco**E**pidemiology (RECORD-PE), have been developed (Benchimol et al., 2015; von Elm et al., 2007). These guidelines clearly specify key study design, data analysis, and result interpretation techniques for the different types of observational studies. Following the STROBE, RECORD-PE guidelines will help ensure that a cohort study has been rigorously designed and analyzed in a way that reduces potential bias.

By adhering to these guidelines and rigorously choosing methods that reduce the risk of bias, investigators can increase the validity of their results and use them to further determine a causal association. While selection bias and confounding factors can be addressed in the study design and/or data analysis, it is most important to understand the threat of bias (e.g., selection bias) or the types of confounding in cohort studies and how they can impact study results.

Establishing Causality

In general, there are three types of associations a cohort study must exclude to convincingly draw a causal conclusion. One of the most important prerequisites to conducting a cohort study is to establish biological plausibility for the hypothesis. As the health-care research sector moves more toward large data investigations, this step is especially important. Indeed, statistical significance can be found for any factors if the data are large enough by the very definition of most common statistical significance tests.

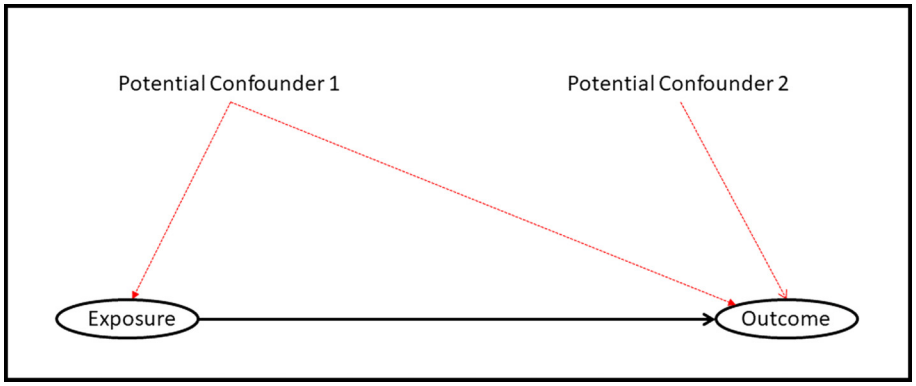

Figure 5 Directed acyclic graph illustration.

When assessing the strength of the causal association purported by a cohort study, it is useful to use five criteria which were established in the first Surgeon General's Report on Smoking and Health (Terry, 1964). First, the association should cohere with existing information and have a biological plausibility, as discussed above. The association should be consistent and specific, and have a clearly established time sequence. Finally, there should be some strength of the association which can be established quantitatively or via a clear dose–response relationship.

Investigators might also consider using structural equation modeling as a framework for causal inference, either through equations or diagrams (e.g., directed acyclic graphs [DAGs]) to assess the relationships between exposure and outcome while including all other known and unknown potential confounding factors. A DAG is illustrated in Fig. 5 demonstrating the causal inference framework for an association between one exposure and an outcome of interest. Using solid arrows to represent the relationship between an exposure and outcome and dashed arrows to represent confounding relationships, investigators can narrow down all confounding effects to determine the true causative nature of an association. Potential confounders might directly affect the exposure, the outcome, or both. DAGs are particularly useful for visualizing potential confounders that cannot be measured to assess their role as true confounders and the potential for residual confounding. Fig. 5 depicts a simple example of an exposure–outcome relationship. Based on the DAG, potential confounder 1 is a true confounder, thus important to measure and include in the analysis. However, potential confounder 2 is not a true confounder, thus the investigator need not to worry about being able to measure it.

Having a thorough understanding of all of the potential relationships between the exposure and the outcome allows investigators to accurately design studies and models while accounting for true confounders and avoiding introducing bias, like collider bias (Fig. 6). For example, using the relationship between vitamin use in pregnancy (exposure) and infant birth defects (outcome), Hernan et al. investigated the minimum necessary set to include in the analysis to account for confounding without introducing bias (Hernán et al., 2002). In this scenario, maternal age (potential cofounder 1), genetic factors (potential confounder 2), and maternal weight gain (potential confounder 3) were all considered as potential confounders. However, upon drawing a DAG, it was determined that maternal weight gain was a collider, as both maternal age and genetic factors determine maternal weight gain. Therefore, none of these factors need to be adjusted for in the analysis, as the collider closes this noncausal pathway.

Beyond a strong theoretical basis for undertaking the study, it is important to reduce the possibility of artifactual (spurious) and indirect (confounded) associations. Spurious associations can arise either due to chance or bias. Chance is unsystematic variation that can be protected against using strong statistical tests and thoroughly establishing a biological hypothesis for the association. Bias

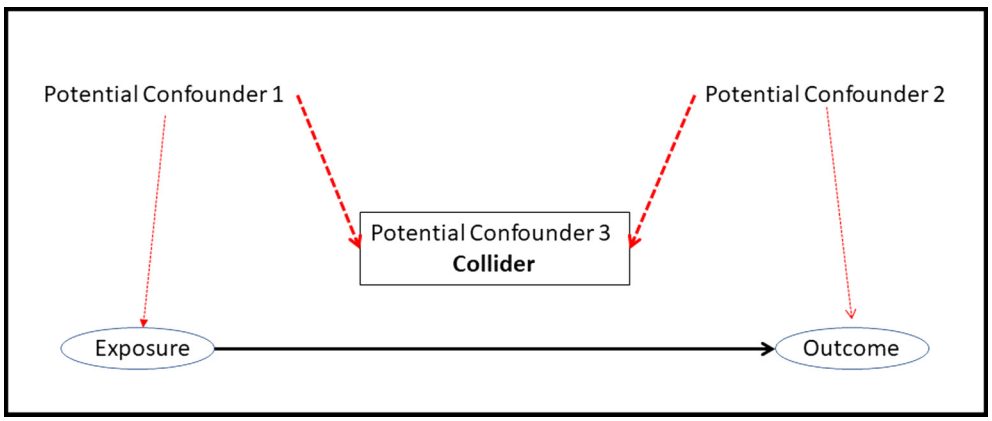

Figure 6 Directed acyclic graph with collider.

is a systematic variation in the data that, once present, cannot be corrected. Protecting against bias in cohort studies is accomplished by rigorously designing the study. Confounded associations can be controlled through random allocation, subject selection (exclusion criteria and matching), and data analysis (stratification, mathematical modeling).

However, the investigator should always remember that even the best methods to adjust for bias are only as good as the theoretical foundation of the research. If important confounders are not measured or are misclassified any adjustment will be inadequate. The student reading research should approach all observational research with a healthy dose of skepticism, and realize that "because human judgment and subject-matter knowledge are fallible, causal inference from observational data is also fallible in ways that causal inference from ideal randomized experiments is not" (Hernán, 2015).

Types of Bias

One of the most common threats to validity in cohort studies is confounding, in which an external variable is 'mixed' with the exposure such that it confounds the effect of the exposure on the outcome of interest. As described in the previous section, in order to be considered a confounder, a variable must be associated with both the exposure and the outcome, but cannot be an effect of the exposure. As an example, consider a cohort study that aims to establish whether an association exists between selective serotonin reuptake inhibitors (SSRIs) and T2DM. To determine whether a subject's weight should be controlled for, the investigator must first determine whether it is associated with the exposure. Indeed, SSRIs have been known to cause weight gain. However, weight gain also has an association with the outcome because T2DM is more common in those with a higher weight. Based on only these two considerations, the investigator might choose to control for weight in this cohort study. However, doing so would actually eliminate the detection of any possible real association between SSRIs and T2DM if the mechanism for that association occurs via an increase in weight. Because the variable of weight gain is an effect of the exposure (SSRI use), it should not be controlled for as a confounder in this hypothetical cohort study. If the investigator is concerned that weight gain is an important factor in this relationship, bias can be reduced by stratifying on different weight categories at baseline, or by adjusting for weight gain using multivariable methods.

As seen in the example above, comorbidities are often important confounders in a cohort study. Thus, it is important to be able to accurately identify and characterize these comorbidities. Measures of comorbidities should be carefully evaluated from the available literature before being used in a cohort study, as improper measures can leave substantial residual confounding (Jackson et al., 2011). Numerous studies have shown that using diagnosis codes to identify comorbidities, especially in the inpatient setting, can lack sensitivity for certain conditions (Fisher et al., 1992; Iezzoni et al., 1992; Powell et al., 2001; Quan et al., 2002). In these cases, a composite weight score (such as the Charlson Comorbidity Index) may be a better measure to use when resolving confounding due to comorbid conditions (Charlson et al., 1987).

Information bias can arise when the information about the exposure or the outcome is not accurate. It can occur during questionnaires if a subject cannot remember information about a drug. Information bias can also be introduced if an interviewer is not blinded to the subject's exposure group. If a prospective cohort study were being conducted to determine the effects of pediatric vaccines on the development of autism and the interviewer believed there was an association, questions could be asked in such a way as to bias those women who the interviewer knew had exposed their children to vaccinations. Interviewers might overstate or understate certain questions based on their personal bias toward the exposure group, even unknowingly. Blinding is the best way to remove this sort of bias.

A related bias occurs if a specific outcome is preferentially diagnosed in an exposed group, which is known as detection bias. For example, suppose a cohort study was designed to compare the incidence of migraines between users and nonusers of a contraceptive. If a physician is aware that a patient is a user of the medication of interest, he or she might be more tempted to diagnose the patient as having the outcome because of detection bias. To avoid this bias, blinding, when possible, plays an important role. In cohort studies using existing data, blinding can be seen through the rigorous design of the study to "ignore" outcome detection until after exposure groups and follow-up are determined.

Protopathic bias, also known as reverse causality bias, arises when an exposure is used to treat an adverse effect that is related to the outcome. Suppose a study was investigating in whether aspirin use in pediatrics causes Reye's Syndrome. As seen in Fig. 7, the relationship in which the investigator is interested is labeled "A." However, Reye's Syndrome can cause a fever which might be treated with aspirin (relationship "B" in Fig. 7). Thus, there is no way for the investigator to determine whether aspirin use is directly causing Reye's Syndrome, or if those with Reye's Syndrome are more likely to be treated with

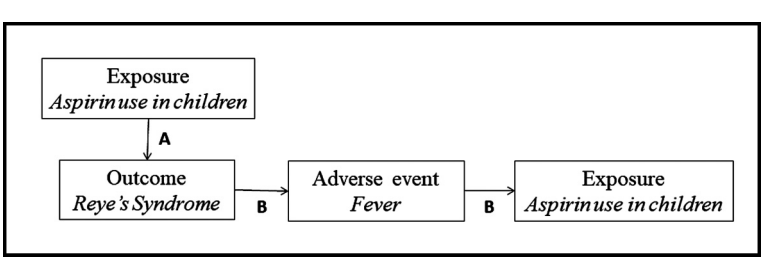

Figure 7 Protopathic bias.

aspirin. In order to reduce this bias, it is important to define the exposure in such a way that its use does not correspond with the outcome. In the example of aspirin and Reye's Syndrome, the investigator could exclude subjects who experience the outcome prior to receiving aspirin.

One type of bias that is specific to retrospective cohort studies is known as immortal person-time (Rothman et al., 2008). This bias arises when inclusion criteria prevent the outcome from occurring for the included subjects. For example, consider a study investigating the incidence of rhabdomyolysis with statin use. The inclusion criteria require subjects to take any statin for at least 3 months to be included in the exposed group. While this type of design may seem useful in that it reduces the possibility of exposure misclassification, it also introduces immortal time bias depending on when follow-up starts. The study is designed in such a way that it excludes anyone who experienced the outcome of interest (rhabdomyolysis in this example) and discontinued the medication prior to 3 months of use. The included exposed subjects are thus "immortal" during the first 3 months of statin use, if these 3 months are included in the follow-up; in addition, only subjects less likely to experience the outcome of interest are being selected for inclusion in the exposed group if the outcome can occur after shorter exposures.

Selection bias can occur when prevalent users are studied instead of new users. This type of selection bias is actually a form of immortal time bias, in which the only subjects included in the exposed group are those who have continued to be exposed long enough to be identified. As an example of the effect this form of selection bias can have on the results of a cohort study, we can consider that several observational studies seemed to suggest that statins improved survival in cancer patients. A study conducted in 2017 set out to emulate a randomized clinical trial (RCT) of statin initiators and nonusers to determine the true relationship between statin use and mortality in cancer patients. After appropriate methods were undertaken to reduce selection and immortal time bias (including requiring users to be incident, and stopping follow-up when drug treatment ceased), the study found no significant mortality benefit with statin use (Emilsson et al., 2017). These results demonstrate that the spurious association identified by previous studies was likely due to immortal time and selection bias, because cancer patients who were taking statins were likely healthy enough to be concerned about their chronic health conditions, and thus more likely to have a longer survival time. Having a clear definition of "time-zero" and syncing treatment assignment with eligibility determination is an important component when designing cohort studies to emulate RCTs and remove bias (García-Albéniz et al., 2017). Ensuring that the start of follow-up and exposure coincide in a cohort study is important to reduce bias, and is another reason new users of a drug are often chosen instead of prevalent users (Lajous et al., 2015).

The healthy patient (or healthy user) bias arises when the health status of a subject influences the likelihood of the outcome. Often, if exposure is defined based on the use of a drug, then the exposed subjects are more likely to be health-conscious and may be less likely to experience an outcome tied to poor health. One rather prominent demonstration of the healthy user bias was in the observational studies investigating the link between estrogen use and breast cancer. Whereas the Women's Health Initiative (WHI) demonstrated a clear increased risk of breast cancer with estrogen use, observational studies failed to identify this link due to the healthy user bias.

Channeling bias, also known as confounding by indication, occurs when a potential association between an exposure and outcome is affected by disease severity. For example, if a drug is prescribed to patients who are already at a higher risk of a particular outcome, the results of a cohort study might indicate that the drug increases the risk for the outcome (Emery and Grahame, 1982). One recent study investigated the associated between inhaled corticosteroids (ICS) and hospitalizations in a group of subjects from an administrative claims database (Filion et al., 2016). The results of this cohort study demonstrated that new users of ICS had higher rates hospitalizations than nonusers. However, after an examination of the data, investigators determined that the ICS of interest had become restricted on the insurance formulary, resulting in only subjects with more severe disease being prescribed. Because those taking the medication were also more likely to experience the outcome independent of their exposure, a channeling bias was introduced. To avoid confounding by indication, an active comparator consisting in a drug recommended for the same indication, or even disease severity, would be preferable over a nonuser group.

Exposure misclassification bias occurs when a subject is incorrectly identified as being exposed or unexposed. This type of bias is especially important when using administrative databases as a data source for a retrospective cohort study. Because the only information on exposure status is gained from claims submitted to a payer, investigators must be aware that there will be a group of subjects who are actually exposed, but because their medication was not billed to payer, are classified as unexposed for the purposes of the study. This can occur as a result of low-cost generic programs that incentive subjects to pay for their medications out-of-pocket, medication claims being submitted to a supplemental payer, or the subject receiving samples of the medication from a provider (Brown et al., 2017; Pauly et al., 2016). If the concern for exposure misclassification is high, the investigator should adjust accordingly in the analysis and result interpretation.

Methods for Reducing Bias

Keeping in mind the many sources of bias in observational research, investigators using cohort study designs have many options to reduce bias and confounding in their studies. Both measured and unmeasured confounders can be addressed through study design as well as in data analysis.

For reducing bias due to known and measured confounders, the cohort study design can match exposed to unexposed subjects. In addition, the investigator can identify potential sources of bias and increase levels of restriction in the design to mimic high and low risk groups, similar to those identified in RCTs (Schneeweiss et al., 2007). When cohort studies are designed to replicate RCTs, the results are closer to those achieved through randomized experiments design (Hernán et al., 2008).

The association between postmenopausal hormone replacement therapy (HRT) and CHD has been controversial. Initially, large observational studies found a reduced risk of CHD among HRT users (Grodstein et al., 2000, 1996), but then the WHI—a large RCT—found that HRT users actually had, a higher risk of CHD than nonusers (The Women's Health Initiative Study Group, 1998), researchers went back to these observational studies and found flaws in methodology that had led to the erroneous conclusions. In one such study, investigators used data from the NHS and attempted to mimic the design of an RCT in every way possible, including the intention-to-treat principle (Hernán et al., 2008). As mentioned in the introduction to this chapter, the NHS is one of the largest cohort studies in women investigating risk factors for chronic disease. Beginning in the United States in 1976 with approximately 120,000 female nurses aged from 30 to 55 years, the study is currently on its third iteration and has nearly 280,000 participants (Brigham and Women's Hospital et al., 2016). Participants receive a questionnaire every 2 years and provide answers about lifestyle, diet, medication use, and diseases.

In this reanalysis of the NHS data, subjects were considered exposed if they reported taking HRT (estrogens and/or progestins) on a questionnaire and were categorized as HRT initiators or noninitiators. The main outcome of interest was the first occurrence of a CHD diagnosis. The investigators' findings suggested that the discrepancies between the WHI and NHS could be explained by differences in follow-up time and time since menopause.

In addition to establishing a causal framework and designing the cohort study as close to an RCT as possible, there are also statistical techniques that can be used to reduce the effects of confounding and bias. These include incorporating propensity scores in analyses with measurable confounders and using instrumental variable analysis in studies with known but unmeasurable confounders. Propensity scores are constructed to model the likelihood that each subject in the study would receive treatment based on theoretically derived baseline conditions. Then, investigators can use this "score" to match subjects, weight observations, or stratify by the propensity to receive treatment (Austin, 2011). Instrumental variable analysis becomes important when investigators know that a certain factor is a confounder but are unable to measure its influence (Baiocchi et al., 2014). In this case, investigators might choose to identify an "instrument" that can represent this unmeasured confounder and explain differences in exposure status. The instrument must affect the exposure directly, only affect the outcome through its relationship on the exposure, and cannot be caused by the exposure. As an example, one study aimed to investigate the association between gastrointestinal complications and the use of nonselective versus selective NSAIDs (Brookhart et al., 2006). However, there were many unmeasured confounders that could obscure this relationship such as aspirin use, smoking status, and alcohol consumption. To reduce bias caused by these unmeasured confounder, investigators used the physician NSAID preference as an instrument and were able to more closely estimate the true effect of NSAID use on gastrointestinal complications.

Strengths and Limitation of Cohort Studies—Comparison with Other Designs

When considering the strength of a particular research design, the classical hierarchy of evidence can aid in an initial assessment, but it is by no means all-inclusive. The original hierarchy of evidence is seen as a pyramid that has case reports providing the least evidence, and systematic reviews and meta-analyses of RCTs as providing the strongest evidence (Guyatt et al., 1995). Cohort studies are positioned higher compared to any other observational study designs, but below interventional studies of any type. However, health professionals analyzing the strength of a research study should be aware that any given level of evidence can be downgraded or upgraded for a variety of reasons. It is important to remember when evaluating research that the best decision-making is informed by a body of evidence, rather than any one piece of evidence (Lapeyre-Mestre et al., 2013). In some areas of research, an RCT may not be ethically or logistically feasible, therefore a well-designed cohort study may provide the best of quality evidence. In other cases, cohort studies may spark an interest or concern and lead to the design of an RCT. In any case, the astute reader will consider all available evidence and make appropriate judgements as to the quality of each piece based on its own merits. Several initiatives provide guidance on such assessment. As mentioned earlier, STROBE was developed to help improve the reporting and design of observational studies in general, and provides specific checklists for each type of study, including cohort studies (Vandenbroucke et al., 2007). More recently, the RECORD-PE statement was developed to address the design and reporting of observational studies, including cohort studies using existing data (Benchimol et al., 2015).

Cohort Studies and Experimental Designs

RCTs continue to hold their place as the most convincing design for establishing causal relationships. This is largely due to the fact that it is the only study design that is accepted to control for both unknown and unmeasurable potential confounders. However, RCTs tend to be expensive and ethical considerations may prevent their use entirely. Additionally, the small sample size, selective population, and short duration of follow-up do not generally lend RCTs to the study of ADEs or other harmful drug-related effects. Thus, researchers must consider other study designs. After RCTs, cohort studies are often considered to be the next most convincing study design (Friis and Sellers, 2004). They allow for evaluation of multiple exposures as well as the causal association with multiple outcomes of interest, while being less expensive and time-consuming compared to RCTs.

The lack of randomization at baseline in cohort studies impacts their ability to control for confounding as compared to RCTs and other experimental designs. However, when methodology is carefully chosen and appropriate statistical techniques are utilized, studies have shown that results similar to large RCTs can be obtained (Benson and Hartz, 2000; Concato et al., 2000) with observational data. For example, finding a good instrument for the instrumental variable approach in cohort studies using existing data can balance both measured and unmeasured confounders, thus providing a similar framework to an RCT. In the absence of a

good instrument, other approaches are available to counteract the potential threats to validity with observational data and provide rigorous methodology for causal inference (Hernán et al., 2008; Ray, 2003; Rohrer, 2018).

Another benefit of cohort studies is that the studied population more closely resembles patients that clinicians might actually encounter. For instance, many RCTs have demonstrated the immense benefits of statin medications. While the results of these studies are important, and can help clinicians make decisions, it was the cohort study that determined that despite these benefits, adherence to statins was extremely low. Without this information, outcomes for patients would have been spuriously low. However, considering the information gained from the cohort study, one can see that indeed benefits demonstrated by RCTs remain. This cohort study was both a public health and a clinical call to action (Jackevicius et al., 2002). An RCT that was large enough to assess adherence would probably be difficult to conduct because of the extreme financial cost associated with administering RCTs. In this sense, cohort studies often serve as a less expensive study design that may provide convincing evidence to later perform an RCT.

In a clinical trial, investigators are certain when subjects begin taking a medication because they assign, and often administer, the drugs of interest. However, in cohort studies it can be difficult to ascertain what is commonly known as "time zero." Thus, the question has arisen whether it is appropriate when assigning user and non-user groups in a cohort study to consider whether users are prevalent or incident. The incident user design has improved the reliability and decreased the bias president and cohort studies (Johnson et al., 2013; Ray, 2003).

In the US, preclinical drug testing usually only involves 500–3000 patients. Based on this sample size, only adverse events that occur in 1 out of 100 patients can be reliably detected (Strom, 2005). Thus, even if an ADE is severe, if it occurs in 1 in 1000 patients or less, it will not be detected using clinical data. In fact, a drug's safety profile at the time it is approved for use on the market is often incomplete. Postmarketing safety surveillance is therefore, essential and has been in place in the United States since the 1950s (Russo et al., 2014).

Cohort Studies and Other Observational Designs

Compared to other observational designs such as case–control studies, selection bias related to the outcome is better controlled in a cohort study because all participants begin follow-up as disease-free (i.e., without the outcome). This also enables cohort studies to evaluate the incidence as opposed to the prevalence of the outcome of interest, making them particularly useful tools in post-marketing surveillance of approved drug products. Furthermore, because participants are selected based on exposure status, a temporal relationship between exposure and outcome can be more convincingly established. Allocation based on exposure status also means that cohort studies are more suited to investigate uncommon exposures, and have the ability to assess multiple outcomes as well as multiple exposures. Historically, cohort studies (i.e., prospective cohort studies) required years to complete resulting in substantially higher costs compared to other observational study designs. In addition, prospective cohort studies were considered less suitable for investigating the occurrence of rare outcomes, which were often investigated through case–control studies, or the newer study designs, such as the nested case–control study and the case-cohort study, both as adaptations of the classical cohort study. In nested case–control studies, subjects are selected from a previously established cohort, but group allocation is based on outcome. Case-cohort studies also allocate groups based on outcome presence, but randomly select controls from the entire cohort (Kelsey et al., 1996). With the wide availability of existing administrative data that allow for establishing large cohorts providing adequate sample size, the relative advantages of case–control designs over cohort design are not as relevant.

Conclusion

In this chapter, we discussed cohort studies and their importance in pharmacoepidemiology. With the increasing availability of existing data and the advancements in methodology, cohort studies are a great tool to investigate the effects of medication use, allowing for assessment of a potential causal relationship between one or multiple exposures with one or multiple outcomes. When using rigorous designs as those implemented in RCTs, cohort studies can build evidence in areas where RCTs are not feasible or pose ethical concerns.

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Methodological Challenges in Epidemiological Studies

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Introduction

It takes several steps to establish a causal association between an exposure and an outcome. The process starts with a well-defined, answerable, study question. The process also involves finding an appropriate data source that have all sufficient data that are required to answer the study question including the exposure, the outcome, and any potential confounders. Selection of an appropriate data source is based on questions such as Are the data representative of the group of interest? Are all important variables appropriately measured or are there possible errors a measurement? Once the data are assessed to be of sufficient quality, it is time to design the study so that it can answer the study question. This includes, in addition to choosing the actual study design such as cross-sectional or cohort study, the definition of the exposure (medication), the outcome, other variables that will be required to adjust the association (confounders) and timing of the measurement (considering the biological plausibility). All of the above are the core of any epidemiological study.

Data Sources

Data sources are discussed elsewhere in this work, but the strengths and challenges utilizing secondary and primary data sources in relation to epidemiological studies are briefly described below.

Utilizing Existing Data Sources

Pharmacoepidemiological studies are most often based on existing data sources (secondary data sources). This means that the data have been collected for other purposes previously, and data are analyzed afterward to answer a specific research question. The most typical existing data sources used are administrative health data (routinely collected data) or data collected for research purposes previously (e.g., large cohort studies or surveys). All these data sources have strengths and challenges that need to be acknowledged.

There are several strengths that make the use of existing data sources attractive for researchers (Table 1), particularly recently when large, routinely collected data sources in different countries have become available for researcher to use. One of the main strengths of utilizing existing data sources is that it is usually far less expensive than primary data collection. The only costs involved in utilizing existing data are data acquisition cost, in some cases, cost of data storage and analysis platform and cost of data analysis.

Utilizing existing data sources also saves time particularly when conducting longitudinal studies. This is particularly important if there is a suspicion that recently approved medication may increase the risk of adverse events that were not detected in premarketing studies due to their lack of power in detecting rare adverse events. Furthermore, existing data sources are often the only data sources with sufficiently large sample sizes to detect rare events, or perform drug–drug comparisons. This applies particularly to routinely collected data because they often cover large regions, or sometimes the whole country. Finally, existing data sources often enable multinational comparison, if comparable data exists across countries.

Table 1 Strengths and challenges of utilizing existing data vs. collecting primary data

	Use of existing data	*Primary data collection*
Strengths	• Cost-effective • Large sample size • Ethical procedures can be simpler	• Can be designed for particular study questions
Challenges	• Limited to existing variables • Data may not have been collected for research purposes • Permissions for data use from data custodians	• Costly • Time consuming • Ethical considerations • Difficulties if recruitment

The benefits of pooled analysis of administrative claims data are illustrated by Furu et al. (2015) who pooled data from all five Nordic countries to investigate whether the use of selective serotonin reuptake inhibitors and venlafaxine in early pregnancy was associated with risk of birth defects. Both antidepressant exposure during pregnancy and birth defects are rare, and without pooling, the data the study would have been underpowered to detect an association to this clinically important question.

Limitations of routinely collected data are that researchers are limited to the variables and time frames available in the data source. This means that one database may not be suitable to a specified research question and that researchers may need to combine several data sources and develop algorithms for deriving variables of interest from different data sources. Routinely collected data are collected for other purposes than research. This means that the data may not be readily usable. It is important that researchers have a good understanding from where the data comes from, how it has been collected, and what was the purpose of data collection. For example, routinely collected hospital data have been used initially for administrative and resource allocation purposes. For example, claims data for insurance purposes include only those eligible for the scheme. People may move in and out of the database based on their eligibility at different points in time. Other challenges are obtaining permission from the data custodians particularly for the use of routinely collected data and linking these datasets to other data sources. These processes change across databases and countries they are held at.

Primary Data Collection

If there are no suitable or accessible data sources available for a particular study question, an alternative is for the research group to collect new data to answer the question. This is called primary data collection. Typical methods for primary data collection are surveys, interviews, or observations. These may involve, for example, self-reports of demographic data and disease history, participant or interview-filled questionnaires using standardized tools (e.g., SF-36 Quality of life instrument, Katz Activities of daily living), or measurement of clinical data such as blood pressure, blood glucose levels, or brain imaging. To collect primary data requires careful planning. Often it is recommended that pilot data will be collected to make sure that you are getting all the data in a correct format in the actual big data collection. Once the data collection is underway, any chances are very difficult to make. One example of primary data collection with a pilot phase is the Australian Life Histories and Health (LHH) Survey (Kendig et al., 2014). LHH was a substudy of the bigger 45 and Up Study of >260,000 participants from the state of New South Wales, Australia. The LHH pilot was conducted among 100 participants, and in total, 2800 participants were invited to the actual LHH survey.

There are some typical challenges of primary data collection. One challenge is the longer duration of primary data collection, particularly if the aim is to recruit a large sample size with multiple data collection points for longitudinal follow-up. Primary data collection usually involves high costs due to requirement of staff, staff training, and other resources. Data that rely on self-report are prone to recall error as people would not always recall their past exposures or medical conditions. One of the big challenges is nonparticipation, including refusal to participate at baseline and attrition during the follow-up. Large nonparticipation rates increase the risk of biased sampling and consecutively biased results. Detecting study outcomes by linking the study cohort to, for example, hospitalization data will help avoid attrition, because outcome will be available for everyone from routinely collected data. However, in most countries or jurisdictions, this would require consent from each study participant. Finally, there are ethical considerations related to collecting sensitive health and medical information from participants and involving participants to attend research sites and collecting clinical data (e.g., blood samples).

Strengths and Weaknesses of Different Study Designs

The choice of optimal study design depends on the purpose of the study, as well as the outcome and exposure. For example, it is not feasible to apply the same design to assess whether a commonly used drug is related to a rare outcome with long latency period, and whether a drug for rare condition has acute toxicity. Brief summary of strengths and weaknesses of different observational study designs is provided in Table 2.

Table 2 Strengths and weaknesses of different study designs

Study design	*Strengths*	*Weaknesses*
Cross-sectional study	• Simple and quick data collection	• Cannot assess incidence • Impossible to disentangle temporal relationship • Cannot control unmeasured confounding
Case–control study	• Feasible for rare outcomes and outcomes with long latency time • Can investigate multiple exposures	• Prone to recall bias (depending on exposure data sources) • Reverse causality can occur • Cannot control unmeasured confounding
Cohort study	• Temporal relationship easier to assess • Can assess rare exposures • Can investigate multiple exposures (and outcomes)	• Cannot control unmeasured confounding • Often not feasible for rare outcomes, or outcomes with long latency period
Self-controlled studies	• Feasible for rare outcomes • Controls for unmeasured fixed confounders	• Must know the latency time for outcome; not the optimal design for outcomes with long latency time

Cross-Sectional Studies

Cross-sectional studies provide a snapshot of the chosen population at a given timepoint. Because they, by definition, have no follow-up and require data collection only once, they are easier and cheaper to conduct than cohort or case–control studies. As the exposure and outcome are measured at the same timepoint, it is impossible to differentiate the cause and effect. Thus, cross-sectional studies cannot be used for assessing causality. Further, depending on the applied data collection method, they may be prone to recall bias. Another limitation is that they cannot assess incidence.

Cross-sectional studies are useful for investigating the prevalence of drug use (or another phenomenon). Thus, they can be used for assessing the burden of disease and prevalence of drug use and for consequent planning and allocating health-care resources. Therefore, although they cannot assess causality, they can still provide valuable information.

For example, a study on older patients' compliance with drug storage recommendations showed that 51.2% of older patients complied with them (Vlieland et al., 2018). In another study, conducted on the patterns of direct anticoagulant (DOAC) prescriptions in 2010–13, the researchers observed that although certain prescription guidelines were followed well, for 58% of patients receiving DOACs, the guidelines were not followed (Diaz et al., 2018). This latter study also illustrates an important fact: the data of a cross-sectional study may well span over (several) years. Therefore, the study design cannot always be inferred from the study period.

Cross-sectional studies can also be serial, which means that the data collected during a longer time period is analyzed in shorter intervals. This kind of studies can be used for comparing the prescription rate of a given drug after changes in policy, or drug availability. For example, the impact of changing availability of tamper-deterrent and nontamper-deterrent oxycodone on prescribing patterns of controlled-release oxycodone was investigated in a Canadian study spanning from 2007 to 2016 (Gomes et al., 2018).

Case–Control Studies

Case–control studies are defined by outcome, and data on exposure are gathered retrospectively. This retrospective nature may introduce information bias (specifically, recall bias) if the cases recall their exposure differently to controls. Another possible source of recall bias is the inclusion of prevalent cases (i.e., those who have had their condition for a longer time). Thus, it is preferable to restrict a case–control study to incident cases as this will avoid several other issues such as different survival (Hill et al., 2003). Selection of appropriate controls is also important, as control selection may introduce selection bias. The controls should ideally be a random sample from the population where the cases were obtained from. For example, studies on congenital malformation are often restricted to live births. This introduces selection bias because the cases and controls are not sampled from the same population as the fetuses/babies with the most severe malformations were removed from the dataset by miscarriages or stillbirths (Suarez et al., 2018). A further limitation of case–control studies is that they provide data on the prevalence of exposure among cases and controls but cannot be used for assessing incidence of the outcome among exposed and unexposed.

Because case–control studies do not require follow-up, they are useful for assessing rare outcomes or outcomes with long latency period. However, especially for conditions with long onset time, it is important to consider protopathic bias (as illustrated with the proton pump inhibitor example in the Assessing the Causality of Results section of this chapter) and the length of the lag time. The same case–control study can be used for assessing several exposures.

Cohort Studies

As opposed to case-control studies, cohort studies are generally prospective (i.e., exposure is measured before the outcome). This means that traditional cohort studies (in which no one has experienced the outcome at the beginning) are not feasible for outcomes with long latency period, as follow-up is costly, and loss to follow-up likely to occur. For the same reason, they are not efficient for

rare outcomes. Further, if the follow-up is long, there may be changes in treatment and diagnostic procedures. This means that the distribution of exposure and outcome may vary temporally. Further, in traditional studies, some selection bias may occur, as persons participating in cohort study tend to differ from the general population. This can affect the generalizability of results. In addition, as the participation in a cohort study can be time consuming, and require ability to return questionnaires, or attend follow-up visits, it can be difficult to engage certain population groups, such as persons with dementia, in participation.

Many of the abovementioned problems can be solved by applying administrative databases. They can be used for obtaining exposure (such as drug use) and outcome (such as dementia or death) data for an existing cohort, or the entire study can be conducted with administrative databases. For example, Gray et al. used computerized pharmacy records to ascertain the exposure to benzodiazepines in an already existing population-based cohort study to assess the association between benzodiazepine use and dementia (Gray et al., 2016). This enabled the authors to retrospectively collect exposure data from the entire follow-up period, which would have otherwise been challenging, biased or impossible as dementia and its undiagnosed prodromal phase would likely affect the individual's ability to accurately report drug use.

In another, entirely register-based study, data from the Finnish national health-care registers were applied to assess whether antipsychotic use is related to a higher risk of hip fracture among persons with Alzheimer's disease (Koponen et al., 2017). This study was based entirely on registers. First, all community-dwelling persons with incident diagnosis of Alzheimer's disease were identified from a national reimbursement register. Data on their antipsychotic use, as well as hip fractures and other comorbidities, were then extracted from other national registers. This enabled the researchers to assess the safety of these drugs in a population group that is frequently prescribed them, but often excluded from randomized controlled studies.

Self-Controlled Studies

Self-controlled designs, such as case-crossover study and self-controlled case series, are attractive as they implicitly control for fixed, unmeasured confounders (Maclure, 1991; Maclure and Mittleman, 2000; Whitaker et al., 2006). In both of these designs, only persons who experienced the outcome of interest are included.

In *self-controlled case series* (Whitaker et al., 2006), the risk of outcome during periods of exposure and nonexposure is compared. Thus, the exposure must be time-varying. Other assumptions are that there is variation in the timing of the outcome, and the exposure is not affected by the outcome, although this can, to some extent be accounted for in the analysis. If recurrent outcomes are analyzed, their occurrence should be independent of each other. It should also be noted that self-controlled case series can measure relative, but not absolute incidence. A worked-up example of application is provided in an accessible tutorial by Whitaker et al. (2006).

The example assessed whether MMR vaccination was related to viral meningitis. In the original study, the investigators obtained data on cases diagnosed with viral meningitis and linked these data to vaccination records. Observation period (i.e., the time during which outcome and exposure were assessed) was the second year of life. Based on previous data, the exposure period was defined to contain days 15–35 after the MMR vaccination. Then the risk of nonviral meningitis during exposed and nonexposed periods was compared. Self-controlled case series has most commonly been applied in vaccine epidemiology, but it is applicable to those exposures with multiple exposure periods (such as other drugs). Further, although the method works best for acute outcomes, it can be used for nonacute outcomes with longer latency time, but then the design is more prone to confounding between age and exposure effects. Further, the likelihood of unmeasured time-varying confounding is larger with longer latency time.

In *case-crossover design* (Maclure, 1991; Maclure and Mittleman, 2000), the exposure frequency during a period immediately before outcome onset is compared with exposure frequencies during control times. The design shares many limitations with self-controlled case series: it works best for acute events and nonrecurrent events. Likewise, the outcome should not impact exposure (or control period(s) should occur before the hazard period). There should be variation (aka crossover) in exposure over time, as only these exposure-discordant persons are informative in the analysis. Further, the probability of exposure should be stable. This assumption is often violated when a new drug comes into market. Therefore, this design cannot be directly applied to such situations (Wang et al., 2014). Selection of hazard and control periods is important as it can affect the results as demonstrated in a screening study of candidate drugs related to higher risk of hip fracture (Tolppanen et al., 2017). In that study, three different scenarios were used to test the sensitivity of results to period definition: (1) hazard period 0–30 and control period 31–61 days before hip fracture, (2) hazard period 0–30 and control period 336–366 days before hip fracture, and (3) hazard period 0–14 and control period 16–30 days before hip fracture. The results were highly dependent on the applied hazard and control periods as 9, 44 and 5 drugs were identified with higher, and 8, 23 and 4 with lower risk of hip fracture in different scenarios. The overlap between drugs identified with different scenarios was small.

Finding the Exposed Participants

There are specific considerations when investigating medications as an exposure in epidemiological studies. Exposure in pharmacoepidemiological studies in more detail is discussed in other chapters of this work. In brief, the following issues need to be considered when using medication as an exposure in epidemiological studies: (1) use of a single ingredient or a medication class, (2) dose of the medication, (3) when the medication use was initiated, and (4) duration of the medication use. Depending on the data

source, it depends whether information is available for all of the four points. It comes down to the research question whether and how important all these points are.

Indeed, one of the main challenges is to find a suitable data source for the study question. Each data source has its strengths and challenges. The strengths of utilizing existing data sources such as dispensing or prescribing data are that (1) data are systematically captured and (2) it allows longitudinal detention on medication exposure. However, exposure on certain medication use may be missed. For example, medication dispensing data often come from medication claims. If medication is not eligible for reimbursement, it may not appear in the claims data. Furthermore, dispensing and prescribing data does not provide information on actual use of medication. Primary data collection on medication exposure often relies on either self-report or view of medication containers or prescriptions. Self-report gives more detailed information on actual use of medications, however, may be prone to recall error and data provided is subjective. Using containers or prescriptions as additional data source alongside self-report reduces recall error. However, it is still unclear whether some information may have been missed.

Another major challenge is to identify exposed and unexposed participants that are comparable, or accounting for possible differences in the analysis. The comparison of people exposed and not exposed to a medication often means that the groups are very different in terms of diseases and severity of diseases, which means that *confounding by indication* will be evident. Confounding by indication is explained later in this chapter.

Selecting the Outcome

Selection of the outcome variable requires the thinking of the study question and what is it that needs to be measured. If the study aims to answer a question on how the use of osteoporosis medication prevents from osteoporotic fractures, then data specifically on osteoporotic fractures need to be identified.

Health outcomes can be crudely divided into two types: surrogate outcomes and hard outcomes. Surrogate (or intermediate) outcomes occur before the hard outcome and are the cause of the hard outcome (Fig. 1). For example, blood pressure or cholesterol level can both be used as surrogate outcomes for cardiovascular disease events, because they both affect the incidence of cardiovascular disease. The advantage of the use of surrogate outcomes is that they usually occur sooner than the actual event, there are more events occurring which means that you may need less participants to detect the outcome, or the outcome is possible to measure as a continuous variable. However, using surrogate outcomes, drawing conclusion of the benefits of treatment will be more challenging. In the example in Fig. 1, the effect of statin use in thought to occur via its effects on LDL-cholesterol. The reduction of LDL cholesterol is, indeed, a good marker of stroke risk reduction (Silverman et al., 2016). However, statins may reduce stroke via other mechanism as well (pleiotropic effects), which would not be captured measuring only the reduction in LDL cholesterol (Oesterle et al., 2017).

Hard outcomes are the "real" outcomes such as mortality, incidence of disease (e.g., stroke, myocardial infarction, and cancer), or hospitalization for a disease. These are the incidences that the treatment is attempting to prevent or delay. These are also the outcomes that people often consider more important. As mentioned earlier, hard outcomes occur later and less frequently than surrogate outcomes, which makes them more challenging to measure. One way of increasing the frequency of hard outcomes is to use composite outcomes. Fig. 2 gives an example of a composite outcome.

In addition to the direct health outcomes such as the previously mentioned surrogate and hard outcomes, soft outcomes can be used. These include, for example, quality of life measures, activities of daily living, or pain level. Soft outcomes are usually subjectively measured, while surrogate and hard outcomes can be measured objectively.

Figure 1 The temporal relationship been exposure variable, surrogate outcome, and the outcome event.

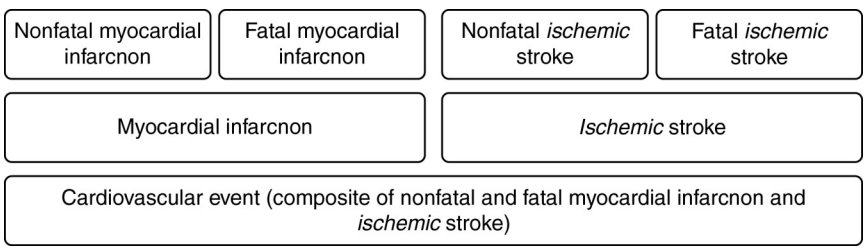

Figure 2 An example of a composite outcome of a cardiovascular event.

One of the biggest challenges in deciding on the outcome is how to ascertain the sensitivity and specificity of the outcome measure. Hospital discharge data is one of the most common data sources used to capture study outcomes. However, relying on hospital discharge data to capture outcomes means that only the most severe cases of events will be captured. For example, investigating falls as an outcome means that only falls leading to hospital admission will be captured. Any falls that lead to an emergency department or general practitioner visit only will not be captured, unless all these databases are linked using a person identifier.

Another example is bleeds. Minor bleeds may not lead to hospital admissions. Another challenge in hospital discharge data is how well medical conditions are coded in the hospital. A Canadian study compared the coding of obesity in hospital discharge database to the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database which had Body Mass Index measured (Martin et al., 2014). Obesity was defined as BMI ≥30 in the APPROACH database and as ICD-10 codes of E65–E68 in the hospital discharge data. The study found that in people who have undergone cardiac catheterization, the sensitivity of obesity coding in the hospital discharge data was only 7.8%, while the specificity was 99%. Negative predictive value was 81% and positive predictive value 66%. See more on how misclassification of outcomes may lead to bias later in this chapter.

An overall challenge in the outcome measure ascertainment is to find true incident cases. Finding incident cases is important to determine causal association between the exposure and outcome (described in more detail in the following paragraph). Incident case means that the person experiences the event for the first time, for example, having the first stroke. If a person has had a stroke at some point in time in the past, is no longer experiencing and incident or first stroke. There is no data source where you can confidently detect person's first stroke and some assumptions have to be made. For example, not having a stroke recorded in a hospital discharge data for the past 5 years could be a good assumption for detecting first strokes. A study conducted using the New South Wales (Australia) hospital separation data reported that using a 1-year look-back period to determine incident strokes, 11% had actually had a stroke previously (Worthington et al., 2017). However, extending the look-back period to 5 years, this misclassification reduces to 4.4% and to further 1% when using a 10-year look-back period.

Finally, time taken to the outcome to occur is crucial to determine as biologically plausible. If the follow-up time from the exposure to the outcome is too short, it means that the true causal association will not be detected. In contrast, if the follow-up time is too long, the extra time may dilute the outcome occurrence as the effect size is probably bigger earlier in the follow-up period than during the later time periods. Examples of outcomes that usually take a long time to develop are dementia (Wilson et al., 2011) and mesothelioma (Nurminen et al., 2003). Determining the ideal follow-up time, both the exposure and the outcome need to be considered. Please refer to the next paragraph for more details on causal assessment.

Assessing the Causality of Results

When interpreting the results of a study, it is important to ask two questions: "Is it real?" and "Does it matter?" This is crucial when one is interpreting the results of his/her own study, but equally relevant when reading or reviewing a scientific article.

The association between drug exposure and outcome can be explained by (1) chance, (2) confounding, (3) bias, or (4) reverse causality. The first one is often assessed with *P*-value (or significance level) (Wasserstein, (edited on behalf of the American Statistical Association Board of Directors) 2016). However, it is important to acknowledge that the *P*-value does not measure the probability that the data were produced by random chance alone (Wasserstein, (edited on behalf of the American Statistical Association Board of Directors) 2016). Rather, *P*-value measures the strength of evidence against the null hypothesis (i.e., no association between the drug and outcome), but importantly, it is not, and it should not be, interpreted as a statement of the importance or causality of the finding and the traditional cutoff (or any other cutoffs) should not be used (Greenland et al., 2016; Sterne and Davey Smith, 2001; Wasserstein, edited on behalf of the American Statistical Association Board of Directors) 2016). The *P*-value does not exclude the other possible explanations for association. Thus, an association with small *P*-value may still be produced by bias or reverse causality.

When assessing whether the results are due to confounding, it is important to consider how confounding may occur in each design. Confounding can be controlled by both study design and analysis methods. If a randomized controlled study was conducted, the key question is whether the random allocation was indeed random so that there was no association between the confounders and exposure? If an observational study was carried out, was confounding adequately controlled by statistical methods such as propensity scores, matching, or adjusting? Were all relevant confounders measured, and how well the measured confounders captured the reality? If there are unmeasured or under measured confounders, is the residual confounding due to these factors large enough to explain the results? In a self-controlled design (see section Self-Controlled Studies of this chapter), it is important to consider whether there were time-variant unmeasured confounders, which may affect the results. Further, it is important to acknowledge that it is not feasible to adjust for all possible factors, and the possible relationships between possible confounders, exposure, and outcomes should be considered. Sometimes the unnecessary adjustment may distort the true underlying association (Hernan et al., 2002).

Bias means that the results or their inference deviate systematically from the truth (Porta et al., 2008). This can be caused by errors in not only data collection, analysis, or interpretation phase but also from publication or review phase (Last, 2001). It is important to acknowledge that bias can most effectively, or entirely controlled, before the analysis phase. Although it may be possible to use statistical approaches to account for some biases, such as use weighting to correct for selection bias (Haneuse et al., 2009), it is more feasible to spend enough time in planning the data collection (including but not limited to participant recruitment, measurement, and data entry) properly. Importantly, bias can occur in all study designs. In addition to assessing the possibility of bias, it is

necessary to consider whether it occurred differentially among exposed and unexposed or those who experienced the outcome. If the misclassification or error is differential, then the direction of bias should be considered. Different type of bias are shortly summarized in section Typical Biases later in this chapter.

The presence of reverse causality (i.e., whether the outcome "caused" the exposure) can be assessed on the basis of study design. Cross-sectional studies are perhaps the most notorious in this regard, but reverse causality can also occur in case–control or cohort studies. In pharmacoepidemiology, reverse causality is often due to protopathic bias, which means that the drug was started, stopped, or otherwise changed due to the manifestation of the underlying outcome (Feinstein, 1985). Indication bias (confounding by indication) can also cause this phenomenon. Confounding by indication means that the risk of adverse event is related to the indication for drug use, but not to the used drug itself (Csizmadi et al., 2007). For example, proton pump inhibitors have been associated with higher risk of gastric cancer. However, when a lag time was applied, the association was abolished (Tamim et al., 2007). Specifically, a lag time means that drug use occurring during a prespecified time period before the outcome event is not considered because it may reflect use due to prodromal symptoms of the outcome. In this case, proton pump inhibitors were often initiated due to gastric complaints, which were the first manifestations of undiagnosed gastric cancer (Tamim et al., 2007).

Finally, if the researcher, or the reader/reviewer of the scientific article, can rule out the chance, confounding, bias, and reverse causality as possible explanations for the observed association, the next question is whether the observed association is clinically significant, or "does it matter?" Large effect sizes are rare, but smaller effect sizes, or weaker associations between drug exposure and outcome, may be important if the drug is commonly used. However, interpretation of small risk, hazard, or odds ratios can be challenging because they may be easily susceptible to bias (Siontis and Ioannidis, 2011).

Typical Biases

Biases can be classified in several ways, as summarized by Delgado-Rodriguez and Llorca (2004). One possibility is to classify them according to the direction of the change they produce to the estimate (such as the hazard ratio of drug exposure and outcome). Bias toward the null (occasionally the term "negative bias" is also used) occurs when the biased estimate is closer to the null value than the true estimate. Away from the null bias (such as the association between proton pump inhibitor use and gastric cancer illustrated by Tamim et al. (2007)) occurs when the observed association is further away from the null value than the true association. Although the definition of bias often includes the term "systematic" (Porta et al., 2008), it is important to acknowledge that also nonsystematic misclassification (or random measurement error or nondifferential misclassification) can lead to bias toward the null (Hutcheon et al., 2010).

Alternatively, the biases can be classified into three groups as follows: selection bias, information bias, and confounding (Kleinbaum et al., 1982). Here, we briefly introduce the most typical biases according to this classification. More extensive listing of specific biases is available from several other textbooks (such as (Csizmadi et al., 2007; Feinstein, 1985; Kleinbaum et al., 1982), and an excellent summary with unrestricted access is provided by Delgado-Rodriguez and Llorca, 2004).

Selection bias occurs when the study population does not represent the target population. If this is nondifferential (i.e., occurs similarly among the exposed and unexposed), it will impact the generalizability of the results. For example, several population groups such as older persons, those with more comorbidities or concomitant drugs alongside the trial drug are often excluded from randomized controlled trials. Thus, the results of randomized controlled trials may have limited external validity or generalizability to a wider patient population (Kennedy-Martin et al., 2015). If the selection bias occurs only or more strongly among one exposure group, or is differential between outcomes, it can lead to an underestimation or overestimation of the association. For example, studies on drug safety during pregnancy are often restricted to live births only. When the drug is actually associated with higher risk of adverse fetal outcome, the observed association in a study restricted to live births is an underestimation, with the degree on underestimation depending on the rate of competing risks (i.e., stillbirth and miscarriage), and the presence of unmeasured confounders and their association with exposure, outcome and competing risks (Khoury et al., 1989; Suarez et al., 2018; Svensson et al., 2014). As data on fetal deaths is not always easily (or at all) available, and early miscarriages are underreported even if such data are available, one possible approach is to conduct selection bias analyses (Greenland, 1996).

Information bias occurs during data collection. One specific subtype is ecological fallacy, which means that data collected and analyzed on a group level are considered to represent actual association on an individual level. However, this subtype does not occur in studies with individual-level data. Other types of information bias, especially relevant in pharmacoepidemiology, include protopathic bias (as illustrated in the proton pump inhibitor and gastric cancer example by Tamim et al., 2007) and misclassification bias (Delgado-Rodriguez and Llorca, 2004). Misclassification bias can occur not only for exposure and outcome variables but also for confounders. The impact and direction of bias depend on the degree of misclassification and how much it differs between the exposure or outcome variables. Nondifferential misclassification occurs equally in between groups, and it often does not impact the point estimate but widens the confidence intervals, which can lead to interpreting the results erroneously as a null association. However, in specific circumstances, such as categorical variables or continuous exposure, the point estimate may also be affected (Dosemeci et al., 1990; Funk and Landi, 2014; Hutcheon et al., 2010), and the estimate may also be an overestimation (Dosemeci et al., 1990).

In pharmacoepidemiology, one possible mechanism for differential misclassification of outcomes by exposure status is the more active health-care use of those persons who are prescribed certain (or any) drugs. The prescription event itself requires contact with health-care professionals, and persons who are prescribed certain drugs may have different health-seeking behaviors or have more

contact with health-care professionals during their follow-up. Thus, they often have higher probability of being diagnosed. Similarly, in studies conducted with administrative databases, persons who do not have contact with health-care professionals will not have any evidence on their comorbidities. If this occurs similarly between groups, the association is biased toward the unadjusted association, while the impact of nondifferential misclassification depends on the strength of association between the confounder and exposure and outcome variable, as reviewed by Funk and Landi (2014).

Confounding occurs when a covariate is associated with exposure and outcome, but it is not on the causal pathway. Different methods for identifying confounders, including statistical testing (such as automatic or manual variable selection based on certain thresholds) and causal network analysis with directed acyclic graphs have been suggested. Approaches that solely rely on statistical tests have been criticized as they may lead to omission of important covariates, or unnecessary adjustment which may bias the association (Hernan et al., 2002). Using birth defects as an example, Hernan et al. illustrate the importance of a priori knowledge on the relationship between exposure, outcome, and covariable considered as a confounder (Hernan et al., 2002). If the covariable is a common cause of the exposure and outcome, or there is an unmeasured common cause for the exposure and outcome which is captured by the covariable, adjusting is correct and it decreases the bias. However, if the covariable is on the causal pathway, or the confounder and exposure or/and outcome have unmeasured common cause, the adjusted estimate is in fact biased. Thus, it is essential to consider which covariables should be adjusted for. Further, if the measured confounders do not adequately capture the actual confounding, it is important to assess the degree of residual confounding and its impact on the conclusions.

Conclusion

This chapter provided an overview to the main aspects of epidemiological studies, their strengths and challenges. More details on each of these aspects specifically related to pharmacoepidemiology are discussed in detail in several other chapters.

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Sources of Data Used in Pharmacoepidemiology and Pharmacovigilance

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Introduction

The utilization of automated/computerized databases for pharmacoepidemiological research in North America dates back to 1980, and focuses on capturing claims data for medical services and treatment (Strom, 2012). Nordic countries also have a long-standing history of utilizing aggregate drug utilization data for research, with pioneering studies conducted in the late 1960s and early 1970 (Wettermark et al., 2013). More recently, the Asian Pharmacoepidemiology Network (AsPEN Collaborators et al.) was formed to provide a mechanism to support the conduct of pharmacoepidemiological research in Asian populations (AsPEN Collaborators et al., 2013). Over the past two decades, there has been increased availability of data sources to conduct pharmacoepidemiology research internationally. These databases offer several advantages including large sample size, lower cost, increased generalizability, methodological flexibility, and with no requirement for direct patient recruitment (Harpe, 2009). These databases accrue patient-level health information over a vast period; which is not possible to assimilate through clinical trials that generally acquire specific information for a few thousand patients typically over 12–18 months (Harpe, 2009). Health databases provide an opportunity to examine populations that are often excluded from randomized controlled trials (RCTs), mainly the elderly, children, and women (Torre and Martins, 2012).

Population-based databases often do not necessarily imply the collection of data on a national level. Regional databases, databases capturing populations visiting general practitioners, or claims/insurance databases are also regarded as population-based databases. Solely hospital medical records (such as intensive care unit data) are not considered population-based since there is no underlying registered catchment population (i.e., a record of all the individuals not referred to a hospital). Furthermore, immunization/medication use/disease registries alone are not considered population-based databases if they cannot capture the population not being vaccinated/exposed/diseased. If the vaccination registries capture defined populations from birth to a specific date, including all vaccinated and unvaccinated subjects in that population, then it is considered population-based (Ferrajolo et al., 2012). It is preferable to include the population in the database which is representative of the general population from which it is drawn; however, at times, it may be beneficial to emphasize the more disadvantaged groups that may not have been involved in the premarketing phase studies, such as infants, children, and oldest-old adults.

An ideal database requires that all information can be easily linked through the patient's unique identifier, the records are updated on a regular basis, and that the records are verifiable and reliable; however no single database is ideal (Strom, 2012). A complete database should include records from both inpatient and outpatient care, emergency medical care, results of all laboratory and radiological tests, all prescribed and over-the-counter medications, as well as alternative therapies for each patient (Torre and Martins, 2012). The implementation of studies through databases necessitates a comprehensive understanding of the strengths and weaknesses of pharmacoepidemiology study designs, the procedure of data collection, enrollment and coverage factors, and similar other factors that could have affected data quality and validity. An understanding of the social, cultural, political, and historical settings of the population under study is also crucial. A lack of awareness of the limitations and failure to understand methodological challenges arising with the use of these databases could lead to the selection of inappropriate study designs, which would misinform

the results (Torre and Martins, 2012). In the current chapter, we will introduce these resources, presenting some of the general principles that apply to the databases utilized in pharmacoepidemiology and pharmacovigilance disciplines.

Once the research question and study design are delineated, an appropriate data source must be identified. Pharmacoepidemiology studies may involve data collected prospectively for the study (i.e., primary data), or data collected for some other purpose (i.e., secondary data). When choosing a data source, special deliberation must be given to the relative strengths and weaknesses of the particular data source available, and whether the selected database is appropriate to address the research question (Harpe et al., 2011).

Primary Data Sources

Primary data are data collected prospectively for the particular study (de novo data collection) (Torre and Martins, 2012). This data may be collected through questionnaires, interviews, or chart reviews. Primary data in general offer increased control over the type and amount of information that is available as compared to secondary data. If the information about specific medication-taking behavior is required, for example, for a medication to be taken with meals, the participant in a study that uses the primary data collection can be questioned. This information would most likely not be obtained through secondary data from prescription dispensing data provided by a pharmacy or routine data collections (Harpe et al., 2011). Case-control studies utilizing hospital or community-based primary data collection have evaluated drug-disease associations for rare complex conditions that require a large study population and in-depth assessment by medical practitioners. Typical examples are studies assessing the risk of Primary Pulmonary Hypertension with appetite-suppressant medications, conducted in France (Abenhaim et al., 1996); medications associated with the development of Stevens–Johnson Syndrome or Toxic Epidermal Necrolysis, primary data available from different countries in Europe (Roujeau et al., 1995); and medication etiology of agranulocytosis and aplastic anemia, with the study population from Israel and Europe (Shapiro, 1983). The limitations of primary data are the expenditure and time involved in investigating a progressive increase in sample size (Harpe et al., 2011). National surveys, registries are classified as primary data, and are discussed next.

National Collections and Surveysand

Internationally, a few countries support the use of national health data for research purposes, which can provide extensive information like the prevalence of smoking and other health- related risk factors, obesity among other health ailments, access to health care, etc. (Cox, 2016). In New Zealand (NZ), the Ministry of Health provides data to researchers via the General Medical Subsidy (GMS) Collection, Laboratory Collection, Mortality Collection, National Immunization Register, NZ Cancer Registry (NZCR), National Minimum Dataset (NMDS), National Maternity Collection (NMC), National Non-admitted Patient Collection (NNAP), Primary Health Organization (PHO) Enrolment Collection, National Patient Flow, Programme for the Integration Of Mental Health Datamart (PRIMHD), etc. The NMDS is a national archive of public and private hospital discharge information, which includes coded clinical data for inpatients and day care patients. The NZCR generates the data for incidences of cancer and survival studies, policy formulation, public health research, and for monitoring screening programs. The GMS claim provides information on subsidies paid to decrease consultation cost with general practitioners for children less than 15 years of age or subsidy/community card holders. NZ Medicines and Medical Devices Safety Authority (Medsafe) manage the medication and safety data. The Pharmaceutical Claims Collection maintains the dispensing data on medication claims for prescribed dispensing that are subsidized by PHARMAC. The PHO registers individual data for primary health care. The Laboratory Collection gathers information on laboratory test carried out in individuals. The NNAP maintains a record of non-institutionalized cases in healthcare facilities. The NMC supplies data on maternal deliveries. PRIMHD generates data on the mental health status of those accessing healthcare. Client Claims Processing System (CCPS) provides data which accounts for disability support events in community-dwelling older people (Nishtala et al., 2017). The National Health Interview Survey (NHIS) has monitored the health of the people of United States of America (USA) since 1957. NHIS data on a varied range of health topics are amassed through personal household interviews, the findings of which have been instrumental in providing data to track health status, healthcare access, and progress toward achieving national health objectives. The National Health and Nutrition Examination Survey is a series of studies intended to assess the health and nutritional status of adults and children in the United States, and it combines interviews and physical examinations. Likewise, in Canada, The Canadian Chronic Disease Surveillance System uses linked administrative data sources from every province and territory to estimate the incidence and prevalence of chronic conditions, and, use of health services and health outcomes (Blais et al., 2014). The Canadian Hospitals Injury Reporting and Prevention Program is a computerized information system that gathers and analyzes data on injuries, especially in children (Crain et al., 2016). The information from the Nord-Trøndelag Health Survey are probably the most complete screening data from Norway, and are especially suitable for epidemiologic studies on blood pressure, diabetes, quality of life, tuberculosis, and other lung diseases; along with data on cardiovascular diseases, lifestyle, disablement, work, and the working environment (Holmen et al., 1990). Some of the important national health surveys conducted in Asia are the National Family Health Survey, District Level Household Survey, and the Annual Health Survey (Dandona et al., 2016).

Registries

The National Committee on Vital and Health Statistics of USA describes registries in the field of medicine and public health as "an organized system that utilizes observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined clinical, scientific, or policy purposes." The term registry is defined both as the act of recording or registering and as the record or entry itself (Gliklich et al., 2014). In epidemiology, the term "register" is implied to the data concerning all cases of a particular disease or similar health-relevant condition in a defined population such that the cases can be related to a population base. Clinical registries gather a defined minimum dataset from individuals undergoing a particular procedure, diagnosed with a disease or utilizing any healthcare resource, and capture data systematically from existing administrative databases, medical records or directly from clinical staff using data collection forms (Hoque et al., 2016).

Appropriately designed and executed patient registries can provide a real-world view of clinical practice, medication safety practices, patient outcomes, and comparative effectiveness. Registries can be useful data sources, which can be viewed as a collection of patient records on a particular subject (Gliklich et al., 2014). Registries have been observed as complementary resources for the intention of supporting the requirements of risk management plans to systematically collect data from clinical practice (Hoque et al., 2016). Registries should be designed and evaluated according to their planned purposes in terms of patient outcomes as (1) describing the natural history of the disease, (2) determining clinical efficiency and/or cost-effectiveness, (3) assessing medication safety or adverse events, and (4) measuring or improving quality of care (Gliklich et al., 2014).

Disease registries comprise of patients who have or have had a disease or condition of interest. They include the population with a particular disease to be well characterized and establish an adverse event profile for different treatments. A disease registry is a tool used for tracking clinical care and outcomes of a defined patient population (Gliklich et al., 2014). Most disease registries support care management for groups of patients with one or more chronic diseases, such as asthma, diabetes, or coronary artery disease. The Finnish Medication and Alzheimer's disease (MEDALZ) study based on disease registries was utilized to investigate the changes in medication and healthcare service use among individuals with Alzheimer's disease and to evaluate the safety and effectiveness of the medications prescribed (Tolppanen et al., 2016). A retrospective cohort study conducted utilizing data from an ongoing General Practice based register study found a high prevalence of depression in patients diagnosed with Parkinson's disease (Leentjens et al., 2003). A case-control study of incident patients in Scotland using the Scottish Motor Neuron Disease Register was performed to identify risk factors for the subsequent development of motor neuron disease (Chancellor et al., 1993). Disease registries can also provide more flexibility for collecting and reporting data from multiple data sources. Although disease registries vary in the amount of information included about medication use, the data collection can be facilitated either by merging with another data source such as administrative claims data, or by survey or interview methods (Harpe et al., 2011). As many stakeholders have interests in diseases, conditions, and healthcare products and services worldwide, it is not surprising that the interest in global patient registries is growing. Product (drug) registries encompass patients exposed to a healthcare product (drug or device) and facilitate the study of drug utilization patterns, including, for example, off-label use. Pregnancy exposure registries focus on possible exposures during pregnancy and post-partum, and also include effects in the offspring (Gliklich et al., 2014).

When utilizing existing registries in pharmacoepidemiology research, it is important to observe the following factors which affect the value and validity of registries and databases: (1) the comprehensiveness of registration of all individuals under study and the registered data, (2) the size of the data source, (3) the registration period in order to relate the exposure and effect to possible induction and latent periods (induction period is the period required for a specific cause to manifest a disease, the latent period is the delay between the particular exposure and the period of manifestation of the disease), (4) data availability, accessibility, and expenses, (5) data format, and (6) the possibilities of linkage with other data sources (Sørensen et al., 2009). One of the major limitations in utilizing administrative registries for research is the data selection and quality, since the methodology of data collection is not according to the researcher's approach, but is predetermined, and sometimes impossible to validate. The validity may also vary between different settings, and validation studies are therefore essential when using registries as a data source (Sørensen et al., 2009). A study conducted in the Netherlands to validate incidence rates of various coronary syndromes by linkage to the "causes of death registry," and either the "hospital discharge registry" or the "cardiology information system" found incongruity in the data collected from the different sources (Merry et al., 2009). In a study directed to validate the Danish Cancer Registry concerning breast cancer, it was observed that data on the extent of disease and treatment were complete, valid, and reliable, but are too unspecified to be valuable in comparative studies (Jensen et al., 2002).

Registries assist in identification of cases for retrospective studies and clinical trials; improve patient management and record-keeping. Registries assist in evaluation and planning of healthcare services; generate insights into risk factors for adverse outcomes, document the effectiveness of therapies in real-world settings, provide insight into the nature of diseases and benefit of treatments in subgroups of patients, and generate comparative benchmark reports to stakeholders, including hospitals, funders, insurers, clinical staff, patients, and consumers (Hoque et al., 2016).

Clinical quality registries (CQRs), coined initially in Sweden, are described as clinical registries designed to improve the quality and safety of care. CQRs are described in their Health Act as "An automated and structured collection of personal data initiated with the purpose to systematically and continuously develop and safeguard quality of care." A national or regional Quality Registry permits comparisons within healthcare at a national or regional level in which personal data have been collected from several caregivers. CQRs help to identify variation in "best practice" treatments and outcomes across healthcare centers, and provide feedback on performances to stimulate quality improvement processes (Hoque et al., 2016).

Some commonly used registries in NZ include birth, death, marriage registries, maintained by the Ministry of Health. Tumor registries are government-supported agencies that amass complete statistics on the incidence, treatment, and outcome of cancer in defined geographic areas. The NZ Health Information System manages the NZ Cancer Registry. The Health Benefits Limited, administered through the Ministry of Health, was responsible for the procurement and supply-chain data before the introduction of the Pharmaceutical Management Agency Limited (PHARMAC). Death certificate registries can be utilized to follow the mortality of any cohort. Other prominent registries in NZ are the Virtual Diabetes Register, National Immunisation Register, National Cervical Screening Programme Register, and the Australian & NZ Hip Fracture Register (Nishtala et al., 2017).

Some patient registries are a branch of a broader research collaborative that connects individual registries to a more extensive network of registries that collect data for one or more conditions. This network provides a shared infrastructure and standardized data collection across registries. Data collected from each registry may be combined for analysis as researcher-generated or patient-powered research networks. The SEER registries, a collaboration of 19 registries created and supervised by the National Cancer Institute, are an example of a researcher-generated research network. The Genetic Alliance Registry and BioBank, a collaboration of more than 1200 individual disease advocacy organizations, are an example of a patient-generated research network (TA, 2013). The 45 and Up Study is a large-scale Australian cohort study of individuals aged 45 and over, randomly sampled from the Medicare Australia enrolment database, which provides researchers with reliable information on a wide range of exposures and outcomes of public health importance for the ageing population. This study is a valuable resource for the investigation of social and economic determinants of healthy ageing; health effects of obesity; overweight and physical activity; impact of environmental factors on healthy ageing; risk factors for, and the detection and management of cancer, cardiovascular disease and mental health problems; use of health services in relation to ageing, including the determinants of use of residential aged care; and health in people aged 80 years and over (45 and Up Study Collaborators, 2008).

Secondary Data

Secondary data comprise of pre-existing data collected for some other purpose, such as for a previous research question (e.g., clinical trial), or to facilitate some process (e.g., hospital discharge records, or claims). Although data from RCTs are not frequently used in pharmacoepidemiology, data from these studies can be used for secondary analyses. A secondary analysis was conducted by Reid et al. to examine the relationship between Pravastatin and bone fractures from the data of a study of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, and found that there was insufficient evidence to support the hypothesis that statins can be protective against fractures. In the original trial, the patients were not recruited on the basis of being at an increased risk for fracture, since the goal of the LIPID trial was to examine the effects of pravastatin on cardiovascular mortality. The enrolled patients were at a relatively lower risk for osteoporotic fractures. The fact that the original aim of the RCT was not the focus of the secondary analysis is an important consideration when using data from previous RCTs for a new study. Secondary data are utilized to study varied aspects of pharmacoepidemiology and pharmacovigilance, including physician prescribing practices, drug utilization, medication adherence, unintended drug effects, and health policy issues (Harpe et al., 2011). Data gathered on patient encounters with the healthcare system are captured in an automated fashion, often electronically. These automated healthcare databases, or transactional databases, are a source of secondary data (Torre and Martins, 2012). All studies based on secondary data collection should be designed with the same critical approach as with studies based on primary data, i.e., specifying hypotheses, estimating sample size, and aiming at reducing both systematic bias and random errors (Sørensen et al., 2009). The primary limitation of secondary data is that the data are not collected for the specific purpose of answering the research question; thus, there may be specific validity challenges that must be considered (Harpe et al., 2011). Administrative data, claims data, electronic medical records can be grouped as secondary data.

Administrative Database

The provision of health care frequently generates digitalized data such as claims data, hospital-based electronic data, and medication prescription records, collectively termed as "administrative database research" (Nojiri, 2015). From a functional viewpoint, databases may be organized around a disease, a provider, a facility, or a sector of the healthcare system. A substantive orientation relates primarily to the type of information contained in the database, such as financial, demographic, or outcome data (Harpe, 2009). The functioning NZ administrative databases include Aotearoa NZ Health Tracker, EpiSurv records (maintained by the Institute of Environmental Science and Research), and NZ Deprivation (NZDep) dataset. The NZDep index is a composite deprivation score, extracted autonomously from census data, which compares socioeconomic positions of small area mesh-blocks among 60–110 individuals based on their location within a given period (Nishtala et al., 2017). It is essential to understand that administrative databases are fundamentally designed for billing and record-keeping purposes, and not primarily intended for research. Administrative databases generally identify endpoints such as cancer, dementia, myocardial infarction, or fracture, since healthcare provision is becoming increasingly digitized. The patient diagnoses, medical procedures, outcomes of visits to emergency departments, and hospital admissions are documented in hospital databases. Each of these systems leaves a trail of digital information describing a patient's course through a healthcare system (Van Walraven and Austin, 2012; Torre and Martins, 2012). Another major disadvantage of administrative data is the non-permanent residence of the population due to migration, and changes in coverage for specific employees and their family members.

Claims Databases

Claims data provide some of the best data on the prescription of medications in pharmacoepidemiology, and arise from an individual's utilization of the facilities at the healthcare system (Strom, 2012). When a patient visits a pharmacy and a medication is dispensed, the pharmacy charges the insurance carrier the cost of that medication along with complete medication details. Similarly, if a patient visits a hospital or a physician for medical care, the providers of care charge the cost of the treatment to the insurance company, and have to justify the expenses with a diagnosis. One of the frequently used and accurate measurement of exposure to medications is outpatient claims prescription/pharmacy records because the pharmacy has to identify which medications were dispensed and all its attributes (milligrams per tablet, number of tablets, etc.) (Torre and Martins, 2012). If there is a common patient identification number for the claims of the pharmacy and medical care, these elements could be linked and analyzed as a longitudinal medical record. Since the medical claims affect reimbursement, and the filing of an incorrect claim for medications dispensed is fraud, claims are often closely audited, e.g., by Medicaid in the USA. There have also been multiple validity checks on medication data in claims files that proved that the data are of extremely high quality, i.e., confirming that the patient was dispensed the same what the claim showed, according to the pharmacy record (Strom, 2012). In processing these claims, healthcare systems generate and store large amounts of data detailing the services provided and the level of payment for those services. To support the processing of these claims, supplementary information such as medical diagnoses may also be submitted along with claim forms. Also, health plans also maintain the necessary demographic information of individuals. The combined information can serve as a useful tool for research purposes (Harpe, 2009).

The quality of data for diagnosis in claims databases is not perfect. The hospital bills an admitted patient for the therapy and justifies it by assigning the International Classification of Diseases-Tenth Revision-Clinical Modification (ICD-10-CM) codes and a Diagnosis Related Group (DRG). The amount reimbursed by the insurer to the hospital is based on the DRG, so there is no motive to provide incorrect ICD-10-CM codes (Strom, 2012). The ICD-10-CM codes, based primarily on the discharge diagnoses assigned by the patient's attending physician are moderately accurate (Strom, 2012). Trained clinical coders have designated the task to code the diagnosis for reimbursement, and inpatient diagnoses are scrutinized for errors (Strom, 2012). Similar to the diagnosis codes, medications are also assigned codes in secondary databases. There is a clear need for a standardized classification system for medications. Whenever an insured individual switches jobs, migrates to another place, or if the employer modifies health plans in the case of employer-sponsored insurance, claims for that individual (and for others associated with the covered individual) will no longer be captured. To tide over this challenge, eligibility data are used to identify individuals who are continuously eligible for benefits during the course of the study; without which the data may appear as the discontinuation of drugs or the resolution of a medical condition when in reality the individual is no longer covered by the same health plan. In the outpatient departments (OPD), the practitioners themselves affirm outpatient diagnoses. The reimbursement in OPD not only depends on the actual diagnosis but also on the procedures undertaken, and the procedure codes point to the intensity of the services provided. Hence, there is neither any incentive for the practitioner to provide incorrect ICD-10-CM diagnosis codes nor any incentive to be particularly careful about the diagnosis provided. Therefore, the outpatient diagnoses are one of the weakest links in claims databases.

In NZ, the Pharmaceutical Collection is a data warehouse to support the management of pharmaceutical subsidies. It comprises of claims and payment information from pharmacists for subsidized dispensing (Nishtala et al., 2017). Few databases are not composed of actual claims, but are derived from other administrative processes, e.g., data from the US Health Maintenance Organizations. The data are almost similar to those of claims data (Strom, 2012). Claims data include a variety of healthcare services, including OPD visits, inpatient hospitalizations, prescription drug events, and durable medical equipment. It is important to know that different types of claims are not repeated in the same database; e.g., a pharmacy benefits manager may process pharmacy claims separately from the rest of the medical claims (Harpe et al., 2011). A study utilized the data from the Australian Department of Veterans' Affairs claims database to assess if the number of comorbid conditions unrelated to diabetes was associated with a delay in therapeutic progression of treatment of diabetes in Australian veterans (Vitry et al., 2010).

Primary Care Electronic Health and Medical Records

An Electronic Health Record (EHR) (Masnoon et al., 2018) is defined as a longitudinal digital record of patient health information generated by one or more encounters in a healthcare setting. EHRs facilitate a patient-centric design providing a 360-degree view of their health and wellness, and support patient tracking, administration, and scheduling of a range of care-related activities (Deloitte, 2015). The EHR also includes data from patient portals or external laboratories and can be shared beyond the practice site (Murray, 2014). The NZ Ministry of Health is working toward the implementation of a National EHR, which implies that patients wouldn't need to repeat their health history whenever they visited a new clinician, or risk missing out important medical details when being consulted; healthcare providers would have access to information from other health professionals their patients were seeing; policy and service planners would be able to utilize data and information to make investment decisions, target public health initiatives and monitor the effectiveness of programs (Ministry of Health, 2017). Data from EHRs are progressively seen as a crucial aspect to the future of pharmacoepidemiology, pharmacovigilance, and clinical research requiring similar observational clinical data (Murray, 2014). The European research initiative EHR4CR has been instrumental in designing many innovative services to support federated clinical research based on the semantic integration of numerous EHR systems across various organizations and nations (Coorevits et al., 2013). The observation of a systematic review and a meta-analysis is that the use of computerized provider

order entry (CPOE) incorporated in EHRs in hospitals, along with clinical decision support, which alerts clinicians to laboratory and medical errors, significantly reduced adverse drug events and prescription errors (Charles et al., 2014; Nuckols et al., 2014). Lyons et al. observed that the incorporation of the CPOE in EHR was a significant predictor of shorter hospital stay and lower mortality (Lyons et al., 2017).

By contrast, EMR is a digital version of paper charts in a medical practitioner's field of work. The EMR is more specific and narrow in scope, focusing on episodic healthcare events. It is designed to support interactions within a setting (e.g., primary care or hospital) or for a particular type of professional (e.g., pediatric/geriatric specialist). EMRs are medical records that act as a repository of patient information and support resourceful capture and access to information. EMRs provide administration functionality and basic connectivity to enable tracking of patients, exchange of information and assist the delivery of care by providing decision support capabilities (Deloitte, 2015). The data obtained from EMRs is ubiquitous, increasingly used for research in pharmacoepidemiology, and is significantly efficient over manual chart reviews. EMRs offer a higher level of detail compared to administrative claims or patient/provider questionnaires. As the EMR is based on real-time data, there is minimum latency period between the generation of data and its availability for research, which can be compared to the three to six month lag time for most administrative claims-based research data sources or national surveys. One drawback of the EMR is the lack of standardization of these databases, since each EMR vendor may use different formats (Harpe et al., 2011). There may not be entries of laboratory reports, progress notes, quality of life measurements, and information on health beliefs or health behaviors in EMRs (Harpe, 2009). The data contained in EMRs are typically complex, given the longitudinal nature and volume of information included, and can be challenging for conducting statistical analysis. Electronic medical records data are recorded as a procedure of clinical patient care, and not specifically for research purposes. The information from one institution (i.e., a single-site study) can be a limitation. Multisite sources can be advantageous in terms of sample size, but there may be problems with data consistency because documentation practices and implemented functions may vary across the participating sites. Although this may not be significant when analyzing data from one institution, it can be problematic when gathering data from multiple institutions that use different EMR vendors. The coding practices of the providers can also be an important consideration (Harpe et al., 2011). The significant limitations of automated databases are related to the quality of data input and the validity of the diagnostic information contained in the database. Training a future workforce to analyze large electronic databases is critical. While the costs of training and equipping the new cadre of big data analysts will be substantial, the missed opportunity of not doing so will likely incur higher costs (Murray, 2014). Despite their availability, a few practitioners may be reluctant to use these databases because they lack familiarity with database research in general (Harpe, 2009).

Electronic databases are a good source of information to lay the foundation for post-marketing research. A system of cross-linked digital medical records may enable researchers and physicians to monitor post-marketing safety and incorporate monitoring benefits. The same research could also illuminate the net public health effect of regulatory decisions (Herings, 2014). The General Practice Research Database (GPRD) in the UK, considered the world's best database of anonymized longitudinal medical records from primary care, has population-based data with over 15 million patients and has been extensively used for published research in the field of pharmacoepidemiology. Seminal observational studies have been conducted using the GPRD database. The GPRD database was recently used to find the differences in types of pregnancy loss following the potential exposure to a statin just before or early in pregnancy (McGrogan et al., 2017). A case-control study utilizing the GPRD found an association between olanzapine, risperidone, and the probability of incident diabetes (Strom, 2012; Torre and Martins, 2012). The association of pioglitazone with an increased risk of bladder cancer in patients with type 2 diabetes was also found using the GPRD database (Wei et al., 2013).

More recently, the electronic medical record databases are being used on a large scale, often replacing paper medical records as the primary document. This facilitates the large data collection for pharmacoepidemiological studies. The validity of the diagnosis data in these databases is better than that in claims databases, as the data are being used for medical care, and not solely for insurance reimbursement purposes. The database is comprehensive, as different medical practitioners can access the complete medical history of the patients (Torre and Martins, 2012). There is no considerable cost of data collection, other than for those subsets of the population for whom medical records are abstracted and/or interviews are conducted. In addition, electronic databases also enhance the representativeness of research by covering the entire population of a region. Moreover, the large sample size permits the study of prescription patterns of medications that are infrequently used, and lists their uncommon effects. Another advantage of digital databases is that they can demonstrate precise drug dispensing patterns, and there is no opportunity for recall and interviewer bias (as they do not rely on patient recall or interviewers to obtain their data). Also, these databases can potentially be linked to external electronic databases (e.g., birth and mortality records, claims), via a unique identification number to enhance the capabilities and scope of research. These databases are useful: (1) for examining rare outcomes because they offer a large sample size; (2) contain a denominator to calculate incidence rates (Sink et al., 2008); (3) when short -term effects of medications are being studied; (4) when objective, laboratory-driven diagnoses are being studied; (5) when recall or interviewer bias could influence the association; (6) when there is limited time; and (7) restricted budget (Strom, 2012).

One of the prime functions of the United States Food Drug Association (FDA) is to monitor the safety of its regulated products with a view to protect public health. The Sentinel initiative is the FDA's national electronic system which has transformed the way researchers monitor the safety of FDA-regulated medicinal products, including drugs, vaccines, biologics, and medical devices. Sentinel augments monitoring the safety of medicinal products in the pharmacovigilance phase, and complements the existing Adverse Event Reporting System. Through this efficient system, the FDA can rapidly and securely access large resources of electronic healthcare data, such as EHR, insurance claims data and registries, or from a diverse group of data partners. Sentinel utilizes a

distributed data approach which permits the FDA to monitor the safety of regulated medicinal products, while securing and safeguarding patient privacy (FDA, 2018).

Other Transactional and Operational Data

Transactional or operational data refers to data that is collected as a result of activities that support the provision of a service, such as medical care. The administrative claims data previously discussed represent a specific subset of transactional data that arise from the submission of healthcare claims for reimbursement. Information is collected about various "transactions" that occur during healthcare encounters, of which some information, like medication dispensing or laboratory results, may not be required for reimbursement, but could be useful for research purposes. Amassing and consolidating data from separate administrative sources such as pharmacy, laboratory, diagnosis, and patient demographic data, into one data warehouse can be tedious, but is often necessary to conduct meaningful research, clinical decision support, and utilization review. Transactional data can also be found outside of healthcare systems. For example, uninsured patients or patients paying cash are generally not represented in pharmacy claims data, for whom the information on dispensing of prescription medications and sales of medical products could be obtained from a pharmacy or a group of pharmacies in a specific area. Also, sales data have been utilized as a method of syndromic surveillance to predict disease outbreaks (Harpe et al., 2011).

Other Data Sources

There are various other sources of data employed in pharmacoepidemiology that do not correspond to any of the previous categories. Results of laboratory tests contained in laboratory collections may be used as surrogates to monitor the outcome of interest; e.g., a reduction in the low-density lipoprotein cholesterol and glycated haemoglobin (HbA1c) are surrogate measures for effectiveness of high cholesterol treatment and diabetes respectively. The laboratory results are more frequently recorded in electronic medical records, whereas administrative claims data usually only provide information about whether a laboratory test was ordered or not and not typically its results unless both the sources are correctly linked.

Data Structure and Linkage

The process of identifying subjects across databases and consolidating their information is called data linkage; e.g., in different sets of medical charts, and in vital records such as birth and death certificates. Studies linking national health records with health survey data are known as data linkage studies (Torre and Martins, 2012). For example, a data linkage study utilizing the Australian Medicare system linked to the Australian Cancer Database and the National Death Index observed an increased incidence of cancer in children, after CT scan exposure (Mathews et al., 2013). A record-linked dataset of all hospital day cases and inpatient admissions in England was utilized to study the association of Klinefelter's syndrome and autoimmune diseases (Seminog et al., 2015). The Veterans Affairs (VA) Diabetes Epidemiology Cohort, a linked national database of all VA patients, with data from VA medical visits, Medicare claims, pharmacy and laboratory records, and patient surveys were utilized to optimize methods for identifying individuals with diabetes, and to obtain the best estimates of diabetes prevalence in the patients of the Department of Veterans Affairs, USA. Linkage could be conducted among distinct data sources or within a single dataset to identify multiple entries (e.g., re-admissions) for an individual. Studies dependent on linkage data may yield biased findings due to errors in data linkage, which relate to specific characteristics of patients and clinical settings. To overcome this, characteristics of unmatched records and a degree of the quality of linkages, like the rates of false positives and false negatives, need to be regularly measured and reported; potential bias in study results needs to be assessed on a case-by-case basis.

The promise for the significance of real-world evidence using databases in the medical field must be balanced against concerns related to observational inherited limitations for bias and confounding. The risk of biased results can be minimized by providing a robust description of the data tables used, with information on why and how they were created; calculating and reporting the accuracy of diagnostic and procedural codes used, and accounting for any time-dependent nature of variables. The hallmark of good research is meticulously vigilant analysis and interpretation (Nojiri, 2015).

Summary of Data Sources Used in Pharmacoepidemiology and Pharmacovigilance

Primary data	*Secondary data*
National surveys	Administrative database
Registries	Claims database
	Electronic medical records

Conclusion and Future Opportunities

Researchers and medical practitioners have always been intrigued by how the future of databases in pharmacoepidemiology will progress. In the last decade, computerized databases based on administrative claims data, medical records, or disease-based registries have rapidly implemented worldwide. Vast amounts of healthcare data will be generated, including data sourced from electronic decision-support systems.

"Big data" has become a buzz-word in healthcare, where the term mainly refers to the enormous and expanding volumes of automated medical information available in the form of electronic health records, administrative or health claims data, or disease and medication monitoring registries. This type of data has been customarily gathered during administrative processes and clinical practice by different healthcare professionals for a long time without its significance being fully recognized and leveraged. Today, big data has a significant role in healthcare, including in pharmacovigilance, which comprises signal detection, substantiation and validation of medication or vaccine safety signals. The practicality of big data in healthcare is increasingly being recognized and seen as an opportunity to transform huge mounds of routinely collected data into scientific evidence. The progressive use of healthcare database networks has resulted in an expanded range of analytic methodologies to harness the large volumes of heterogeneous data.

The EU-ADR European project includes innovative pharmacovigilance research methods through the application of a web platform for providing advanced medication data exploration and assessment features. Millions of EHRs can be mined for specific drug-events. Advanced distributed computing methods are tailored for coordinating the execution of data-mining and statistical analysis tasks, which allows a ranked drug-event list, eliminating spurious entries and highlighting the relationships with high- risk potential (Oliveira et al., 2013).

In conclusion, the availability of healthcare data from several sources and the increasingly robust statistical tools to analyze such data are an opportunity to study medication utilization and safety on ever wider scales and in greater detail. Frequently used "big data" sources like the medical records, health insurance claims, and linked medication or disease registries should not be considered in isolation, but as part of a more comprehensive data context along with complementary methods and other data sources, such as spontaneous reporting systems and social media. The combined use of the variety of databases in a distributed database network enhances the power and potential of medication utilization and safety studies.

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Special Population Studies to Inform Medication Safety—Pediatrics

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Introduction

The history of including children in clinical trials is relatively short. Until recently, children were rarely included in the clinical trials mainly due to ethical concerns. More specifically, children are often considered as lacking decision-making ability, and alternatively, their parents or legal guardians represent children's interest. However, subject's autonomy can be potentially threatened when parents give consent while children refuse to participate in the research or vice versa. Meanwhile, there are questions about whether children are capable of comprehending risks and benefits associated with the research and protecting their well-being (Nijhawan et al., 2013). Regardless, research involving children deals with unique challenges to the informed consent process. In addition, the pediatric population represents a wide spectrum of different physiologies, ranging from the preterm newborn infant to the adolescent. During the process of maturation and growth, dynamic changes occur in body proportions and composition, which have a substantial impact on efficacy and toxicity of medicines. Therefore, it is necessary to stratify pediatric patient population into subcategories based on their developmental stage, in order to accurately determine dosage regimens of medicines given to children. As a result, securing the sufficient sample size to preserve statistical power, the lack of age-specific efficacy and safety assessments, and difficulties in identifying clinically feasible end points and appropriate comparators add the complexity of pediatric research (Sampson et al., 2012).

These limitations result in the lack of evidence in pediatric treatments, particularly concerning off-label prescriptions (i.e., unlicensed use of drugs) and suboptimal dosing. Due to challenges in pediatric clinical trials, a number of widely used drugs do not have pediatric labeling. Health-care providers must rely on studies conducted in adults, by extrapolating data from those and applying it to children. In fact, a systematic review study conducted by Cuzzolin et al. showed that 23%–60% of children in different practice settings across different countries are prescribed drugs off-label (Cuzzolin et al., 2006). However, these extrapolations create an environment with a higher risk of drug toxicity and unknown adverse side effects in children. Children are not small adults, and pharmacokinetic profiles of many drugs are not the same between the two populations. Another concern surrounding pediatric medication treatments is related to family self-medication, which is defined as the practice in which a family member (often a parent) selects and administers medicines to their child based on their judgment without consulting health-care professionals. As the World Health Organization (WHO) reported, over-the-counter, traditional and herbal medicines that are readily available are often inappropriately used in children (World Health Organization, 2007). This is in part because medicines are often distributed through unofficial and unregistered routes in many low-income countries. As a result, children may be given medicine without consulting any health-care professionals.

Shirkey, in 1968, used the term, "therapeutic orphans" to describe pediatric patients and the dilemma regarding pediatric drug labeling (Shirkey, 1968). More specifically, it is to reflect the moral and ethical dilemma in which children subjects are excluded from clinical trials to minimize potential harm imposed on them, while this effort will result in the inevitable application of a double standard between adult and child in treatment practice. The standards of drug efficacy and safety cannot be applied equally to both children and adults because they are different with respect to pharmacokinetics and pharmacodynamics. For example, most drugs that are primarily excreted through a renal system are eliminated at a faster rate in children between the ages of 2 and 12 years than adults (age > 18). Moreover, differences in size and perfusion of organs between children and adults influence a drug's behavior in

the body (Ginsberg et al., 2002). For example, levetiracetam, an antiepileptic drug, was shown to have a 30%–40% faster rate of clearance and a shorter half-life in 6–12-year-old patients than in adults. As such, the maintenance dose of levetiracetam in children should be 30%–40% higher than the recommended dose in adults (Pellock et al., 2001).

This chapter provides an overview of regulatory interventions in pediatric research and its impact on pediatric drug use and pharmacovigilance systems. Also, drug safety considerations related to pediatric subpopulations including pregnant women and neonates are summarized. Then, drug categories of antimicrobials and psychotropic medications in the context of prescribing practice and drug safety in pediatrics are reviewed. The chapter will focus on antimicrobials and psychotropic medications because it is reported by the International Society of Pharmacoepidemiology (ISPE) Pediatric Special Interest (PSI) Group that psychiatry/mental health and infectious disease are the areas of the most pressing clinical questions that need to addressed by pediatric pharmacoepidemiology and pharmacovigilance studies (Lasky et al., 2016). Lastly, this chapter discusses current needs in pharmacovigilance methods in pediatrics.

Legislative History of Pediatric Drug Use

Background

Pediatric pharmacovigilance and pharmacoepidemiology have stemmed from public demand for regulatory scrutiny, in response to some of the unexpected adverse side effects that primarily affected children, such as the "thalidomide disaster." During the late 1950s, a number of pregnant women used thalidomide to alleviate their morning sickness and nausea. However, within a few years of the widespread use, it became clear that thalidomide caused birth defects in children of those who used the drug. Australian physician William McBridge wrote to the *Lancet* to report the increased deformities in babies born from thalidomide users at his hospital (Mcbride, 1961). The most common forms of birth defects included phocomelia (i.e., malformations of limbs), congenital heart disease, and other congenital defects affecting the ear and eye (Miller and Strömland, 1999). This tragic incident that affected more than 10,000 babies spurred governments to adopt standards to evaluate the risk of new pharmaceutical agents and regulate commercial advertisements.

Aspirin-induced Reye's syndrome in children is another case that fostered the demand for more regulated assessments and monitoring of adverse drug reactions (ADRs) before and after a drug is marketed. Pharmacoepidemiological studies were conducted to identify adverse side effects that are specific to pediatric patients who use aspirin. Hurwitz et al. conducted a case–control study to assess the possible association between Reye's syndrome and salicylates (Hurwitz et al., 1987). They identified 27 patients with the confirmed diagnosis of Reye's syndrome and matched them with controls based on age, race, and type and timing of onset antecedent illness such as chicken-pox, respiratory illness, or gastrointestinal illness. As a result, a strong association was observed between salicylates and the presence of Reye's syndrome (odds ratio 40, lower 95% confidence limit 5.8).

In the history of regulations specific to pediatric drug use, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) of the United States (US) in early 2000s, and the Paediatric Regulation of the European Union (EU) in 2007 played an essential role to promote pediatric drug labeling and evidence-based practice in treating children.

The United States

The BPCA intends to improve drug labeling for pediatric population in two pathways. First, for drugs that are still on patent, it provides an incentive for drug manufacturers to conduct pediatric studies by offering an additional 6 months of patent protection and market exclusivity. This 6-month extension is not limited to the drug that was studied in pediatric populations but applied to any of the manufacturer's formulations that have the same active drug ingredient. Second, for drugs that are off-patent, the US National Institutes of Health (NIH) would prioritize therapeutic areas in which on- and off-patent drug products should be further studied in children and fund pediatric clinical trials and pharmacoepidemiological studies in those areas.

Under the PREA, drug manufacturers are required to submit pediatric studies during the new drug approval process if the Food and Drug Administration (FDA) determines that the drug is expected to be used by a number of children and that there is insufficient information available to ensure the safety and effectiveness if used in children.

Europe

Partly inspired by these legislative developments in the United States, the EU enacted the Paediatric Regulation in 2007. The Paediatric Regulation mandates drug manufacturers to establish a pediatric research and development program, the Paediatric Investigation Plan (PIP), for drugs that are on a patent or under the new drug authorization process. Unless a drug is subject to a deferral or waiver, the drug manufacturer is obligated to describe their plan to measure pediatric health outcomes of the drug. As an incentive, if the manufacturer complies with the regulation, they receive a 6-month extension of the patent protection and market exclusivity. On the other hand, if the manufacturer fails to comply with the regulation, the new drug may not be authorized by the European Medicines Agency (EMA) or the respective (adult) marketing authorization may be canceled. For older off-patent drugs, the Paediatric Use Marketing Authorisation (PUMA) was implemented to promote pediatric research in which indications and appropriate formulations of medicines are exclusively developed for use in children.

The Impact of Regulation on Pediatric Medicine

Generally, it is considered that government regulations have made progress in the practice of pediatric medicine. Some of the progress includes better detection of adverse side effects, more appropriate drug dosing and formulations for children, and the development of new treatments for children. For example, in 2003, the drug manufacturer of paroxetine, GlaxoSmithKline, alerted the FDA with a potential risk of suicidal ideation and behavior in paroxetine-treated pediatric patients. Based on that report, the FDA requested several other drug manufacturers of similar antidepressants including selective serotonin reuptake inhibitors (SSRIs) to search for suicide-related adverse events in their antidepressant databases and share patient-level data with the FDA. The FDA derived data from 4582 patients in 24 trials and conducted a meta-analysis to estimate the overall risk of suicidality associated with antidepressants (Hammad et al., 2006). As a result, it was estimated that the overall risk ratio for all antidepressants across all indications was 1.95 (95% Confidence Interval, 95% CI, 1.28–2.98). The overall risk ratio for SSRIs (e.g., paroxetine) was 1.66 (95% CI 1.02–2.68). The overall risk difference for all antidepressants across all indications was 0.02 (95% CI 0.01–0.03). The result indicated a statistically significant and positive association between the use of antidepressants in pediatric patients and a risk of suicidality. In 2004, the FDA issued black box warnings indicating that antidepressants are associated with an increased risk of suicidal thinking and behavior in children. In addition to the ADR of antidepressants, potential ADRs of several other drugs used in children were identified during the postmarketing reviews under regulations; neuropsychiatric symptoms including delirium and confusion associated with oseltamivir; neonatal syndrome associated with SSRI; cardiovascular risks associated with attention-deficit/hyperactivity disorder (ADHD) medicines; and deaths associated with accidental exposure to opioid transdermal system.

Pediatric Subpopulations

Pregnant Women

It has been reported in recent studies that prescription drug use during pregnancy is quite prevalent across different therapeutic categories (Daw et al., 2011; Lupattelli et al., 2014). Moreover, it is anticipated that the rate of drug use during the pregnancy would increase as the number of women having children in older age (childbearing age >35) increases (Mathews and Hamilton, 2014). It is because older women are more likely to have preexisting health problems than younger women. Unintentional exposure to medication may occur when the mother does not realize her pregnancy. Medication use during the pregnancy is an important challenge since it affects both the mother and child. While several drugs were shown to be harmful to the fetus, pharmacotherapy may be necessary in some cases if the mother's untreated acute or chronic illness causes adverse effects on the patient and further affect the child as a result. However, data and evidence to help determine drug and dosage regimen during pregnancy are limited. Only a few studies have assessed the mechanism of drug action and pharmacokinetics pertaining to physiological changes during pregnancy and whether the drug crosses the placenta (Mazer-Amirshahi et al., 2014).

Extensive nausea and vomiting during the pregnancy can decrease the drug absorption substantially. Even though some pregnant women do not have such problems, they still undergo changes in maternal weight, total body fat, total body water, gastric volume, bile content and excretion, and gastrointestinal motility (Abduljalil et al., 2012; Zhao et al., 2014). Liver and kidney are also affected by pregnancy. The activity of some metabolic enzymes such as cytochrome P450 (CYP) 3A4, CYP2D6, and CYP2C9 changes during the pregnancy and alters the rate and extent of drug metabolism in patients (Anderson, 2005; Anderson and Carr, 2009). For example, codeine is metabolized by CYP 2D6, and this enzyme is induced during pregnancy. This increases the rate of codeine metabolism in patients and could result in drug overdose (Lam et al., 2014). Changes in glomerular filtration rate (GFR), creatinine clearance, and renal blood supply during pregnancy may expedite the elimination of drugs that are excreted through the renal system (Hebert et al., 2005). In addition, some individual factors such as gestational age, singleton vs. multiple gestations, the history of alcohol consumption, and tobacco use can affect the pharmacokinetic action of a drug (Zhao et al., 2014).

Another important implication of medication use during pregnancy is related to the differential interaction between a drug and fetal development in each trimester. It is because the physiological changes progress over the course of pregnancy. With the increased maternal and placental blood flow during the third trimester, drugs may transfer across the placenta at a faster rate than the first or second trimester. For example, a recent Danish study involving more than 64,000 children reported that children whose mother took acetaminophen during the second and third trimesters were at a higher risk of ADHD-like behavioral problems or hyperkinetic disorders. However, the risk was not significant for women who used the drug only during the first trimester (Liew et al., 2014). Another example of differential interaction between a drug and fetal development is nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of miscarriage and malformations. If used in the first trimester, NSAIDs are associated with an increased risk of miscarriage and malformations. Contrarily, if used after 30 weeks' of gestation, they are associated with an increased risk of premature closure of fetal ductus arteriosus and oligohydramnios (Antonucci et al., 2012).

Currently, the most well-known pregnancy risk classification systems are from Sweden, Australia, and the United States. These systems categorize medications to risk groups based on the fetal risk (Schaefer et al., 2015). Although they provide a great value when consulting drug use during pregnancy, pharmacologic effects of many drugs are still unknown. The FDA and EMA recommend pharmaceutical companies to establish pregnancy exposure registries for products that may be used during pregnancy (European Medicines Agency, 2005; Food and Drug Administration, 2002) to promote pregnancy labeling and clinical trials in pregnant women. A pregnancy registry is a program that enrolls a group of pregnant women and collects data on medicine exposure and other factors associated with different pregnancy outcomes (e.g., spontaneous abortions, elective terminations, fetal deaths/stillbirths, and

live births). This type of registry can be very valuable when examining major teratogenicity and detect adverse pregnancy outcomes that warrant further investigation.

Neonates

Neonates are a pediatric subpopulation that places unique challenges to pharmacotherapy. First, it is difficult to appropriately dose medications during the neonatal period, because neonates experience rapid physiological changes that affect pharmacokinetics. Second, due to lack of available dosage forms and drug delivery systems that are specifically designed for neonates, adult formulations are often diluted and administered in small volumes over a period of time. Such practice is prone to administration errors (e.g., errors in dosage calculation and dilution), especially in an intensive care or emergency situation (Rosati and Nahata, 1983). Third, due to the inability of patients to describe a reaction to a medication, some health outcomes may be unintentionally overlooked during the medical decision-making process.

Growth and maturation are the major factors that predict pharmacokinetics and they must be taken into account when determining proper therapeutic dosage for neonates. The levels of growth and maturation are quantified by birth weight, current weight, and age (postnatal, gestational, or postmenstrual age). Disease characteristics, critical illness, specialized therapies, and the expression of organ-specific transporters may further interfer with the variability of maturation in this patient population (Allegaert and van den Anker, 2015; Ku and Smith, 2015).

Currently, insufficient data exist regarding benefits and risks of a pharmacotherapy for neonates. The lack of published drug information and drug labeling resulted in an off-label or unlicensed use of medicine (Allegaert and van den Anker, 2015; Kemper et al., 2011). It was also reported that neonates are commonly exposed to polypharmacy (i.e., multiple medicine use) (Clark et al., 2006). Most likely contributed to such controversial medical practices prevailing in neonatal care, it appears that medical errors and adverse events occur frequently in neonates and infants. In fact, in a cross-sectional study on neonatal intensive care unit (NICU), medical error reports in 54 health-care facilities (n = 1256), approximately 47% of medication errors were due to wrong medication, dose, schedule, or infusion rate (Suresh et al., 2004). Other medical error categories included: error in administration or method of using a treatment (14%); patient misidentification (11%); other system failure (9%); error or delay in diagnosis (7%); and error in the performance of an operation, procedure, or test (4%). Importantly, out of 673 reports in which clinical outcomes of the medical error were reported, 181 (27%) resulted in actual harm. Another study on NICU medication error reports (n = 6749) revealed that approximately 48.2% of all medication error reports were contributed to administering errors (Stavroudis et al., 2010). Other categories included errors involving the transcription phase (18.4%); mistakes in the prescribing phase (14%); mistakes in the dispensing phase (11.9%); and monitoring errors (1.4%). In this study, 4% of reported medication errors resulted in harm.

In the literature, one of the most extensively discussed ADRs in neonatal care is related to the treatment of patent ductus arteriosus (PDA) using NSAIDs. In approximately 70% of preterm infants weighing less than 1000 g and 29 weeks of gestational age, the functional and anatomical closure of the ductus is delayed or does not occur (Bancalari et al., 2005). The PDA can be effectively treated with indomethacin or ibuprofen. Meanwhile, the debate of which NSAID agent is safer goes back to 1970s when indomethacin was initially introduced as the drug of choice for the PDA treatment. Although it was effective for closing ductus arteriosus, neonates who were treated with indomethacin showed severe adverse reactions including a decrease in cerebral blood flow and oxygen consumption (Edwards et al., 1990; McCormick et al., 1993), permanent renal dysfunction (Betkerur et al., 1981), and necrotizing enterocolitis (Cassady et al., 1989). As the alternative to indomethacin, ibuprofen was suggested as it appeared as a safer agent (Van Overmeire et al., 2000). However, other serious adverse side effects associated with ibuprofen were soon reported. These include pulmonary hypertension (Adamska et al., 2005; Gournay et al., 2002) and renal dysfunction (Allegaert et al., 2005). Regarding the treatment of PDA using ibuprofen and indomethacin, Ohlsson et al. published a review in the Cochrane Library in 2008 (Ohlsson et al., 2008). They stated, "In view of the lack of long-term outcome data and potential side effects for both drugs, one drug cannot be recommended over the other as the therapy of choice for a PDA." However, later in the 2010 update of the review (Ohlsson et al., 2010), they found a significant reduction in the risk of necrotizing enterocolitis in the ibuprofen group compared to the indomethacin group. With this finding, they stated, "Based on the currently available information, ibuprofen does appear to confer net benefits over indomethacin for the treatment of a PDA." This conclusion remains in their most recently updated review in 2015 (Ohlsson et al., 2015).

Issues in Pharmacovigilance of Specific Drug Categories

Antimicrobials

Children experience bacterial and viral infections more frequently than adults because the immune system is not fully developed in childhood (Gebel et al., 2008). Also, a growing number of children are exposed to environments in which microorganisms are more easily transmitted from person to person, such as group child care (Bradley and Vandell, 2007). More specifically, sociocultural changes that have occurred internationally over the last several decades have encouraged mothers of young children to work outside of the home. Consequently, demand for out of home child care such as child care facilities has also increased (Holmes et al., 1996). This trend had an important impact on public health by increasing the incidence of infectious disease in young children (Holmes et al., 1996). Children attending group child care are more likely to develop communicable illness including upper respiratory tract infections (URTIs) and common cold (Ball et al., 2002; Nafstad et al., 1999).

Antimicrobials play a major role in the treatment of infectious disease and are one of the most widely prescribed drugs in pediatrics (Buccellato et al., 2015; Chai et al., 2012). However, it has been reported in a number of pharmacoepidemiological studies that antimicrobials are over- or misused in children (Amadeo et al., 2010; McCaig et al., 2003; Nash et al., 2002). For example, excessive use of antimicrobial combinations was observed in 21 European countries (37% of all antimicrobial prescriptions for children) (Amadeo et al., 2010). Also, in the United States, more broad-spectrum antimicrobial agents such as azithromycin and clarithromycin, quinolones, and amoxicillin/clavulanate have been increasingly used among children, raising concerns regarding the development of antimicrobial resistance (McCaig et al., 2003). Uncomplicated URTIs and common colds are often easily self-treated, and the use of antimicrobials is generally not necessary. In fact, antimicrobials do not lead to an improvement of URTI and common cold symptoms, but only increase the risk of adverse side effects (Arroll et al., 2008; Fahey et al., 1998). Nonetheless, a considerable number of antimicrobials are given to children for these conditions. According to the study by Kronman et al., the number of potentially preventable antimicrobial prescriptions for acute respiratory tract infections (ARTIs) in children in the United States is nearly 11.4 million per year (56.9% of ARTI encounters in office-based primary care settings) (Kronman et al., 2014). In addition, with some degree of variability, the use of antimicrobials is prevalent across countries. In a study of pediatric antimicrobial use across 6 countries on 3 continents between 2008 and 2012, it was estimated that South Korea had the highest rate of antimicrobial use (3.41 prescribed courses per child-year for the age group of 0–2 years), followed by Italy (1.6), Spain (1.5), Pedianet, Italy (1.4), United States (1.1), Germany (1.0), and Norway (0.5 courses per child-year for 0–2 years) (Youngster et al., 2017).

Inappropriate and unnecessary prescribing of antimicrobials poses serious public health problems at both individual and population level. It is because such practice not only increases the risk of ADRs to individual patients but also promotes antimicrobial resistance in the entire population. Pharmacoepidemiological studies have associated antimicrobial use during early years of life with several negative health outcomes including imbalances in gut microbiota (dysbiosis) (Vangay et al., 2015), obesity (Bailey et al., 2014; Jess, 2014), allergic disorders (Droste et al., 2000; Ong et al., 2014), and inflammatory bowel diseases (Ng et al., 2013). In addition to this direct harm to the patient, inappropriate antimicrobial consumption could result in the environmental spread of resistant organisms in a community (Bronzwaer et al., 2002; Goossens et al., 2005). After a wide range of bacteria is inhibited or killed by an antibiotic, other organisms begin to proliferate in the space (van der Waaij, 1987). These surviving organisms may acquire antibiotic resistance at various rates (Dancer, 2001; Garau, 2003). Since antimicrobial-resistant organisms are more difficult, or impossible, to eradicate, it is critical to treat the primary infection appropriately during the initial treatment. In fact, in a clinical trial involving 904 adult patients with severe sepsis or early septic shock in North American and Europe, it was shown that inappropriate initial antimicrobial treatment was significantly associated with increased 28-day mortality, after adjusting for differences in patient demographics, vital signs, blood and other microbiological cultures, and measurements of end-organ dysfunction (Harbarth et al., 2003).

Psychotropic Drugs

Psychotropic drugs have long been used for mental disorder treatments in children. While nondrug therapies are available (e.g., behavioral therapy) and generally perceived as less invasive, drug intervention may be necessary depending on the severity of illness and other risk factors associated with each patient. Over the last few decades, the rate of psychotropic medication prescriptions for children has rapidly increased across countries, particularly in the United States (Steinhausen, 2015). More specifically, in the year 2000, the prevalence of all-class psychotropic medication prescriptions in youth was 2.9% in Netherlands and 2.0% in Germany, while it was 6.7% in the United States (Zito et al., 2008). This trend is accompanied by a growing concern that children may be overprescribed with psychotropic medications, especially for the conditions such as ADHD (Sohn et al., 2016; Zito et al., 2008). The elevated acceptance of pharmacotherapy in treating childhood mental disorder is in part contributed to successful discoveries of psychotropic drugs for pediatric use (Domino et al., 2008; Sohn et al., 2016). Also, it was argued that cost containment strategies exercised by managed care have led to the increased demand for psychotropic drugs over alternative therapies (Domino, 2012; Rapoport, 2013). More specifically, to reduce health-care costs, expensive psychiatric care is primarily allocated to medication clinics, and nondrug therapies are provided mainly by nonphysicians including psychologists, social workers, and counselors. As Rapaport speculated, "(I)t is probable, that the increase in medication use results in part from the desire of physicians to be helpful with what they have at hand given their lack of flexibility with respect alternate treatment delivery" (Rapoport, 2013).

Among psychotropic medications that are available for pediatric use, antipsychotics have been subject to a major criticism. Antipsychotic medications are used for the treatment of mental disorders including psychosis, schizophrenia, and bipolar disorder. These medications can be broadly categorized into two classes: (1) first-generation antipsychotics that were discovered in the 1950s and (2) second-generation antipsychotics that were introduced during 1990s. Second-generation antipsychotics were marketed as a safer agent as they showed reducing adverse side effects that were common in the first-generation agents, such as extrapyramidal symptoms. This resulted in the prevalent use of second-generation antipsychotics not only for the licensed indications (e.g., schizophrenia, psychoses) but also for off-label conditions and symptoms (e.g., ADHD). However, several postmarketing clinical trials and pharmacoepidemiological studies evaluated the risk of second-generation antipsychotics and reported that children taking these drugs are at a greater risk of weight gain (Sporn et al., 2007), cardiometabolic syndrome (Correll et al., 2009), and type 2 diabetes (Sohn et al. 2015).

Antidepressant treatment in children has also been extensively discussed. While double-blind clinical trials have shown that SSRIs could be successfully used in children to treat depression (Pine, 2002), the extent of knowledge and understanding about

antidepressant treatment in children is still limited compared to what is known in adults. Great variations in the effect size (Hetrick et al., 2007) and the confirmed risk of suicidality (Hammad et al., 2006) raise a concern whether the benefits of antidepressant treatment would outweigh the risks to children.

Current Needs in Pediatric Pharmacovigilance

Some ADRs can be identified during the drug development process, but knowledge about the drug effectiveness in actual clinical practice and the long-term adverse side effects is limited when the medicine is first introduced in the market. The effectiveness and safety profile of a drug treatment needs to be continuously evaluated throughout the life cycle of the drug.

During the premarketing assessment, investigators should consider targeting pediatric population. The detailed information of the pathology of the disease and the pharmacologic activity and the toxicity profile of a drug will expedite the risk assessment when planning a pharmacotherapy for children. Preclinical studies with juvenile animals may also identify important pointers for a further investigation for potential ADRs in children.

However, the current drug regulatory systems are hampered with a number of weaknesses (Ray and Stein, 2006). Because the authority of drug regulatory agencies is mainly focused on premarketing studies, planned data collection about drug efficacy and safety occurs almost exclusively in clinical trials in which the care environment is highly protocolized and relatively short-term. In addition, potential bias in publications that were funded by drug manufacturers, which is derived from conflicts of interest and the economic motivations of the drug manufacturer, has been demonstrated in the literature (Landefeld, 2004; Ray et al., 1993; Turner et al., 2008). For this reason, postmarketing medicine surveillance is particularly crucial for new pediatric medicines. Furthermore, considering that the off-label or unlicensed use of medicines is prevalent and there are challenges in conducting clinical trials in children, more standardized methods need to be developed to assess physician's prescribing practices as well as to study the treatment effects of a medicine as used in actual practice.

Spontaneous ADR reporting systems are an essential means to detect safety signals or other issues in the postmarketing period, especially in pediatrics. These systems often involve registries that are established by government agencies or health-care organizations, such as the Yellow Card Scheme in the United Kingdom (UK) or the FDA Adverse Events Reporting System (FAERS) in the United States. Although they are useful for capturing early warnings of potential ADRs, it has been recognized that the spontaneous ADR reporting systems have some limitations. First, the reporting of an ADR is voluntary and the reporting rate is low. In an acute hospital setting in the United Kingdom, it was estimated that only 6.3% of potential yellow card cases were reported to the system over a 3-year period (Smith et al., 1996). Obstacles to the spontaneous reporting of ADRs include problems with diagnosis of ADRs (i.e., some health-care professionals do not report unless they are certain about the causality assessment of the ADR.), lack of awareness of pharmacovigilance system, problems with the clinical workload, and problems related to potential conflicts (legal liability) and fear of a breach of confidentiality with patients' data (Vallano et al., 2005). Second, during the reporting process, little information on potential confounding variables is collected, and as a result, the apparent association between an adverse event and a drug may have been confounded. To confirm the independent association between the drug and the observed adverse event, methodologically rigorous studies with a greater statistical power may need to be conducted. Third, identifying a reasonable comparator group is challenging when examining data from the spontaneous ADR reporting system, especially when there is a possibility that the medical condition that the medicine is used for is the cause of the adverse event.

Some countries have developed intensified spontaneous reporting systems in which a list of specific medications is more closely monitored during the early phase of postmarketing surveillance. For example, the EMA publishes a list of medicines under additional monitoring and requires the drug manufacturer of a listed medicine to display a black inverted triangle on their drug package. These medicines include agents that contain new active substances or new biologicals, medicines with the marketing-authorization holder, medicines given conditional approval, and medicines that are identified by the European Commission or the Pharmacovigilance Risk Assessment Committee (PRAC). Another way to apply the intensified ADR reporting system is to target a defined cohort. In this system, the ADR reporting targets specific medicines of interest in a defined group of patients. Ndagije et al. reported on a pilot study of the targeted spontaneous reporting system in Uganda, in which patients with HIV infection in two regional pharmacovigilance centers were closely monitored to investigate the association between tenofovir and renal toxicity (Ndagije et al., 2015).

Further advances in pharmacovigilance can originate from the evaluation of large health care datasets using established study designs in pharmacoepidemiology. Pharmacoepidemiology has been a major contributor to studies of adverse drug events. Furthermore, its scope has also included the study of several other issues related to clinical pharmacology. As seen in the use of antimicrobials and psychotropics in pediatrics, pharmacoepidemiological research is instrumental in assessing physicians' prescribing practices and quantifying the risk of a medicine on potential adverse side events. In addition, it has been suggested that retrospective and prospective monitoring from computerized medical records may be more time-efficient compared to other intensive surveillance systems that demand more efforts and time from healthcare professionals (World Health Organization, 2007).

As the final line of defense, the health-care professionals are primarily responsible for the assessment of drug safety and benefit–risk analysis. When a new medicine is marketed, it is exposed to individuals with different ages, sex, and other genetic factors in addition to different comorbidities. The role of health-care professionals is essential for drug safety monitoring because they are most adequately trained to observe health outcomes in response to a new drug therapy.

Summary

Safe and effective use of medications in children is of great importance as data and information on pediatric pharmacotherapy from clinical trials are limited. Challenges in conducting pediatric clinical trials include ethical issues related to obtaining informed consent, securing the sufficient sample size, lack of information on age-specific efficacy and safety assessments, and difficulties in determining clinically reasonable end-points and comparators. As a result, health-care providers often extrapolate data from studies conducted in adults and apply it to children. These extrapolations increase the risk of drug toxicity and unknown adverse side effects in children because the pharmacokinetics and pharmacodynamics of children are different from that of adults.

After several unexpected adverse side effects that primarily affected children, such as the thalidomide disaster and aspirin-induced Reye's syndrome, regulatory actions were taken by some developed countries. For example, the US and EU implemented legislation that requires drug manufacturers to investigate efficacy and safety of the medicine in the population for which it is aimed and marketed. These regulations resulted in the better detection of adverse side effects, more appropriate dosage regimen and formulations for children, and the development of new treatments for children.

The pediatric population covers a wide spectrum of different physiologies, ranging from the preterm newborn infant to the adolescent. Therefore, special considerations based on the stage of development have to be made in treating subpopulations of children. In particular, a medication treatment in pregnant women can be difficult as it affects both the mother and child. While some drugs cause adverse side effects in the fetus, drug therapy may be still needed if the mother's untreated illness creates a more harmful environment for the fetus. Nonetheless, limited data are available on the pharmacology and pharmacokinetics of many drugs, pertaining to physiological changes in pregnancy and how it affects the fetus. Currently, several countries and pharmaceutical companies make pregnancy exposure registries available to prospectively observe pregnant women regarding their exposure to drugs and other biopharmaceutical products over the course of their pregnancy. Neonates are another important pediatric subpopulation. Neonates go through rapid physiological changes that affect pharmacology and pharmacokinetics of a drug, making it difficult to determine appropriate dosage and dosing schedule. Also, dosage forms and drug delivery systems for neonates are often not available. Therefore, neonates are vulnerable to medication errors in dosage calculation or dilution. In fact, it was reported that medical errors and adverse events occur more frequently in neonates and infants than adults.

Among issues related to specific therapeutic categories, drug safety in the pediatric use of antimicrobials and psychotropic agents are of particular concern. Inappropriate use of antimicrobials in self-managed infections such as URTIs and common colds is prevalent across countries. Such practice is under criticism because it increases the risk of adverse side effects to the individual patient, and it also affects the entire population by spreading antimicrobial resistance. For psychotropic drugs, the rapid increase in psychotropic prescriptions for children has raised concerns that children may be overprescribed with psychotropic medications including second-generation antipsychotics and antidepressants. More specifically, the drug's potential benefits may not be greater than the potential risks in some pediatric patients.

The current drug regulatory systems do not effectively monitor and prevent rare or long-term side effects. It is because structured data collection occurs almost exclusively during the premarketing assessment by the drug manufacturer. Because premarketing clinical trials are not adequate to observe long-term treatment effects of drug use in actual clinical practice, and the off-label prescription occurs frequently in children; postmarketing medicine surveillance is pivotal for pediatric pharmacovigilance. Spontaneous ADR reporting systems are used as an essential tool to collect data on potential adverse side effects. While there are several limitations in the system, it is effective in detecting safety signals that are otherwise unknown. Evaluating large health-care datasets using pharmacoepidemiology can address some of the shortcomings of the spontaneous reporting system. Most importantly, health-care professionals play a key role in identifying potential drug-related adverse events and assessing the benefits and risks of a medication used in children.

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Comparative Effectiveness Research

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Introduction

Internationally, drug approval relies on evidence gained from placebo-controlled randomized clinical trials (RCTs). This type of evidence gives regulators information on the efficacy of the drug compared to a placebo. Generally, efficacy concerns itself with how well a particular treatment works under ideal conditions, such as in the RCTs used in preapproval studies. However, the conditions under which subjects use medications before market approval are certainly dissimilar to those in the normal course of medical practice. It is under these more common circumstances that a drug's effectiveness can be determined. In most therapeutic areas, there are multiple treatment options with limited evidence comparing one treatment to another in the real-world setting. It is this gap in knowledge between efficacy and effectiveness that comparative effectiveness research (CER) seeks to fill.

Colloquially speaking, CER aims to answer the following question: "What treatment works best under which circumstances for whom?" Depending on the target audience of the research, investigators conducting CER can aim to generate scientific evidence to inform individual-level clinical decisions or system-level policy decisions. It is this goal of CER that distinguishes it from the more general field of evidence-based medicine (EBM). While EBM and CER both inform clinical decision-making, EBM primarily focuses on treatment efficacy, while CER's ultimate goal is to inform decisions based on how treatments are used in regular clinical practice (effectiveness). The difference in purpose between EBM and CER influences how researchers regard different study designs, as will be discussed later.

The formal definition of CER has changed throughout the years. In this chapter, we will focus on a definition set forth by the Institute of Medicine in the United States (US) (IOM): "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care" (Institute of Medicine, 2009). In general, CER compares two or more treatment strategies, although "standard of care" and "watchful waiting" can also be considered treatments.

Often, CER relies on real-world data (RWD), defined according to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) as any data obtained outside of an RCT (Berger et al., 2017). ISPOR, working together with the International Society for Pharmacoepidemiology (ISPE), created a task force to standardize recommendations about how to properly conduct studies using RWD. These recommendations will be discussed in further detail in the second section of this chapter.

CER and patient-centered outcomes research (PCOR) are closely intertwined and will be referenced interchangeably often in this chapter. It is important to note, however, that there are nuanced differences between CER and PCOR, namely that while much of PCOR is CER, not all CER is technically PCOR. Throughout the world, CER and PCOR are often considered interchangeable. In the United States in particular, the discussion of CER largely shifted to incorporate PCOR surrounding the passage of the landmark health care reform legislation, the Patient Protection and Affordable Care Act (The Patient Protection and Affordable Care Act, 2010). Though nearly all legislators and the public agreed that there was a need for better quality evidence in the health care decision-making process, much of the American body was wary about the interrelation between CER and cost-effectiveness analysis, which had become equated with health care rationing in the political arena (Leonhardt, 2009). Further, there was recognition that

patients' voices were a key factor in understanding how medications should be studied and used. Thus, much of the discourse shifted from referring to "comparative effectiveness research" to discussing "patient-centered outcomes research" (Rich, 2012). Subsequently, the Patient-Centered Outcomes Research Institute (PCORI) was established as a funding body for research, defining its aim as helping "people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options" (Patient-Centered Outcomes Research Institute, 2013). To accomplish this goal, PCORI highlights comparisons and outcomes of medications, medical devices, and health systems while incorporating diverse participants and settings.

It is important to note that while PCORI in the United States is charged with setting national CER priorities and managing CER funding, it is strictly forbidden from basing its recommendations on cost-effectiveness information. This is in contrast to many other parts of the world where cost-effectiveness research is an integral component of CER. While similar methods are often used in both CER and cost-effectiveness research, the latter also considers the cost of the treatments and other health care utilization measures. Many nations throughout the world evaluate cost-effectiveness when determining national medication formularies, including Australia, Canada, the United Kingdom (UK), France, Germany, Italy, New Zealand, Norway, and Switzerland (The Commonwealth Fund, 2013). In this chapter, we will focus only on CER.

CER has been on the rise worldwide for nearly two decades. The UK's National Institute for Health and Clinical Excellence (founded in 1999) pioneered the shift to patient-centered outcomes and with it, the push to perform CER. By 2007, the Congressional Budget Office in the US released a report calling for more CER, followed by an allocation of more than $1 billion to CER as part of the American Recovery and Reinvestment Act in 2009 (American Recovery and Reinvestment Act, 2009; Congressional Budget Office, 2007). In 2010, the US created PCORI as an independent funding organization for CER as part of its health-care reform, as discussed above. More recently, the 21st Century Cures Act was passed in the United States with a goal to "accelerate the discovery, development, and delivery" of new biomedical products (21st Century Cures Act, 2016). This new law requires the US Food and Drug Administration (FDA) to establish a program and guidelines within five years that would determine how real-world evidence (RWE) such as CER should be used not only for new drug approval, but also for new indications for already-approved drugs and to support postapproval requirements. While this law does not change current approval standards, it does enable the use of RWE to obtain information on outcomes that are too costly or otherwise too difficult to obtain from traditional RCTs. Likewise, the GetReal project of the Innovative Medicines Initiative (IMI) in the European Union (EU) was established in 2013 as a public–private consortium with a goal of demonstrating how RWE can be incorporated throughout the drug approval process (Nordon et al., 2016).

In this chapter, we will discuss the study designs that are available to investigators interested in conducting CER, including both interventional and noninterventional study designs. We will follow this with a discussion of important stakeholders in CER and how each works in tandem to push forward the evidence prioritization, generation, and dissemination generated through CER.

Study Designs

As discussed in the introduction, CER operates on a different paradigm than EBM, owing to its focus on impacting health-care decision-making for patients based on clinical practice. Consequently, the hierarchy of evidence sources in CER differs from the one traditionally taught for EBM. Often depicted visually as a pyramid, an inherent assumption is that higher levels provide better quality evidence than lower levels. While there have been many different iterations of the original hierarchy, new modes of categorizing evidence emphasize study design appropriateness to the study question, suggesting that different clinical questions might optimally be answered using different methodological approaches (Concato, 2004). Regardless, most researchers agree that decision-making should rely on the whole body of evidence, rather than the results of one particular study based solely on the study design. In CER, a strength-of-evidence rather than level-of-evidence model is used (Marko and Weil, 2010). The Agency for Healthcare Research and Quality recommends analyzing at least four "domains" to determine strength of evidence, depicted in **Fig. 1** (Owens et al., 2009). Each of these domains receives a score, and the result is a composite score that grades the evidence based on the level of confidence that the evidence reflects a true effect.

With this framework for evidence in mind, CER uses well-known study designs such as systematic reviews, meta-analyses, and both experimental and nonexperimental studies. Randomized, controlled, large simple, and pragmatic trials are examples of experimental, or interventional, study designs used in CER. Noninterventional studies include both retrospective and prospective observational studies wherein the investigator does not assign interventions.

While RCTs have generally been considered the gold-standard in EBM (Guyatt et al., 1995), RCT evidence can be limited due to the strict inclusion criteria required. Traditional RCTs are also known as explanatory trials, as their purpose is to explain the fundamental verification of a biological or physiological hypothesis (Schwartz and Lellouch, 1967). RCTs are certainly important aspects of CER: when the U.S. Congress tasked the Institute of Medicine (IOM) with identifying national priorities for the conduct of CER, they suggested using RCTs in 49 of their top 100 recommendations (Institute of Medicine, 2009). However, other study designs and methodologies are often used in CER that can more readily incorporate RWE. Though explanatory trials offer results with the greatest level of certainty, many CER questions can only be addressed with study designs that inherently produce results with more uncertainty. For example, a hospital's choice of wash cloth for patients in the intensive care unit would probably not warrant the resources required for an RCT, but it is an important question nonetheless.

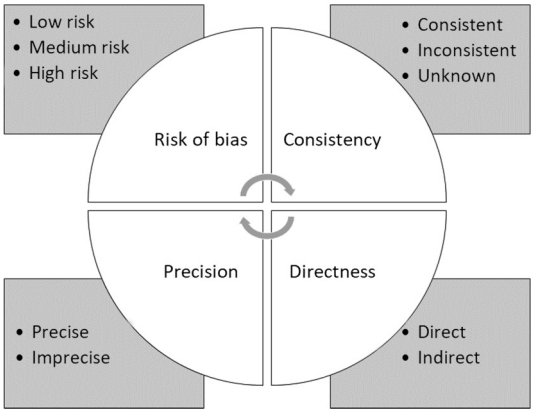

Figure 1 Comparative effectiveness strength of evidence

For all CER study designs, the assumption of clinical and personal equipoise should be maintained. Clinical equipoise is the assumption that one treatment is not better than the other. Personal equipoise is the assumption that the provider does not have a preference of one treatment over the other (Cook and Sheets, 2011).

This section will cover different study designs that produce results with varying degrees of uncertainty—both interventional and noninterventional—that are employed to provide patients, practitioners, and product and policy makers with the answers they seek.

Interventional Research

As discussed in the introduction, many studies involving drugs are designed to maximize their ability to determine efficacy, which is how well the drug performs under ideal circumstances. However, health care professionals realized as early as the 1960s that information gained from these explanatory trials was not always relevant to clinical practice and began to desire study designs that would more closely estimate a drug's effectiveness and inform clinical practice (Fiore and Lavori, 2016).

These designs, known as pragmatic, large simple, or point-of-care trials often aim to keep disturbance to clinical practice at a minimum (Shih et al., 2015). This requires dedicated effort during the study planning phase to balance the clinical relevance of measured outcomes with the feasibility of obtaining those outcomes as part of normal care. These designs would ideally include a population of patients with similar characteristics to those being treated in regular clinical care, a comparison group treated with a common clinical alternative, and meaningful outcome measures. More lenient subject exclusion would result in a more accurate estimate of potential harm, and more realistic conditions (that often result in lower adherence) may be able to determine effectiveness more accurately (Hernán and Hernández-Díaz, 2012; Thorpe et al., 2009). These more realistic study designs have been termed pragmatic clinical trials (PCTs) and have also been known as large simple or point-of-care trials. A comparison of pragmatic and explanatory trials using the standard PICOT framework has been suggested in the literature and is adapted in **Table 1** (Williams et al., 2015).

Designing Interventional Studies in CER

There is no unique tool to determine whether a study design is pragmatic or not, but the Pragmatic Explanatory Continuum Indicator Summary (PRECIS) and the updated PRECIS-2 tools highlight the concept of pragmatism and highlighted specific dimensions of a PCT that should be considered (Loudon et al., 2015; Thorpe et al., 2009). This tool evaluates the level of pragmatism within nine domains of a study design, including the recruitment of investigators and participants, the delivery of the intervention within the trial, and the natures of follow-up and outcomes.

Regarding recruitment into a PCT, investigators should consider the extent to which trial participants are similar to clinical patients, how much effort is required to recruit those subjects outside of normal practice, and how the settings of the trial are different from usual care. These considerations are especially important when studying diseases with a high burden of comorbidity, such as

Table 1 Comparison of pragmatic and explanatory trials

	Pragmatic trial: tests effectiveness	*Explanatory trial: tests efficacy*
Patient	Actual patients in practice	Strictly selected, healthy subjects
Intervention	Flexible, allows changes	Strictly defined, few changes allowed
Comparison	Head-to-head, standard of care	Often placebo; standard of care possible
Outcome	Clinically important	Surrogate or objective
Time	Long follow-up	Short follow-up

Type 2 Diabetes Mellitus (T2DM). Patients with T2DM often have comorbid hypertension, hyperlipidemia, and obesity, yet these patients would normally be excluded from RCTs. This makes health care professionals' decisions on appropriate therapy even more complicated. One example involves patients who are treated with insulin therapy, which has several approved delivery options. Currently on the market are vials of insulin which patients draw into syringes and self-administer, prefilled syringes, and continuous subcutaneous insulin infusions (CSII). When faced with a patient who has uncontrolled blood glucose and T2DM, a practitioner is faced with a conundrum that might be solved with a PCT. One such trial was performed with a CSII device investigating how these different methods of insulin delivery work in clinical practice (Abbott et al., 2017). The study randomized sites to the CSII or standard of care optimization and patients were treated according to routine clinical practice. The primary outcome was change in hemoglobin A1c (HbA1c) from baseline to the end of the study, and investigators found that patients with the CSII had larger drops in HbA1c than those using other methods of insulin delivery. Subjects in this study were recruited through a simple discussion with their provider at a regular clinic appointment and were followed according to routine practice for up to 4 months. Subjects purchased their insulin delivery devices as they had been and had an end-of-study visit that did not impose a schedule of regular visits. In every way possible, regular clinical practice was not interrupted. These data provided RWE about the effectiveness of different insulin delivery devices in treating T2DM.

In addition to considering the recruitment process, investigators should ensure that a PCT allows the same amount of flexibility in how the intervention is delivered and how patients are monitored as in usual care. Many RCTs are labor-intensive for patients, requiring extra visits to providers, and have rigid requirements for treatment delivery. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial was a large, randomized, double-blind pragmatic trial that was conducted in 623 North American practice sites to determine whether incidence of coronary heart disease and myocardial infarction differed among four antihypertensive treatments: chlorthalidone, amlodipine, lisinopril, and doxazosin (ALLHAT Collaborative Research Group, 2002). This trial allowed variation in study drug number and dose based on patient tolerance and clinical judgement, which nonpragmatic trials rarely allow. The study protocol also allowed rechallenges with medications attempted previously, which is common in clinical practice but extremely rare in most RCTs. These aspects allowed the trial to estimate the true effectiveness of these antihypertensives and have ultimately led to substantial changes in practice, including the understanding that many newer and more expensive antihypertensives were no more effective than older diuretics used to treat hypertension (Chrysant, 2003). This shift in clinical framework opened the doors to clinically appropriate and cost-effective hypertension treatment for many patients.

Finally, in a PCT, investigators should consider the extent to which the primary trial outcome is relevant to participants and ensure to include all data. Appropriate outcome measurements are particularly important in pragmatic trials. For example, the Salford Lung Study aimed to evaluate the real-world effectiveness of a new once daily long-acting corticosteroid/long-acting beta agonist dry powdered inhaler for the treatment of asthma and chronic obstructive pulmonary disease (COPD) (Vestbo et al., 2016; Woodcock et al., 2015). Patients were randomized (but not masked) to the new investigative treatment or to the continuation of regular clinical care. Once randomized, patients enrolled in the study received routine care and were followed through their electronic medical record for 12 months. Throughout the study, physicians prescribed treatments as they would in regular practice, and the patients received medications from their own pharmacy. Safety monitoring was conducted throughout the trial through near real-time evaluation of the patients' electronic medical record. Whereas most studies in this field assess only restricted outcomes such as forced expiratory volume, the primary outcome in this study was the Asthma Control Test (ACT) score, which is a clinically relevant measure of overall asthma control. Practitioners could interpret this outcome and apply it to their practice more easily than less clinically relevant outcome measures.

Another important consideration of outcome measurement in PCTs is that long-term follow-up is often labor-intensive for investigators. One way to extend outcome measurement efficiently is for investigators to follow the patients' clinical experience through administrative claims or electronic medical record data. The Salford Lung Study is one PCT that utilized the electronic medical record for study follow-up. The study location was optimal in that patients enrolled were from one metropolitan area in the United Kingdom, and all medical records were linked, which allowed for extensive follow-up. In other fragmented health systems, this may result in methodologic challenges. In the United States, the Dialysis Clinical Outcomes Revisited pragmatic trial compared the effectiveness of sevelamer and calcium-based phosphate binders among patients who were receiving hemodialysis (St Peter et al., 2008). Using administrative claims data for these subjects allowed investigators to more accurately capture baseline comorbidities as well as outcomes, including hospitalization and death date and cause. These relevant outcome measures were particularly important markers of treatment effectiveness in this population. The US federal government has shown that linking clinical and administrative claims data is a priority by investing in a large Multi-Payer Claims Database (Conway and VanLare, 2010). Countries in Europe have also taken an active role in promoting PCTs for the purpose of extending follow-up in clinically relevant patient populations. New EU regulations expected to be implemented in 2019 provide specific guidance to lower some administrative barriers to conducting PCTs (European Parliament and Council, 2014).

Research in Practice

Many PCTs were first designed as quality improvement projects and later produced generalizable results. One such example involved a pragmatic cluster-randomized, crossover, controlled study comparing bathing with chlorhexidine cloths to bathing with non-antimicrobial cloths among critically ill patients (Noto et al., 2015). The authors obtained a waiver of informed consent as a quality improvement step, and patients were not blinded to the intervention due to the difference in appearance between cloths. They found

that the antimicrobial bathing did not improve any of the outcome measures of infection rates. Published results such as these are applicable to other institutions that may be performing this practice without an evidence basis.

Though pragmatic trials attempt to determine real-world effectiveness, there are limitations associated with this approach. The definition of "real-world" often depends on many factors, such as the practice environment. The UK primary care sites recruited from the Salford Lung Study may not be generalizable to populations in other parts of the world, highlighting the potential that the external validity of some PCTs may be a point of concern. An example of geographic differences impacting the results of pragmatic trials is evident in the European Carotid Surgery Trial, which investigated the effectiveness of endarterectomies for carotid stenosis (Masuhr et al., 1998). The differences in clinical practice sites both within and between European countries resulted in different measurements of the outcome, which affected the study's estimation of the treatment effectiveness.

Another potential shortcoming of PCTs is the difficulty of designing a study that meets standard research protocols and also allows patients to experience normal clinical care. An analysis of two simple pragmatic trials conducted in the United Kingdom demonstrates that the approval process for these studies took over three years and that less than 5% of originally interested clinical sites recruited patients for the studies (van Staa et al., 2014). This analysis also brought to light qualitative insights to PCT implementation, such as physician preference that patients with acute illnesses be excluded and that recruitment be as simple as a "flag" during patient consultation.

Furthermore, PCTs may not be able to identify small differences in treatment effectiveness because the populations are designed to be broad and diverse. The large sample sizes and long follow-up time required in PCTs also mean that many are long and labor-intensive. The ALLHAT trial discussed above took nearly 8 years to complete and cost an estimated $130 million (Goldberg et al., 2011).

Regulatory organizations have recognized the need for pragmatic trials as well as their limitations and have responded in suit. In the United States, PCORI has awarded over $350 million as of November 2017 for PCTs studying conditions including cancer, behavioral health, muscular/skeletal system disorders, respiratory, cardiovascular, and digestive system diseases, and many more (Patient-Centered Outcomes Research Institute, 2017). The European Union has also recognized the need to increase the efficiency of these trials, and with regulations set to be enforced in 2019 have defined a new type of clinical trial, the "low-intervention" clinical trial (European Parliament and Council, 2014). Many PCTs may be classified as "low-intervention" trials, thus have fewer administrative barriers.

Noninterventional Research

Whereas the use and design of PCTs are relatively new innovations in CER, most of the evidence generated thus far from CER is noninterventional (observational) in nature. In these studies, investigators do not assign treatment status, but rather observe behavior as it happens in the real-world. This can be done using data that already exist, such as administrative claims data or electronic health records, or investigators can design prospective observational studies that choose participants based on characteristics of interest. "Natural," or ecological experiments occur when treatments are distributed in a population for a reason unrelated to their health status or prognosis. This may occur as a result of formulary changes, or because of geographic differences in innovation or trends.

When a research question requires a large population or long follow-up, observational studies are particularly well-suited to provide evidence more feasibly than the time-consuming and expensive explanatory and pragmatic trials. CER using noninterventional study designs are particularly appropriate to investigate the extent to which RCT results apply to the real-world, extremely rare or poorly studied conditions, current treatment practices, or other situations in which RCTs have not or cannot be conducted. In addition, observational studies are able to capture all types of patients, whereas traditional explanatory interventional studies are generally restricted to healthier individuals. Despite these benefits, because observational CER is not randomized or controlled, there are many opportunities for confounding to influence any potential association that interests investigators, such as confounding by indication and self-selection. Furthermore, because data in most CER retrospective studies are collected for purposes other than answering an investigator's specific research question, investigators must deal with missing data on certain important characteristics.

In the field of CER, like in most EBM, decision makers tend to be more reluctant to implement changes based on information gained from noninterventional studies compared to RCTs. While it is true that observational studies have higher levels of bias and confounding due to nonrandomization, a carefully designed observational study can minimize these effects, and potentially approach the minimal levels of bias observed in RCTs (Danaei et al., 2013). In fact, multiple studies have shown that results from well-designed observational research do not differ systematically from experimental studies if the study question and population are aligned (Benson and Hartz, 2000; Concato et al., 2000; Lipsey and Wilson, 1993).

The ISPOR special joint task force has made seven recommendations regarding good procedural practices for observational studies (Berger et al., 2017). The first recommendation is that researchers are clear as to whether they are performing an exploratory or hypothesis-testing (HETE) study. If performing a HETE study, they should clearly state their a priori hypothesis and publish both a study protocol and analysis plan publicly. Once results are obtained, they should also present the extent to which they deviated from their original study protocol and the reasons for deviations, if any. They should provide enough information in publications for other researchers to replicate their findings, and they should also be able to replicate their own findings in a different data source and population. Finally, the authors should be objective when discussing the weaknesses of their study and be sure to include key stakeholders in design, conducting, and disseminating the results of HETE studies.

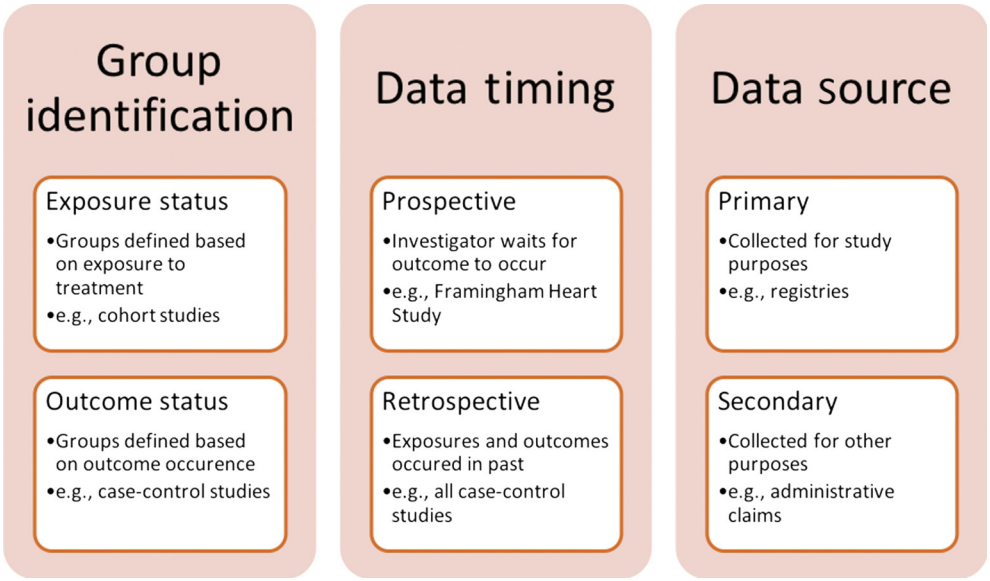

Figure 2 Components of observational CER

Designing Non-Interventional Studies in CER

When CER utilizes observational study designs to answer questions, investigators must consider three main components in order to appropriately design a study, as visualized in Fig. 2: group identification, data timing, and data source. In this section, we will discuss each of these in turn.

Group identification

Of the three main types of noninterventional study designs used in CER, each can be classified based on the characteristic used to identify comparison groups. Studies that define groups based on exposure status are known as cohort studies. In these studies, subjects are divided into groups based on whether or not they use the drug of interest. This is in contrast to identifying groups based on outcome status, as is done in case–control studies. Investigators originally assign subjects to groups based on whether or not they have experienced an outcome of interest, then analyze which subjects in each group were exposed to a particular treatment. Because cross-sectional studies assess both exposure and outcome at the same time, groups are identified based on both characteristics.

Data timing

Another factor that differentiates observational from interventional CER is the ability for researchers to conduct both prospective and retrospective studies. In prospective noninterventional CER, the investigator begins researching subjects before any outcomes of interest occur and follows subjects forward in time. One such example is a prospective cohort study investigating the effect of varenicline versus nicotine replacement therapy (NRT) on smoking abstinence rates (Kotz et al., 2014). Data were gathered from a survey administered to participants in England, and subjects were followed up after 6 months. Investigators found that subjects who used varenicline had greater success in smoking abstinence than those using NRT alone. Because data were collected prospectively, the time required to complete the study was longer than if the researchers had taken a retrospective approach. Other examples of prospectively collected data used in CER are the Framingham Heart Study and the Nurses' Health Study. Retrospective studies in CER are very common because of the advantages they offer over PCTs and prospective observational studies in the time required to conduct research. In retrospective cohort and case–control studies, exposure to treatment and occurrence of the outcome of interest have already occurred in subjects when the investigator begins the study. Looking back in time to establish exposure and outcome (basing groups on either exposure or outcome status in cohort and case–control studies respectively) expedites the study time and reduces costs. Cohort studies can be either prospective or retrospective; however, as case–control studies choose group status based on the occurrence of the outcome, they are necessarily retrospective.

Data source

In CER, observational study designs can rely on either primary or secondary data sources. Primary data arise when the investigator collects information about study participants in order to address a specific research question or hypothesis. Data collected from cross-sectional surveys or prospective cohort studies are considered primary data. These types of data are also generated for observational CER through the use of disease- or exposure-specific registries. In the United States, a large disease-based registry used in CER is the Surveillance, Epidemiology, and End Results (SEER) program (National Cancer Institute, 2018). Beginning in 1973, the SEER program has actively collected data on cancer cases for the purpose of conducting research to reduce the burden of cancer. These registries collect information on patient demographics, tumor site, various cancer markers, first course of treatment,

and patient survival. Because the National Cancer Institute maintains this data, its quality remains high. In addition to this vital information, SEER data can also be linked with administrative claims (a type of secondary data) to provide a more complete patient picture. One study used SEER linked to Medicare claims data to investigate the effectiveness of adding bevacizumab to standard chemotherapy in nonsquamous cell nonsmall cell lung cancer (NSCLC) in older adults (Zhu et al., 2012). A previous RCT had shown a slight survival advantage with this adjuvant therapy, and bevacizumab gained an FDA approval for this indication. However, NSCLC mainly occurs in older adults, and only a small portion of subjects in the RCT were 65 years or older. Investigators in this study were able to analyze outcomes for older patients and did not find a substantial survival advantage over the standard of care. Studies like these highlight the importance of CER in providing information on clinically relevant populations.

If investigators do not collect data for the purposes of their research, but instead use data that have been collected for other purposes, then the research uses secondary data. This type of data can be generated from routine record-keeping processes (such as administrative claims and electronic health records), regulatory processes, or even from repurposed trial data. This last type of secondary data demonstrates that even when data are originally collected for research purposes, an investigator can use it to answer a different question, making it secondary for their purposes. The Fracture Intervention Trial (FIT) was an RCT designed to investigate whether alendronate usage resulted in a lower fracture rate in older women with low bone density (Black et al., 1993). The trial completed subject recruitment in 1993, but later investigators were able to use that same data to answer a slightly different research question. Because alendronate is removed from the body through the kidneys, investigators were interested in determining whether its ability to reduce fracture rate and its potential to cause adverse reactions were augmented by poor renal function in a population of older women with low bone density (Jamal et al., 2007). It was found that alendronate did not perform differently in women with poor renal function, and such women did not experience more adverse effects. Such secondary analyses of existing data provide answers to important clinical questions that health care providers may encounter in their practices.

Research in Practice

While the use of RCTs and PCTs is often preferred in CER, there are certain circumstances in which observational study designs are particularly useful. If an RCT or PCT is impractical due to its potential expense, time required, or ethical considerations, an observational study can provide needed information. Such was the case when investigators were interested in the effectiveness of warfarin for stroke prevention in patients with atrial fibrillation. Large RCTs had shown an overwhelming benefit, but these trials included mainly younger people with few comorbidities. A systematic review comparing RCTs to actual clinical practice showed that patients in RCTs investigating warfarin safety were on average six years younger (range from 3 to 11) with 10% fewer comorbid conditions than the general clinical population (Evans and Kalra, 2001). To strengthen the evidence on using warfarin for this purpose, investigators used data from the Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study, which included administrative claims data on patients in the Kaiser Permanente health maintenance organization in northern California, United States (Go et al., 1999). Using an observational study, investigators were able to control for many different comorbidities and time-varying factors. Ultimately, they were able to confirm that in this population, warfarin users had a 51% lower risk of thromboembolism compared to nonusers (Go et al., 2003).

Another circumstance in which observational CER may be preferable to interventional trials is when the presence of an association does not have sufficient evidence to warrant a more cumbersome trial. These hypothesis-generating studies are often performed observationally initially. This is especially relevant for research questions pertaining to the way in which specific subpopulations respond to a given treatment. Even if some data exists suggesting that one of three particular treatments reduces hospital length of stay, for example, investigators might be interested in whether those trends hold for a particular minority or group of patients with a particular comorbidity. Although hypothesis-generating studies such as these often need to be followed-up with larger, potentially randomized, trials they nevertheless have their place in CER.

Furthermore, CER uses noninterventional study designs to evaluate prescribing practices in the real-world. One such example exists in treatment guidelines for chronic obstructive pulmonary disease (COPD), which recommend treating flare-ups with low doses of systemic corticosteroids (Global Initiative for Chronic Obstructive Lung Disease, 2017). However, evidence for low-dose treatment was derived from only a few, small RCTs and thus there was concern that physicians were actually prescribing higher dose corticosteroids, which carried much higher risks. Furthermore, there was no consensus about whether intravenous or oral therapy should be used initially. Because the question of whether patient outcomes are better when treated with low- versus high-dose corticosteroids required a very large population, researchers set out to investigate this question using a cohort study design (Lindenauer, 2010). Investigators found that among more than 80,000 patients with COPD exacerbations, low-dose oral corticosteroids worked just as well (and were safer) than high-dose intravenous corticosteroids, but that physicians were more likely to prescribe the latter. In order to achieve enough statistical power to show these results in an RCT, about 30,000 patients would need to be recruited. Policy makers can use information gained from such studies to inform prescribing practices and determine extent to which guidelines are being followed.

Though there are many instances in which this type of CER is warranted, a discussion of observational research design requires a basic understanding of the concepts of bias and confounding. Bias, also known as systematic error, occurs when differences among research subjects occur randomly and can be considered "noise." Both experimental and nonexperimental studies are prone to bias, which can be minimized using randomization to balance out differences between treatment groups. Evidence-based research organizations generally divide bias into four categories as seen in **Table 2**: selection bias, confounding by indication, performance and detection bias, and attrition bias (Higgins and Green, 2011; National Institute for Health and Clinical Excellence, 2012). Many

Table 2 Types of bias in observational studies

Type of bias	*Description*	*Best addressed by*
Selection	The effect of a treatment on an outcome is distorted by the way in which subjects are selected into the study	Rigorous inclusion criteria
Confounding by indication	The indication for a treatment changes based on patient risk/prognosis, thus impacting the outcome	Randomization, controlling for known confounders, matching
Performance or detection	Systematic differences between treatment groups other than the treatment	Blinding
Attrition	Systematic differences in how subjects are lost between treatment groups	Rigorous follow-up

interventional study designs address these biases through randomization, so investigators conducting CER using observational study designs should always identify, measure, and adjust for potential confounding factors in order to provide valid results.

Factors in observational research (such as self-selection instead of randomization) can confound the relationship between a given outcome and treatment of interest. Thus, many different methods are employed in noninterventional CER to address this concern, such as propensity scores, regressions, and instrumental variables. There is no universally accepted standardized method to address such confounding, so CER investigators must demonstrate a thorough understanding of the potential biases and explanation of their choice of adjustment. The lack of standardized guidance for confounder adjustment is a recognized problem in CER, and PCORI is currently in the finishing stages of a project to develop an "observational analysis methodology decision tree (OAMDT) for recommending optimal analysis method(s) for a given data set" (Landsittel, 2018).

Although specific recommendations for reducing confounding in observational CER do not yet exist, international standards have been set to encourage such study designing, including the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and a report from ISPOR (Berger et al., 2017; von Elm et al., 2007). Furthermore, investigators should follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines as closely as is feasible (Hernán, 2011). Though these guidelines are specifically for RCTs, emulating such designs in observational research reduces confounding. Designing noninterventional CER studies with an RCT in mind would involve correctly identifying "zero-time" for eligibility and baseline characteristics, clearly specifying inclusion and exclusion criteria, adjusting for confounding, and using appropriate statistical techniques (Hernán et al., 2016). One particular area in observational research that has been shown to be troubling is including prevalent users in studies. Whereas most well-designed RCTs always exclude subjects who are already on the treatment of interest (prevalent users)—which allows for the examination of the effect of initiating said treatment—some observational studies often include users who have been taking the drug of interest for some time. Failing to exclude prevalent users from observational studies can result in biased estimates as was shown in some observational studies that investigated the effect of hormone replacement therapy in postmenopausal women on coronary artery disease. Many provided estimates that were in conflict with RCTs examining the same question, but a recent study found that if researchers had excluded prevalent users in observational studies, they would have reached the same conclusions as the RCTs (Danaei et al., 2012).

Interest Groups

There are many stakeholders who might be interested in CER at various stages of its development and implementation. Researchers have divided the classes of interested people into what are known as the "7Ps," which are visualized in **Figure 3** (Concannon et al., 2012). A systematic review of stakeholder engagement between 2003 and 2012 found that engagement was highly variable, but more common in earlier stages of research, often before the research was underway (Concannon et al., 2014). Overall, patients were frequently engaged, followed by clinicians. Other decision makers, including policy makers, payers, and pharmaceutical manufacturers were engaged infrequently.

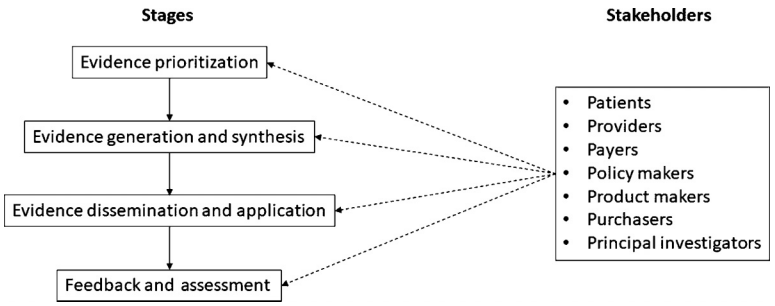

Figure 3 Comparative effectiveness research stages and stakeholders. Source: Concannon, T.W., Fuster, M., Saunders, T., Patel, K., Wong, J.B., Leslie, L.K., Lau, J. A. 2014. Systematic Review of Stakeholder Engagement in Comparative Effectiveness and Patient-Centered Outcomes Research. J. Gen. Intern. Med. 29, 1692–1701.

These "7Ps" in CER can perhaps be broken down into four broad groups: academic researchers, the public, regulatory agencies, and members of the pharmaceutical industry. Each has their own incentives and goals with CER.

Those who conduct most of the CER available today are academic researchers (or principal investigators in Fig. 3). Because they are responsible for most of the evidence generation and synthesis in CER, researchers play a critical role in engaging other stakeholders. As discussed earlier, a key facet of CER that sets it apart from other EBM is its focus on impacting decision-making on an individual and system-level. Whereas in most EBM, researchers can conduct their work with little understanding of the needs of end-users, those working in CER must ensure that research findings are aligned with the needs of those who will be making decisions. In order to do so, it is important that academic researchers involve stakeholders from all areas (the public, regulatory bodies, and the pharmaceutical industry) to properly prioritize, generate, and disseminate comparative effectiveness evidence (Deverka et al., 2012).

Because CER is so often discussed in relation to patient care, it follows that both patients and health-care providers are major stakeholders in the research. Providers have a vested interest in CER because this type of evidence often answers their specific clinical questions whereas placebo-controlled evidence is not often directly relevant. Ultimately, the health of patients is on the line, so their interest is also crucial. In fact, many organizations including the Cochrane Collaboration have raised the issue, and regulatory bodies have also taken note of this. The earliest government funding of CER in the United States occurred in 1972 with the Office of Technology Assessment. Since 1999, the National Health Service in the United Kingdom has had a clear policy directive to involve the public in research, as this involvement has been shown to increase in both relevance and quality of research (Department of Health, 1999). Of course, health-care providers include not only prescribers but also pharmacists. As one of the most accessible health care providers in the health system, pharmacists can play a critical role in encouraging patients to participate in CER and also in applying the results of CER to their own practice. Pharmacists can stand as proponents of CER regardless of their practice site, which will push forward the agenda of including more real-world evidence in health care. When both patients and providers can be active participants, the evidence generated will not only be relevant to their real-world experience, but researchers will be able to more efficiently conduct their research with such input.

As was the case in the United Kingdom, regulatory bodies must occasionally step in to encourage the public's involvement in research. This chapter has discussed the American federal government's interest in patient-centered outcomes research with the establishment of PCORI, as well as the UK's GetReal initiative. However, governments are not the only regulatory bodies involved and interested in CER. The European Medicines Agency (EMA) is a decentralized agency that operates similarly to the US FDA by assessing marketing applications for drugs in Europe, though it does not have all the regulatory authority. The EMA has taken an interest in CER and has developed infrastructure allowing them to monitor postmarketing safety signals and require postauthorization effectiveness studies of manufacturers (The European Commission, 2014). As regulatory bodies become more interested in CER studies, more specific guidance on their conduct is expected, as well as more oversight into postmarketing requirements.

Certainly, pharmaceutical product manufacturers and payers have an interest in CER. If regulatory bodies make drug approval conditional on CER evidence, payers will need to be assured that they will be reimbursed while more evidence is generated. This is especially important in countries such as France, where drug coinsurances vary by effectiveness, ranging from 0% for highly effective drugs to 100% based on therapeutic value (The Commonwealth Fund, 2013). Manufacturers may in fact have a disincentive to supporting CER since results may support their direct competitors. To highlight this concern, we can consider that prior to the funding increase for CER in the United States in 2009, industry lobbyists fought to ensure that three of the 15 members governing the newly created private–public research entity would be occupied by representatives from industry, and while this provision did make it into the Senate Finance Committee's bill, it did not make it into public law (Selker and Wood, 2009).

When all stakeholders work together, researchers will fully understand the questions the public needs answered, regulators will have the appropriate information they need to moderate drug approval, and industry members will be able to contribute to the available evidence base. To ensure this participation, researchers should tailor their work to stakeholders' information needs and be able to demonstrate how their work will impact each stakeholder in the real-world. Unfortunately, even when stakeholders are involved, not all CER is implemented immediately. For example, the results of a RCT demonstrated that initially performing percutaneous coronary interventions (PCIs) in patients with stable coronary artery disease (CAD) did not reduce risk of death or major cardiovascular events compared with optimal therapy using medications alone (Boden et al., 2007). Many thought that this study would result in a sharp decline in the use of PCIs for initial therapy in stable CAD, but this did not occur (Winstein, 2010). Some speculate that this is due to misaligned reimbursement incentives (facilities may receive higher reimbursements for performing surgical procedures), lack of trust in new information due to opaque research practices, or lack of physician engagement in new practices. In fact, one IOM study found that widespread adoption of an intervention takes on average 17 years (Institute of Medicine, 2001). As CER becomes more popularized and methods become more sophisticated, the goal is for uptake of new information to accelerate.

Conclusion

Comparative effectiveness research is a complex area that involves many types of research, including traditional EBM, patient-centered outcomes research, and cost-effectiveness analyses. Within the last two decades, the health care providers, regulatory agencies, industry, and ultimately the public have become invested in conducting of this type of research, and we have seen its use

expand accordingly. As CER continues to evolve in the coming years, everyone involved will see an increase in quality data applicable to real-world situations.

Glossary

Evidence-based medicine The practice of medicine wherein high-quality research is used to formulate guidelines and direct patient care

Explanatory trial A type of clinical trial that is conducted under ideal circumstances with strict inclusion criteria; generally used to determine efficacy, e.g., randomized-controlled trials

Pragmatic trial A type of clinical trial that is conducted under more realistic circumstances with more relaxed inclusion criteria; generally used to determine effectiveness

Real-world data/evidence In general, any data gained outside of a randomized-controlled trial that represents patient characteristics and circumstances found in clinical practice

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Economic Evaluation of Pharmaceuticals

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Introduction

Overview of Health Economics

Health economics is the branch of economics concerned with the cost, effectiveness, value, and consumption of health care, while *pharmacoeconomics* refers specifically to the health economics of pharmacotherapy. *Health technology assessment* (HTA) is a component of health economics and describes the systematic approach to evaluating the health effects and costs of health-care interventions and the specific determination of their efficiency. HTAs are undertaken as an exercise in scholarship and/or to inform decision-making in health-care practice and policy in the real-world.

HTA addresses the question of *technical efficiency*; that is, whether or not a specific intervention is delivered in the most efficient manner. By contrast, *allocative efficiency* considers the question of how to distribute health-care resources efficiently and takes into account multiple interventions and opportunity costs. This chapter will provide an overview of the economic evaluation of pharmacotherapies and describe the HTA processes used to assess drugs.

The Need for Economic Evaluations

Clinical trials (or meta-analyses of such trials) provide the highest level of evidence regarding the *efficacy* of drugs. The question regarding the efficacy of medicines is "Can drugs work?" The concept of efficacy is distinct from that of *effectiveness*, which refers to the more real-world evidence of the benefit of medicines, taking into account real-world usage (uptake, adverse drug events, compliance, and persistence) (Liew et al., 2002). The relevant question is "Do drugs work?" and measures of effectiveness are drawn from pharmacoepidemiological studies regarding real-world usage. The economic evaluation of medicines seeks to estimate

their *cost-effectiveness*. It extends real-world evidence one step further by addressing the question "Are drugs worth it?" Economic evaluations of medicines combine measures of efficacy and effectiveness with measures of costs. Hence, they are reliant on data from clinical trials, pharmacoepidemiological studies, and costing studies (Haynes, 1999).

There is often a large gap between efficacy and effectiveness because clinical trials are usually undertaken on highly circumscribed populations under tightly controlled study environments. Typically, they have narrow foci in terms of outcomes and are short in duration (up to 5 or so years). Furthermore, in clinical trials of pharmacotherapy, adherence to drug treatment is often greater than would be observed in practice.

There may also be a gap between effectiveness and cost-effectiveness. Highly effective interventions may be so costly that they are not cost-effective, or conversely, cheap interventions may not need to be highly effective in order to be cost-effective. In addition, the funding of health care varies considerably from country to country, and what may be a cost-effective intervention for one country may not be for another. Thresholds for cost-effectiveness are also variable, depending on a country's capacity to afford health care.

Yet, despite all the heterogeneity across different drug markets, a constant fact is that costs and cost-effectiveness are crucial determinants of the feasibility and affordability of pharmacotherapy.

Types of Economic Evaluations

This section describes the different approaches to economic evaluation of pharmacotherapy. There are a number of methods available, with the most common being *cost-effectiveness analysis* (CEA) (**Table 1**), *cost-utility analysis* (CUA) (**Table 2**), and *cost-benefit analysis* (CBA). These differ according to the outcomes being considered, but are common in that they all are tools of HTA; that is, they address the question of the technical efficiency of specific health-care interventions.

In each of CEA, CUA, and CBA, the economic evaluation of the health-care intervention under consideration (the *intervention*) is undertaken in comparison to a relevant reference (the *comparator*). Marginal differences in costs and outcomes between the intervention and the comparator are the outputs of interest.

Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) (Drummond, 2005) reports the net cost of a health-care intervention per unit of gain in health outcome of achieved by that health-care intervention. The health outcome is measured in an objective way, and the most common unit of measure is *life years gained* (LYG) (Brazier et al., In Press). However, it can be any clinical outcome, such as deaths prevented, cases successfully treated, symptom-free days, and percentage reductions in biomarkers (e.g., cholesterol level and blood pressure) (Ciani, In Press). The net cost of intervention is calculated by summing the cost of intervention and long-term care and subtracting from this downstream savings (cost offsets) achieved through avoidance of the health outcomes.

The net cost per unit gain in health outcome is the *incremental cost-effectiveness ratio* (ICER) (Drummond, 2005), which is the main output of interest in CEA.

$$\text{ICER} = \frac{\text{Cost}_i - \text{Cost}_c}{\text{Outcome}_i - \text{Outcome}_c}$$

Cost_i = cost of intervention

Cost_c = cost of comparator

Outcome_i = outcome associated with intervention

Outcome_c = outcome associated with comparator

An example of a CEA is provided in **Box 1**.

Box 1

A CEA (Ademi et al., 2016) was undertaken to determine the cost-effectiveness of eplerenone compared with usual care in patients with chronic heart failure and New York Heart Association Class II symptoms. The setting was the Australian healthcare system. It was estimated that over a 10-year time horizon, for each patient compared with usual care, eplerenone would lead to 0.25 LYG at a net cost of AUD $6980. This equated to an ICER of AUD $28,001 per LYG (Table 1).

Table 1 Cost-effectiveness analysis (Ademi et al., 2016) of eplerenone versus usual care

	Years of life lived	*Total costs (AUD)*	*ICER (cost/LYG)*
Usual care	6.07	$4869	
Eplerenone	6.32	$11,849	
Difference	0.25	$6980	$28,001

ICER, Incremental cost-effectiveness ratio; *LYG*, life-year gained.

Box 2

In the same study described in Box (Ademi et al., 2016), a CUA was also undertaken to estimate gains in terms of QALYs. It was estimated that over a 10-year time horizon, for each patient compared with usual care, eplerenone would lead to 0.19 QALYs gained at a net cost of AUD $6980. This equated to an ICER of AUD $37,452 per QALY gained (Table 2).

Table 2 Cost-utility analysis (Ademi et al., 2016) of eplerenone versus usual care

	QALYs lived	*Total costs (AUD)*	*ICER (cost/QALY)*
Usual care	4.39	$4869	
Eplerenone	4.58	$11,849	
Difference	0.19	$6980	$37,452

ICER, Incremental cost-effectiveness ratio; *QALY*, quality-adjusted life year.

Cost-Utility Analysis

A cost-utility analysis (CUA) follows the same principle as a CEA, but the health outcome is measured in terms of *quality adjusted life years* (QALYs), which are discussed in Section 4. Consequently, the ICER is presented in terms of net cost per QALY gained (or lost) (Drummond, 2005).

A distinct advantage of using QALYs as an outcome is that it takes into consideration both the quantity and quality of life in a single summary measure. This is especially useful if multiple health outcomes are relevant to the economic evaluation. For example, the benefits of low-dose aspirin are a reduction in risk of atherothrombotic cardiovascular disease, but its adverse effects include peptic ulceration and bleeding. An example of a CUA is provided in **Box 2**.

For both CEAs and CUAs, a *cost-effectiveness plane* can be used to graphically represent ICERs generated from the evaluation (Fig. 1), with the differences in costs plotted along the vertical axis and differences in health outcomes plotted on the horizontal axis.

Note that the cost-effectiveness plane allows for the fact that the intervention can lead to worse health outcomes (less effectiveness), compared to the comparator. For example, if prescribed to people at very low risk of atherothrombotic cardiovascular disease and very high risk of bleeding, the net effects of low-dose aspirin might be adversarial rather than beneficial (Ademi et al., 2013a). The plane also accounts for the fact that the intervention may lead to net cost savings because the cost offsets are greater than the costs of the intervention. For example, if prescribed to people at very high risk of atherothrombotic cardiovascular disease and very low risk of bleeding, the net effects of low-dose aspirin might be so beneficial such that downstream costs averted from avoidance of atherothrombotic cardiovascular disease would surpass those of aspirin treatment (Ademi et al., 2013a).

For most health-care interventions, net costs and net effects plot in the north-east (upper right) quadrant of the cost-effectiveness plane; that is, they incur net costs (more costly than the comparator) and lead to net health benefits (more effective than the comparator). The ICER associated with an intervention is indicated by a straight line drawn from the origin of the plane to where it

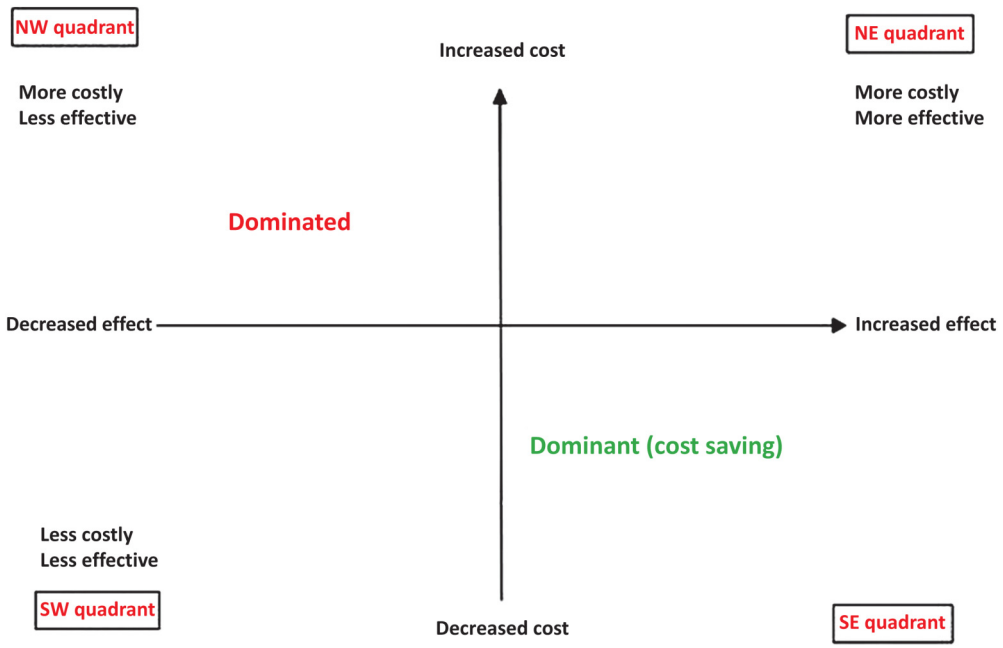

Figure 1 Cost-effectiveness plane utilized to represent ICERs in CEAs and CUAs. *NW*, north-west; *NE*, north-east; *SW*, south-west; *SE*, south-east.

plots in the north-east quadrant. The less steep this line is, implying more effects at lower costs, the lesser the ICER (the more cost-effective it is).

Plotting the net costs and net effects of multiple interventions on a cost-effectiveness plane allows for the comparison of their cost-effectiveness. It should be noted, however, that interventions should be compared only when the settings for the evaluations are equivalent; that is, same time horizon, same health-care system, and ideally, the same comparator.

If relative to the comparator, the intervention is more effective and less costly, then it is considered a *dominant* intervention (south-east quadrant). On the other hand, if the intervention is less effective and more costly, then it is considered a *dominated* intervention (north-west quadrant). For both dominant and dominated interventions, cost-effectiveness ratios are not calculated. This is because there is no need to measure the extent to which an intervention dominates its comparator, or is dominated by its comparator; in either situation, it is clear than one is better than the other.

Cost-Benefit Analysis

The principle of a cost-benefit analysis (CBA) is that all costs and treatment effects (benefits) are measured in equivalent units using only monetary values. That is, only net costs are explicitly expressed. Health outcomes are considered, but measured only in terms of their impact on costs. Costs may be those met by patients, the health-care system, or the general population (Ariyaratne et al., 2013).

The main advantage of CBAs is that they easily allow for budget planning. They can be used to compare treatment interventions that do not have comparable outcome measures and can help with resource allocation. Because only costs are explicitly measured in CBAs, ICERs are not derived.

The main limitation of CBAs is that it is often problematic to attach monetary values to health outcomes. As outlined by Drummond et al. (2005), attaching monetary value to health is commonly reflected by *willingness to pay* (WTP) using a human capital approach. A decision is made regarding how much an individual or society is willing to pay for better outcomes, or how much they are willing to save for poorer ones.

To illustrate a framework of a CBA (in terms of WTP), consider two treatment options (interventions A and B) for hyperkalemia among patients with chronic kidney disease. Intervention A is more effective in reducing serum potassium levels but is more expensive. The total costs over 1 year are $2000 and $1000 for interventions A and B, respectively. Assume that patients are willing to pay a mean cost of $1500 annually for the extra benefit. The net benefit of intervention A versus intervention B is thus $500 ($1500–$1000). The net benefit is thus reported aspositive; the preferred option is intervention A.

Other Types of Economic Evaluations

The principle underpinning a cost-minimization analysis (CMA) is that the interventions being considered have identical effectiveness, and thus the least costly intervention should be favored (Drummond, 2005). CMAs can incorporate the same outcomes measures as other main economic evaluations such as CEAs and CUAs. A common criticism of CMAs is that they are often undertaken on the basis of an observed lack (Briggs and O'Brien, 2001) of statistical significance in superiority studies interventions versus comparators. In clinical trials, lack of superiority does not necessarily imply equivalence or noninferiority between two treatments.

A cost-consequence analysis (CCA) is a form of economic evaluation in which outcomes are reported separately from costs, and there is no specific preference for one outcome measure over another (Drummond, 2005). CCAs typically report a range of outcomes and granular cost information. The intention of this approach is that the reader or decision maker can form their own opinion about the relevance and importance of various health interventions.

Costs

Perspectives

An important aspect of economic evaluations of pharmacotherapy is the *perspective* from which the results are considered; that is, the party paying for the costs. The main perspectives are those of the patient, the health-care system, a third-party payer, and the society as a whole. The perspective adopted determines the costs to be measured (Drummond, 2005), and as costs can vary considerably depending on perspective, the results of economic evaluations can vary across different perspectives. Most economic evaluations adopt either the *health system perspective* or the *societal perspective*, while the patient perspective is rarely adopted. The third-party perspective is mostly undertaken by third-party payers themselves, such as health insurance companies. For the purpose of this chapter, only the health system and societal perspectives will be discussed.

Measuring Costs

Economic evaluations can incorporate a range of costs, which can be grouped into two main types of costs: *direct* and *indirect* (Elliott and Payne, 2005). Direct costs can further be divided into direct medical and direct nonmedical costs.

Direct Medical Costs

Most economic evaluations of health interventions are limited to measurement of direct costs. Direct costs are related specifically to the relevant condition, are mostly borne by the health-care system, and are expressed as either fixed or variable (Drummond, 2005;

Elliott and Payne, 2005). Examples of variable costs include those of the treatments themselves and associated supplies and diagnostic tests, while examples of fixed costs include those of building capital, service infrastructure costs, and other overheads. The latter are largely constant as long as the intervention is being delivered by the same provider.

Direct Nonmedical Costs

Direct nonmedical costs are still directly relevant to the intervention, but not for the intervention itself. Examples include patient and family out-of-pocket expenditure on transportation and accommodation, and costs incurred within the health system for social and other support services.

Indirect Costs

Indirect costs are those consequent to reduced productivity from disease, among both patients and their caregivers. Loss of productivity occurs due to time off work (absenteeism), reduced productivity while at work (presenteeism), and early retirement. This reflects the *human capital approach*.

Indirect costs often make up a significant portion of the total cost of a disease or condition to society but are difficult to measure, and as such, are often not included in economic evaluations of pharmacotherapy. However, guidelines for economic evaluations of pharmacotherapy strongly recommend the inclusion of indirect costs (Drummond, 2005).

The magnitude of indirect costs is dependent on the disease. For example, diabetes and depression affect people of working age, and hence incur significant indirect costs, whereas dementia tends to be limited to older people post working age, and does not incur much productivity loss other than among caregivers. For all economic evaluations, it is also important to determine whose indirect costs are being measured (the patient or the caregiver), and how the activity was costed (i.e., disease episodes, at time of treatment, or after treatment).

Discounting

In economic evaluations, estimates of costs beyond 1 year into the future are usually *discounted* (Claxton et al., 2011; Krahn and Gafni, 1993; Severens and Milne, 2004), because the value of money in the future is less than at the present time (even after taking in considering inflation). This reflects human nature's preference for immediate gratification, and if not immediately, then as soon as possible.

Likewise, health benefits incurred in the future (e.g., years of life or QALYs lived) are also discounted. There are several formulae used for discounting, a common one of which is presented below.

$$\text{Discounted value} = \frac{x}{(1+r)^t}$$

x = undiscounted value of the cost or outcome of interest

r = annual discount rate

t = number of years beyond the first year

In general, the higher the discount rate (Claxton et al., 2011; Krahn and Gafni, 1993) applied to future costs and benefits, the lesser the favorable results of economic evaluations of pharmacotherapy. Hence, failure to appropriately discount future benefits and costs in economic evaluations leads to over-estimation of the cost-effectiveness of pharmacotherapy.

In Australia (Guidelines, 2016), an annual discount rate of 5.0% is usually applied to both future costs and benefits. The United Kingdom (National Institute for Health and Clinical Excellence, 2013), France (Haute Autorité de santé, 2012), Canada (Canadian Agency for Drugs, In Press), and Finland (Application Instructions, In Press) also apply the same annual discount rate for both cost and benefits, but the rates vary between 1.5% and 5.0%. Other countries use differential annual discount rates for costs and benefits. For example, the Netherlands (Guidelines for pharmacoeconomic, In Press) uses a discounting rate of 4.0% for costs and 1.5% for benefits (health outcomes).

Health Effects

The most common measures of the health effects of pharmacotherapy used in economic evaluations are clinical outcomes, *patient reported outcome measures*, LYG, and QALYs gained (or lost) (Brazier et al., In Press; Drummond, 2005).

Clinical Outcomes

Clinical outcomes are measurable changes in health as a result of pharmacotherapy. Important clinical outcomes are usually reported in clinical trials and include morbidity endpoints, such as Myocardial infarction or stroke, and mortality.

Other measures often reported in clinical trials are surrogate (intermediate) outcomes (Fleming and Powers, 2012). A surrogate outcome is defined as "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful outcome that

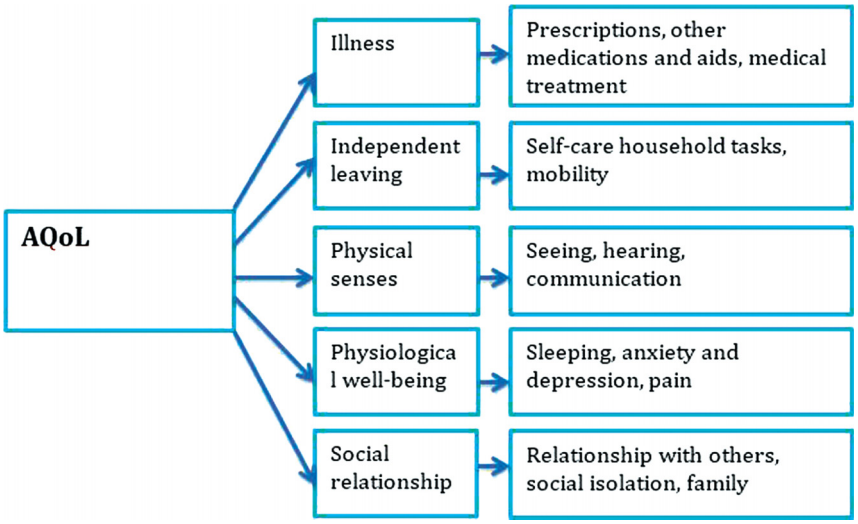

Figure 2 AQoL-assessment of quality of life.

measures directly how a patient feels, functions or survives" (Bucher et al., 1999). Examples include blood pressure as a surrogate for stroke or low-density lipoprotein cholesterol for myocardial infarction or ankle brachial index for peripheral arterial disease.

Patient-Reported Outcome Measures (PROMs)

Patient reported outcome measures (PROMs) are those directly reported by patients to provide a measure of benefit or harm from their own perspective. PROMs are collected using instruments (mostly self-completed questionnaires) that reflect health status, or the different aspects of physical, mental, and social well-being. An example is the assessment of quality of life (AQoL) tool (Hawthorne et al., 1999), illustrated in Fig. 2.

PROMs can be either generic or disease specific. The most commonly used generic PROMs for health-related quality assessment is the EuroQol five-dimension scale (EQ-5D) (Balestroni and Bertolotti, 2012). The five dimensions nominally considered pertain to mobility, pain/discomfort, usual activities, self-care, and anxiety/depression, and these can be measured on either three (EQ-5D-3L) or five (EQ-5D-5L) levels: "no problems," "slight problems," "moderate problems," "severe problems" and "extreme problems," For example, generic PROMs can be used in absolute terms, such as improvement in walking, or can be used to report overall changes perceived from previous pharmacotherapies. Generic PROMs allow for the assessment of a variety of conditions and interventions, whereas a disease-specific instrument better target the assessment of a particular disease, group of patients, or intervention. As such, generic and disease-specific instruments might give different results. Generic instruments are more relatable and useful to decision makers, which disease-specific instruments might be more useful to patients or physicians.

Life Years Gained and Quality-Adjusted Life Years Gained

LYG (or life years lost) and QALYs gained (or lost) are the most widely used measures of health effects in the economic evaluations of pharmacotherapy (Ademi et al., 2013b; Brazier et al., In Press). Both are summary measures, taking into account the potential for drug treatments to both save life or quality-adjusted life (through their beneficial effects), as well as to reduce these (through their adverse effects).

LYG conferred by health intervention is calculated by subtracting the expected years of life lived by patients assigned to the intervention by the expected years of life lived by patients assigned to the comparator. That is, it is the difference in expected years of life lived between the intervention and comparator patients or groups of patients. LYG is usually derived from modeling analyses, which are discussed in Section 6.

QALYs take into account impairment in quality of life as a consequence of disease and "penalise" time lived accordingly. To calculate QALYs, years lived are multiplied by *utilities* (Brazier et al., In press), which are weights used to reflect quality of life, and which range from 0 (zero quality of life) to 1.0 (full quality of life). For example, if the utility associated with moderately severe stroke is 0.70, then a person living 1 year with moderately severe stroke lives 0.70 QALYs. One QALY is the equivalent of 1 year of healthy life lived. The concept of a QALY is illustrated in Fig. 3.

The entire bar represents the total years lived by a person or a group of people. The solid part of the bar represents the years lived in full health (QALYs) and without impairment in quality of life. The hashed part of the bar represents years lived with disability and with impaired quality of life.

Cumulative QALYs lived over a period of time can be estimated by plotting utilities over time and measuring the area under the curve of the plotted line. Cumulative QALYs can then be compared for an intervention versus its comparator. To demonstrate, consider the hypothetical example illustrated in Fig. 4.

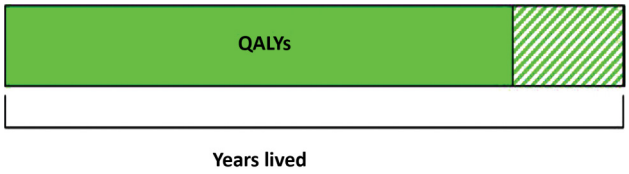

Figure 3 Example of QALYs versus years lived.

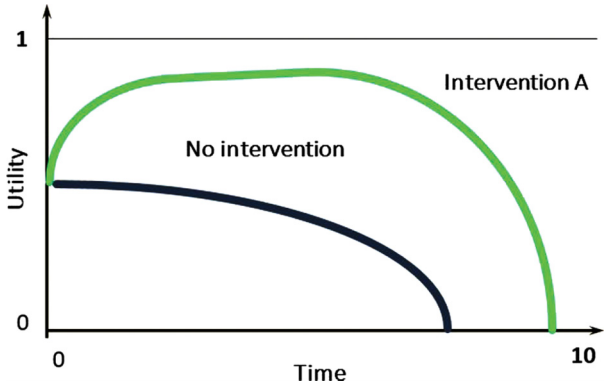

Figure 4 Cumulative quality adjusted life years over time.

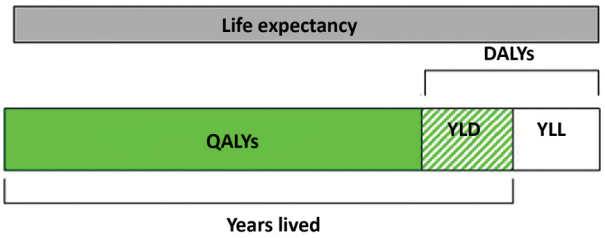

Figure 5 Example of disability adjusted life years versus years lived and quality adjusted life years.

The Figure plots utilities over time for patients after the onset of a disease at time = 0. The gray line represents a scenario without intervention. The utility starts at 0.5 and decreases gradually over time until death. The area under the curve is equivalent to approximately 3.0 QALYs. The green line represents a scenario with an intervention that both improves quality of life and extends it. The utility starts at 0.5, but increases for a little while until it reaches 0.8, then plateaus for a few years, before decreasing until death. The area under the curve is equivalent to approximately 6.0 QALYs.

Measures of the health effects of interventions can also be expressed in terms of *disability-adjusted life years* (DALYs) avoided. DALYs measure burden of disease and take into account both premature mortality due to disease, as well as years lived with disability. Premature mortality is estimated by subtracting the actual years lived by a person or a group of people by the life expectancy of that person or group of people. The concept of DALYs is illustrated in Fig. 5.

The gray bar represents the life expectancy of person or a group of people. The green bar represents the actual years lived by a person or a group of people. The solid part of the green bar represents the years lived in full health (QALYs). The hashed part of the green bar represents *years lived with disability* (YLD), and the white bar represents *years of life lost* (YLL) due to premature mortality from disease. DALYs are the sum of YLD and YLL.

In Fig. 5, the distinction between QALYs and DALYs is made clear. Both take into account the time lived with disability (and consequent reduced quality of life) due to disease. However, QALYs measure quality-adjusted time lived, while DALYs measure quality-adjusted time lost.

Economic Evaluations Alongside Clinical Trials

This section reports on a number of issues that are specifically related to conducting economic evaluations alongside clinical trials. *Trial-based economic evaluations* are designed where possible to estimate the effectiveness of interventions (instead of efficacy) and collect information on health service use and related costs (Ramsey et al., 2015).

Table 3 Analysis plan considerations for trial-based economic evaluations

Type of trial design
Hypothesis and objectives
Population of interest
Intervention
Appropriate comparator
Outcomes
Quality of life
Follow-up time
Appropriate power/sample calculations
Medical services use
Statistical analysis
Type of analysis
Subgroup analysis
Data collection elements
Presentation of results

This section will deal with issues specific to trial-based economic evaluations of pharmacotherapy: (1) the analysis plan before conducting trial-based economic evaluations; (2) analysis of cost data; and (3) the display of results and uncertainty considerations.

Analysis Plan

An analysis plan describes different data elements and steps that need to be taken before the commencement of trial-based economic evaluations (Glick et al., 2014). **Table 3** lists the key aspects that should be taken into consideration.

A study should define clearly the trial design (e.g., parallel group or crossover study) and its intent, (e.g., superiority or noninferiority) (Brown and Lilford, 2006). The analysis plan should provide a clear set of objectives and hypotheses, incorporate information on the population, intervention, comparator of interest, and define clearly the primary and secondary endpoints. The latter will of course include costs.

As described by Hlatky et al. (2006), the measurement of economic endpoints incorporates two components, namely, the quantity of medical services utilised (collected in the trial) and the unit cost (prices) of these services. The formula to calculate the total costs per patient in clinical trials is as follows:

$$C_a = \sum Q_{ar} P_r$$

C_a = cost per patient

Q_{ar} = quantity of resources r used for patient a

P_r = the unit costs for resource r

Health care resources collected in trial-based evaluations include those of treatments, hospitalizations, personnel, and rehabilitation and home-care services. However, unit costs of these resources are usually collected retrospectively and outside of the clinical trial, as specific unit costs from a single hospital are not regarded as the best source of information (Hlatky et al., 2006) when results are to be represented on a national level. To represent costs nationally, unit costs are usually drawn from national fee schedules.

As highlighted in Section 4, the measurement of health-related quality of life is also important for the assessment of pharmacotherapies in a trial-based economic evaluation. The analysis plan should include the necessary available algorithms required to calculate utilities.

The time horizon for a trial-based evaluation is obviously limited to the duration of the trial, while the appropriate time horizon may well exceed this. For example, the benefits of pharmacotherapy may continue to accrue long after the time duration of a trial, which as mentioned previously, may be short. Regardless, the analysis plan should specify the time horizon as well as the time points at which health effects and costs are measured.

Sample size estimations in clinical trials are usually based on the minimum number of study participants in both groups. However, the number of study participants required for economic assessments of pharmacotherapy can vary from what is needed for the clinical evaluation. That said, in order to minimize potential bias and to be transparent, it is preferable to avoid having clinical trial and economic evaluation sample sizes that are markedly different.

It is also important to capture all relevant health-care utilization during follow-up, particularly those that are expected to differ significantly between the intervention and comparator groups. If only a fraction of health-care utilization is measured, the economic outcomes between groups may be significantly underestimated (Glick et al., 2014). Conversely, collecting a large amount of unnecessary data would pose a practical burden to running the clinical trial. As such, trial-based economic evaluations often focus on estimating only direct medical costs and enroll only a subset of subjects in the clinical trial.

An analysis plan should also highlight the statistical methods utilized to deal with cost data, as well as the type of analysis and subgroup analysis (i.e., where the pharmacotherapy benefit might be more evident in one subgroup of participants) conducted. Furthermore, data collection elements from primary and secondary sources should be described in detail. Some data elements can only be collected prospectively (Glick et al., 2014) through case report forms, electronic medical records, or by providing booklets to patients that serve as a memory aid in follow-up or telephone interviews. Other data elements, such as unit costs and those highlighted above, can be collected retrospectively. Finally, the analysis plan should report on how results will be measured and displayed, in terms of cost per LYG and/or cost per QALY gained.

Analysis of Cost Data

When performing an economic evaluation, it is crucial to test whether there are statistical differences in costs between pharmacotherapies. The first step is to understand and identify the nature and distribution of cost data. Cost data are typically positively skewed, with a relatively low number of patients with high costs and an absence of negative costs (Elliott and Payne, 2005; Glick et al., 2014).

When dealing with skewed data, as per Drummond et al. (2005), the recommendation is to provide a summary of standard descriptive statistics, with histograms to visually represent the distributions of costs in terms of mean, median, and percentiles.

Nowadays, the most common statistical method used to test for differences between treatments in trial-based economic evaluations is based on nonparametric bootstrapping (Glick et al., 2014). Bootstrapping is a statistical technique that was developed by Efron (Efron and Tibshirani, 1994) and is based on resampling, which examines how the value of a statistic (costs) would vary if it was resampled multiple times. To manage this, the resampling of observable data is conducted using computer software such as Stata: data analysis and statistical software, R (programming language), or statistical analysis software (SAS). For example, with a set of observed cost data for 200 people in two treatment groups (A and B), one would repeatedly sample from the observed data. The point estimates of means and differences in means (the point estimates in this case refer to cost) for the 200 people are directly derived from the data set, while the empirical distribution of the difference in means, standard errors, confidence intervals, and *p*-values (Efron and Tibshirani, 1994; Glick et al., 2014) are all derived from the bootstrapping (resampling) of the same data set.

To measure the variability, a sample of size N_a is repeatedly and randomly drawn "with replacement," where N_a is equal to the number of study participants in treatment group A (i.e., $n = 100$). The same process is performed for treatment group B ($n = 100$). In this instance, "replacement" means that when an individual item is drawn it is not removed from the subsequent possible sample pool, such that it can be selected more than once in the same sample. The repetition of this many times over for both treatment group A and B provides with a series of resamples (i.e., bootstraps), where each resample differs from one another.

If resampling was performed without replacement (i.e., no item can be randomly picked twice in the same sample), the resamples (bootstraps) would simply replicate the analysis of the original trial data. As per Efron et al. (Efron and Tibshirani, 1994), it is recommended that to receive a robust result, 1000 resamples should be utilized to estimate bootstrap confidence intervals.

In trial-based economic evaluations, it is preferred to conduct not only a univariate analysis but also a multivariable analysis, as a multivariable model can adjust for the significant number of factors involved, such as subgroups, severity of diseases, and countries. There are a number of multivariable models available, and which to utilize depends upon the sample size and distribution of cost data.

The most common models performed are generalized linear models, using a logarithmic link function with a gamma distribution of errors (Ademi et al., 2010; Glick et al., 2014). Regression models are also common, and such models may be favored over others due to their ease of interpretation (Mihaylova et al., 2011), as the coefficient difference between two treatment groups provides a direct estimate of arithmetic mean of cost. Other models such as zero-inflated negative binomial models are used when there is a presence of a substantial proportion of null values (e.g., hospitalization costs).

Display of Results and Consideration of Uncertainty

As discussed in Section 2, the key output of interest in economic evaluations is the ICER. The differences in effects and costs between a pharmacotherapy and its comparator can also be depicted on the cost-effectiveness plane (as shown in **Fig. 1**). Analyses for trial-based economic evaluations should be performed using an intention-to-treat approach. If the analyses adopt a time horizon of more than one year, costs and effects should be discounted based on rates typically used for the drug market of interest.

As will be discussed more broadly in the next section, it is important to represent the uncertainty of results derived from trial-based economic evaluations. Estimates of costs and health effects are associated with uncertainty, and as a consequence, these need to be expressed.

Lastly, trial-based economic evaluations (as well as modeled economic evaluations) should adhere to established standards for reporting results of health economics of pharmacotherapy, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, in order to allow for scrutiny of their findings (Husereau et al., 2013).

Economic Evaluations Using Modeling

Section 5 discussed the collection of data regarding health effects and costs required for trial-based economic evaluations. However, the duration of clinical trials is often shorter than the time period over which pharmacotherapy is delivered in practice and almost

always so for chronic diseases. Therefore, the costs and effects of pharmacotherapy often need to be extrapolated beyond the duration for which information is directly available from clinical trials. In these situations, economic evaluations have to be based on modeling.

This section will cover common methods used in *modeled economic evaluations* of pharmacotherapy: *decision analysis*, *Markov modeling,* and *Monte Carlo simulation* to capture uncertainty. There are other approaches to modeled economic evaluations (such as discrete event simulation and neural networks), but these are far less popular, and will not be covered here.

Decision Analysis

Decision analysis (Lilford et al., 1998) is a method commonly used to quantify the downstream consequences of health-care choices, including pharmacotherapy, in order to inform decision-making. In economic evaluations, the consequences of interest are health effects and costs, as discussed in previous sections.

Decision analysis is usually conceptualized as a *decision tree*, which outlines and quantifies the consequences of the two or more options of a decision to be made. Fig. 6 provides a simple, hypothetical example of a decision about whether or not to start drug therapy. Therapy is associated with both potential benefit (decrease in the risk of "disease A") and harm (increase in the risk of "disease B").

The square is the *decision node*, the point where options are defined. In this example, the two choices are "No drug therapy" and "Drug therapy." The circles represent *chance nodes*, from which emanate the possible consequences of each choice. These are called *transition states*. Both options in the example have the same four possible transition states: "Remain in good health," "Develop 'disease A' (but stay alive)," "Develop 'disease B' (but stay alive)," and "Die" (from any cause). The underlying likelihoods of their occurring are indicated below the relevant subbranches and are called *transition probabilities*. The sum of all transition probabilities emanating from a chance node is always one, meaning the transition states are exhaustive (capture all possible consequences) and mutually exclusive (no overlap).

In the example, compared to no drug therapy, drug therapy is associated with a lesser likelihood of developing nonfatal "disease A" (16% vs. 20%) and of dying (9% vs. 10%), but a greater likelihood of developing nonfatal "disease B" (22% vs. 20%). These figures might be based on the findings of a clinical trial of the drug, which showed that compared to placebo, the drug reduced the relative likelihood of "disease A" and death by 20% and 10%, respectively, and increased the relative likelihood of "disease B" and death by 10%. Based on changes to the transition probabilities of "disease A," "disease B," and death, the net change to the transition probability for the transition state "Remain in good health" is increased from 50% to 53%.

The triangles are *terminal nodes*, where the health impact of each consequence, called a *payoff*, is quantified. In economic evaluations, payoffs are direct measures of health effects and costs, which have been discussed in previous chapters. Assume that in the example illustrated in Fig. 6 that the utilities associated with "good health," "disease A," "disease B," and "death" are 1.0, 0.8,

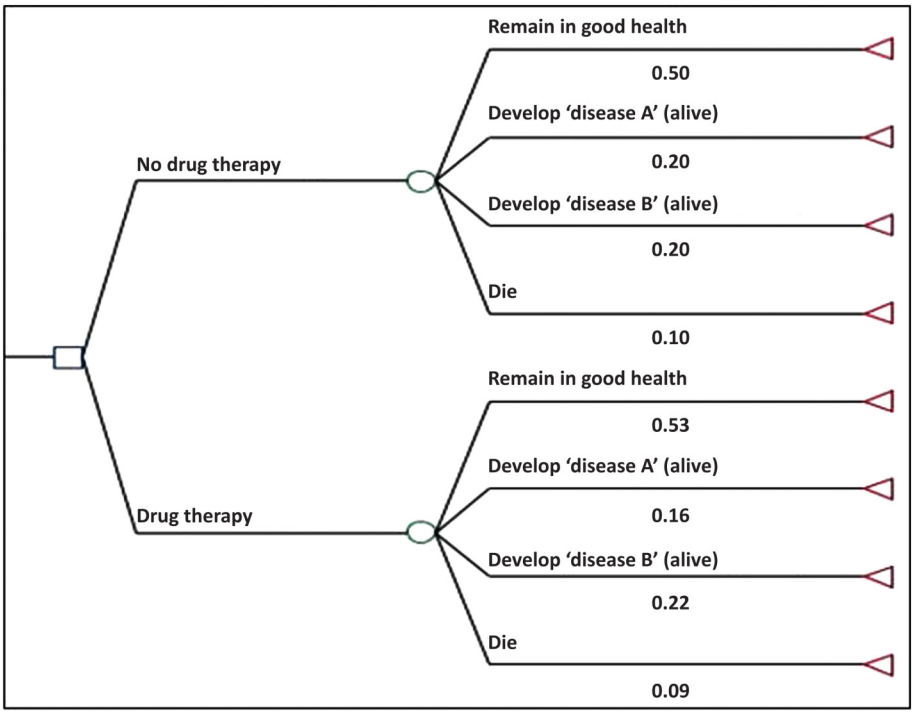

Figure 6 Hypothetical example of a decision tree.

0.6, and 0, respectively. To analyze (evaluate) a decision tree, the "expected value" of each branch is calculated by multiplying the payoff associated with each transition by the probability of it occurring, and then summing these. That is, the expected value of each branch ("No drug therapy" and "Drug therapy") is: Σ (payoff"*transition probability"). In effect, the expected value is a weighted-average payoff associated with the option. In the example, the expected value of "No drug therapy" is 0.78 utility (0.50*1.0 + 0.20*0.8 + 0.20*0.60 + 0.10*0), and the expected value of "Drug therapy" is 0.79 utility (0.53*1.0 + 0.16*0.80 + 0.22*0.60 + 0.09*0). Therefore, on average, drug therapy would provide a (slightly) more favorable health return compared to no drug therapy. Despite that it increases the risk of the more severe "disease B," this is insufficient to offset its beneficial effects on the risk of nonfatal "disease A" and death.

In terms of costs, assume that the costs associated with "good health," "disease A," "disease B," and "death" are $0, $100, $500, and $200, respectively. Analysis of the tree would then lead to expected dollar values of "No drug therapy" and "Drug therapy" being $140 (0.50*$0 + 0.20*$100 + 0.20*$500 + 0.10*$200) and $144 (0.53*$0 + 0.16*$100 + 0.22*$500 + 0.09*$200), respectively. If the cost of drug therapy is assumed to be $300, then the net cost of drug therapy would be $300 + ($144–$140) = $304.

Overall, in the example, on average, if drug therapy was to be delivered, it would increase utility by 0.01 (from 0.78 to 0.79), but cost $304 dollars more.

By itself, decision analysis considers only one sequence of events within one time-frame. This is a limitation if the conditions being simulated have different sequential stages, and/or data inputs (such as transition probabilities or costs) evolve with time. To overcome this inherent limitation of basic decision analysis, Markov modeling (Briggs and Sculpher, 1998) is often employed.

Markov Modeling

Fig. 7 illustrates an extension of the situation depicted in Fig. 6, in which multiple sequential events over multiple, cyclical time periods is considered.

After a subject develops "disease A," that subject may later develop "disease B," and vice versa. Recovery from either diseases is not assumed to be possible (and hence there is no transition back to "healthy"). Any subject is also susceptible to death at any time. To capture all possible events, multiple "health states" need to be incorporated into the model, each with its own set of possible transitions. The exception is death, from which no transitions can be made. Death is considered an absorbing state.

Analysis of Markov decision trees does not involve just a single transition of subjects from left to right across the branches, but rather involves repeated recycling, over discrete time periods called *cycles*, between the terminal nodes (except in the case of absorbing states) and the encircled "M"s, which are called *Markov nodes*. Markov nodes represent the points to which individuals return at the end of each cycle, and are channelled to one of the health states to begin the next cycle, either one previously occupied or another, depending on the transition they just made.

The above process describes Markov modeling (Briggs and Sculpher, 1998), named after the Russian mathematician Andrei Markov (1856–1922).

The key features of a Markov model are as follows:

- That subjects reside in one of a finite set of mutually exclusive *health states*.
- That time is represented by discrete periods called *cycles*, and individuals move between health states via *transition states*, or remain in their current health states, at the end of each cycle.
- That movements are governed by *transition probabilities* that are specific to each health state and each cycle.

Evaluation of a decision tree analysis, which incorporates Markov modeling, is straight-forward: expected values are calculated at the end of each cycle and summed at the end of the simulation.

The main advantage of incorporating Markov modeling into a decision analysis is that is allows for the simulation of more complex consequences of an option, as is illustrated above. Not only can a greater number of possible events be simulated, but they can also be simulated for lengthier periods downstream.

For Markov models with long time horizons, it is important to account for the fact that many data inputs (such as transition probabilities, utilities, and costs) evolve over time. For example, as the age of model subjects increases with repeated cycles, their risks of diseases will increase. Hence, cycle-specific inputs are often needed for Markov models. For some inputs, cycle-specificity is easily estimated, such as age-related changes to risks of disease, but for others, it poses a challenge due to a lack of data, such as age-specificity of disease costs and utilities.

The main limitation of Markov models is that with any cycle, the possible transitions which individuals can make depend only on the state they are in, and not on how they arrived at that state. That is, Markov modeling "lacks memory." For example, in Fig. 7, the health state "Alive with disease A" makes no distinction as to how long subjects have had "disease A." In later cycles of the model, subjects occupying that health state will have only recently arrived, while others may have been there for many cycles. The problem may be overcome by including as many health states as is required to reflect important disease combinations. For example, separate health states could be included that distinguish "disease A" by the time since its onset ("Alive with 'disease A' occurring within the last year," "Alive with 'disease A' occurring within between 1 and 5 years ago," and so on). However, inclusion of too many health states into a Markov model can render it unwieldy. Paradoxically, a complex Markov model that attempts to more accurately reflect multiple related conditions may be subject to more uncertainty because of the need for more data inputs and assumptions to be made about them. A compromise is needed that optimally balances the need to reflect relevant outcomes and reduces uncertainty.

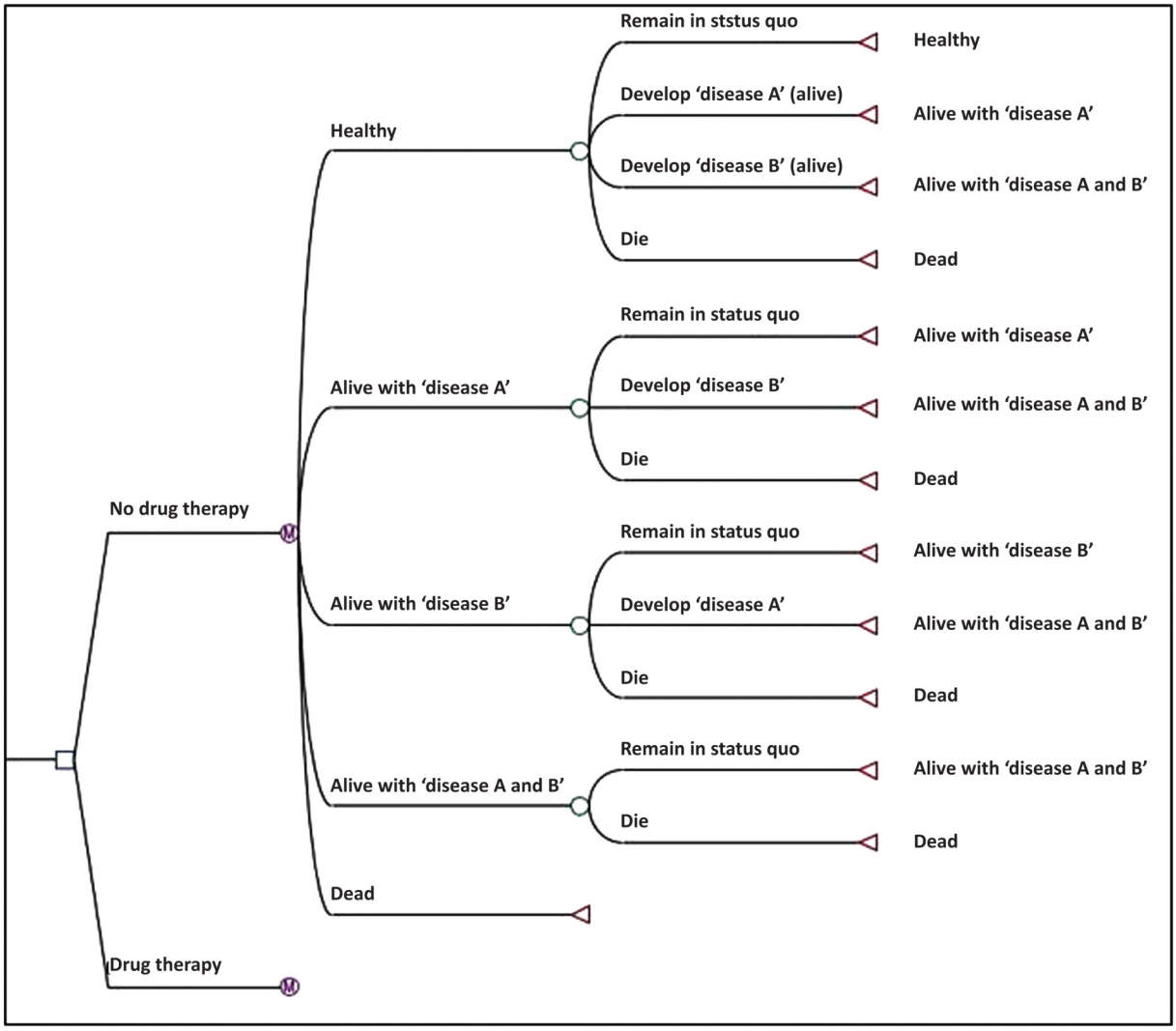

Figure 7 Hypothetical example of a Markov decision tree.

Monte Carlo Simulation

Because modeling is based on conjecture, it is important that uncertainty be expressed in the modeling outputs. Models are vulnerable to uncertainty because they rely on multiple data inputs, and as the number of inputs and modeling steps increase, so too will uncertainty in outputs. In addition, assumptions have to be made in many instances, which serve to increase uncertainty even further.

Monte Carlo simulation (Briggs, 2000) refers to a method of undertaking multiple simulations of a model, each time taking samples from specified uncertainty ranges of the model's inputs (as opposed to point estimates). These uncertainty ranges are most often expressed as probability distributions. Probability distributions describe the range of possible values for a parameter as well as the probability of each value occurring. Common types of probability distributions include "gamma," "uniform," "normal," and "triangular," as illustrated in Fig. 8. Probability distributions that relate to data inputs for a model are often called *input distributions*.

As Monte Carlo simulation involves multiple simulations, it therefore generates multiple outputs, from which probability distributions can also be derived. These are often called *output distributions*. With only a small number of iterations in a Monte Carlo simulation, the output distribution is not well defined. However, as more iterations are run, the output distribution becomes definable and is said to become stable. This phenomenon is known as *convergence*. A sufficient number of iterations must be undertaken in Monte Carlo simulation such that convergence of an output distribution occurs.

Monte Carlo simulation modeling is also known as *stochastic* modeling. This defines a type of modeling in which there is a range of possible outputs that is dependent on the probabilistic nature of inputs. In contrast, models whose outputs are fixed because their inputs do not vary are known as *deterministic* models.

In Monte Carlo simulation, the results of each iteration can also be depicted graphically to demonstrate the range of the uncertainty, as illustrated in Fig. 9. The cluster of results in the north-east quadrant is drawn from multiple analyses. The spread

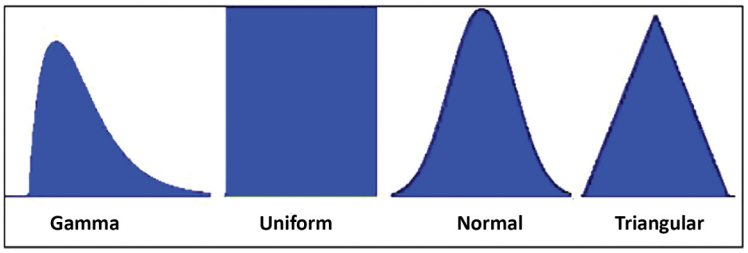

Figure 8 Common types of probability distributions used in uncertainty analyses.

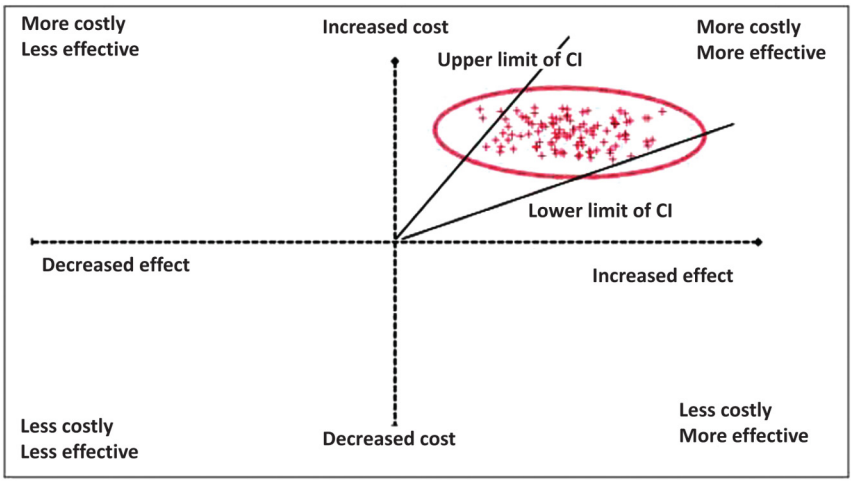

Figure 9 The results of Monte Carlo uncertainty analyses depicted on a cost-effectiveness plane.

of this cluster provides a reflection of the uncertainty in the analyses. In Fig. 9, reference lines representing the lower and upper limit of the range of ICERs are also shown.

Commonly Used Software Packages for Modeled Economic Evaluations

Microsoft Excel (Microsoft Corporation, Redmond, WA) is also widely used to undertake pharmacoeconomic analyses. Being entirely flexible, it can be programmed to simulate decision analysis and Markov modeling. Monte Carlo simulation is enabled in Excel via programming in Visual Basic, or with the use of add-on macros, such as @RISK (Palisade Corporation, Ithaca, NY).

TreeAge (TreeAge Software Inc., Williamstown, MA) is a commonly used software package designed specifically for decision analyses. It is a powerful program that also allows for construction of complex Markov models and incorporates uncertainty analyses via Monte Carlo simulation.

Utilization of Economic Evaluations by Decision Makers

Around the world, health policy decision makers and payers are compelled to ensure delivery of quality health care under ever-tighter budgetary constraints and increasing demand. This situation is fuelled by many factors, chief among which are ageing populations, expensive health technologies, and financial uncertainty. Especially among countries that provide universal health care for their populations, or are striving to it, the process of deciding which health technologies to invest in is a major challenge. Decision-making has to take into account the complex interplay among medical, social, economic, and ethical factors. The way in which health systems are organized is also obviously important. In many countries, such as Australia and Canada, funding for some aspects of health care is provided by the Federal government, but delivered by State or Provincial governments.

Table 4 lists the key countries around the world in which the costs of pharmacotherapies are largely subsidized, and the drug reimbursement authorities in each of these countries that undertake or commission formal HTAs to guide decision-making. Whether or not the findings of HTAs are mandated to be used in decision-making is also noted. The countries listed in Table 4 are among the first to have implemented subsidized pharmacotherapy for their populations (i.e., they are "mature" drug reimbursement markets) and hence are leaders in the science (and art) of pharmacoeconomic evaluations. These countries and their drug reimbursement authorities also have significant global or regional influence because of the size of the markets over which their deliberations have direct or indirect implications.

Table 4 Key countries with "mature" drug reimbursement markets and their major drug-related health technology assessment (HTA) authorities

Country	*Drug-related HTA authority*	*Legislative requirement regarding HTA and decision-making*
Australia	Pharmaceutical benefits Advisory Committee (PBAC)	Results of HTAs have to be considered
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	No formal requirement to consider results of HTAs.
Germany	Gemeinsamer Bundesausschuss (G-BA, Federal Joint Committee) and Institute for Quality and Efficiency in Health Care (IQWiG)	Results of HTAs have to be considered
Republic of Korea (South Korea)	National Evidence-Based healthcare Collaborating Agency (NECA)	Results of HTAs have to be considered
Republic of China (Taiwan)	National Health Insurance Administration (NHIA)	Results of HTAs have to be considered
United Kingdom	National Institute for Health and Care Excellence (NICE)	Results of HTAs have to be considered

HTA, Health technology assessment.

There is also cross-referencing among the major reimbursement authorities around the world. For example, decisions made by the UK National Institute for Health and Care Excellence (NICE) are often noted by the Australian Pharmaceutical Benefits Advisory Committee (PBAC), and vice versa.

Given concerns about growing health budgets, more and more countries are adopting HTA to assist with decision-making around pharmacotherapies, or are signaling that they will. For example, Japan introduced a HTA system for evaluating drugs in 2016 (despite that it has funded a universal health-care system since 1961), and there are strong indications that HTA will be used in the future listing, pricing, and reimbursement of drugs at a national level in China.

The Future

As discussed in Section 7, there is growing awareness of the need for HTA in decision-making around the world. This is a driving interest in pharmacoeconomics, both as a science and as a tool to inform health practice and policy. As discussed in Section 4, measures of health effects are also becoming broader, including to incorporate patient-relevant outcomes. Furthermore, new methods for data analysis and advances in data technology are changing the way economic evaluations of pharmacotherapies can be undertaken. In particular, three important, and inter-linked, ongoing developments warrant discussion: *clinical registries*, data technology, and *propensity score analysis* to estimate the efficacy of drugs.

Clinical registries (Wilcox and McNeil, 2016) represent an important method for monitoring the quality of health care. They are essentially longitudinal observational studies that systematically collect data in a uniform manner for populations identified by a specific exposure, disease, or drug. Measures of interest typically include clinical processes and practice, as well as key health outcomes such as death and disease complications. PROMs and costs are also increasingly being incorporated into clinical registries, as these outcomes inform not only the quality but also the "value," of health care. Of the various types of clinical registries, drug registries (Reid, 2015) are perhaps the easiest to mount, because identification of eligible subjects (patients who are prescribed the drug of interest) is relatively straightforward. However, the tracking of outcomes, other than the prescription of other drugs, is generally not easier than for other types of clinical registries (Ariyaratne et al., 2013).

One of the reasons behind the rising popularity of clinical registries is the increasing sophistication in techniques for data collection and analysis. Data linkage, which identifies individuals across different datasets, already offers a convenient way to capture outcomes, including costs, without having to measure these directly "in the field." For example, a drug claims dataset can be linked to a death registry to identify people who were dispensed certain medications and subsequently died, or linked to a hospitalization dataset to identify subsequent hospitalizations for particular conditions, as well as their associated costs. Hence, the downstream health effects of drugs can be estimated, as well as costs. Another advantage of data linkage is that it can be undertaken after outcomes have occurred, meaning that large and mature longitudinal cohorts can be assembled retrospectively. In future, artificial intelligence (machine learning) will also allow for easy analyses of unstructured text (such as free text entries in electronic prescriptions), as well as PROMs. The latter could even be sourced from data contained within "everyday" data sources, such as social media, as long as adequate ethical clearance is obtained. Lastly, ever-evolving improvements in data security, involving both hardware and software platforms, will further facilitate data capture and processing from a broad range of sources. "Big data" and the "internet of things" promise much, but the exchange and use of data need to be properly governed.

Given the increasing ease with which longitudinal observational studies (including drug registries) can be undertaken, it is also important that methods have also evolved to allow for the unbiased assessment of the efficacy of drugs in these studies. Propensity score matching (D'Agostino, 2007) represents a way to assemble two or more groups for comparison so that they appear like they had been randomized to a specific drug or its comparator. In short, the method involves logistic regression analyses to determine the likelihood (propensity) of each person within a cohort being on the drug, and then matching people who were on the drug to those who were not on the basis of propensity scores (Ademi et al., 2013c). Outcomes are then compared between the groups.

On a global scale, economic evaluations of pharmacotherapies is a relatively new field, but it is one which is growing rapidly, especially as more and more countries adopt HTAs to help with decision-making in funding health care, and as new methods an new data technology emerge.

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Methodological Considerations in Pharmacoepidemiology and Pharmacovigilance Studies

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Introduction

Much of the developments in pharmacoepidemiology are triggered by historical changes in legislation or misadventures related to pharmaceuticals. For example, the United States (US) Food and Drug Administration's (FDA) Food, Drug, and Cosmetic Act in 1938 on medication safety, and the Kefauver-Harris Amendments in 1962 of medication efficacy were introduced to ensure medications marketed in the United States are safe and efficacious (FDA 2012). The latter was prompted by the thalidomide crisis in 1961, where up to 100,000 children were born with congenital anomalies such as phocomelia (FDA 2012). This was also the prompt for the establishment of the World Health Organization's program for International Drug Monitoring in 1968. The thalidomide-related deformities were reported first by Australian obstetrician McBride (McBride, 1961). He reported observing a deformity incidence of 20% in babies of women taking thalidomide when the usual incidence was 1.5% without thalidomide exposure. (McBride, 1961).

Pharmacoepidemiology in based on general epidemiological methods. However, there are some specific differences when medications are assessed as exposure compared with for example environmental, social, and occupational exposures. One benefit in measuring medication exposure compared to other exposures is that it is quite easy to capture very specific exposure in terms of timing and amount depending on the data source used. Despite this, there is a debate among people in the pharmacoepidemiology field on exposure measurement definitions, however, this is natural. For example, results from observational studies are often compared to results from randomized controlled trials where everything happens in a controlled environment.

Being such a young discipline, pharmacoepidemiology has evolved rapidly and new methodologies are applied from other epidemiology disciplines, or new methodologies are developed. Examples of these novel methodologies are discussed in this chapter.

Definition of Medication Exposure

Various data sources for medication exposure have been utilized in pharmacoepidemiological research. Surveys and interviews are common data sources for drug utilization studies; however, automated or electronic databases are more frequently utilized in pharmacoepidemiological research. Most of these databases were primarily founded for administrative purposes, and therefore may lack some important information restricting their potential use.

Strengths and Limitations of Using Different Data Sources in Pharmacoepidemiological Studies

Survey and Interview-Based Data

Information on medication use can be acquired in various questionnaire-based methods, including surveys, interviews, and diaries of used medications. Questionnaires on medication use require a careful design due to complexity of medication use, including the nature of the disease medication is used for, the number of medications available for the same condition, the number of products of the same medication, and complexity of medication regimens which often include more than one concomitant medication for a specific condition. The main strength of surveys and interview-based data is that participants are asked to report their actual medication use (West, 1997). They can be also asked about the regularity of use, dosing, and dose times per day. For medication that are used "as needed," participants may be asked to describe how often they have used these medications. In surveys and interviews, also use of over-the-counter (OTC) medications, nutritional supplements, vitamins, and herbal medications can be assessed, whereas these are rarely included in electronic databases. The reasons for medication use, nonadherence, and other important factors, such as sociodemographic factors, physical functioning, quality of life, and health behavior, may also be assessed in surveys or interviews.

However, survey and interview data on medication exposure are restricted to a certain time point or time period and during this time period medicines use is queried. Questionnaires often ask current medication use, referring to medication use within previous week/month or during a previous episode of the disease (Gama et al., 2009). For this reason, these data sources report primarily cross-sectional medication use. Even in the case of repeated questionnaires, changes in medication use between interviews or surveys may not be documented. Misclassification of medication exposure based on interview data has been found prominent when measuring chronic medication use. For example, in a study on calcium channel blockers, 1.5% of baseline users who were interviewed did not actually use these medications, and 15.5% of baseline nonusers initiated calcium channel blocker during a median of 7.6 years of follow-up with pharmacy dispensing data (Beiderbeck et al., 2004).

One of the concerns in self-reported medication use is recall error. Participants may have problems recalling which medications they have used and underreporting increases if time period in which medication use is assessed is lengthy (West et al., 1995). Persons using medications regularly or for longer duration are more likely to recall the medication they use compared to persons who only have one dispensing. Recall problems are also related to being able to name the medication product, substance, or dose, whereas pictures, availability of medication containers, or a list of medications may enhance recall (Kimmel et al., 2003). Many factors may impact recall. Older age may reduce recall (West et al., 1995), whereas more frequent use of other medications may enhance it (Kimmel et al., 2003). Modes of data collection by questionnaires may impact the results (Bowling, 2005; Choi and Pak, 2005). These include the ways the respondents are contacted, how the questionnaire is delivered, and the way in which questions are phrased. Even minor changes in wording, the order of questions, or response format can lead to differences in the results. One study showed that three different measures resulted in different prevalence of analgesic use: "weekly analgesic use in general," "analgesic use for pain symptoms within the past week," and "giving the name of any analgesic used within the past week" (Ademi et al., 2007). In general, questions involving indication for medication, medication names, pictures, and other memory aids have resulted in higher prevalence of use (Gama et al., 2009).

The utilization of medicines has specific features related to the acute or chronic nature of the diseases and their severity, the number of drugs available for the same condition, the number of medicines including the same active ingredients, and the varying complexity of the treatment regimens, all requiring a careful design of the questionnaires to ensure unbiased evaluations.

The sample size in questionnaires, surveys, and especially interviews is restricted by resources and time allocated in the study. A small sample size reduces generalizability and statistical power of the study. Participation rate may also be low. Low participation rate reduces generalizability of the results as refusal or drop-out from the study may not be random, and may lead to selection bias. Differential participation due to background factors may be called as participation bias. For example, severely ill or persons with disabilities may be more likely to nonparticipation and drop-out (Haapea et al., 2007; Lissner et al., 2003). In addition, nonparticipation has been associated with older age, health behaviors such as smoking and alcohol consumption, and social factors as well as higher mortality. Reporting bias is related to intentional over- or underreporting of medication exposure. Participants may under- or overreport medication use for various reasons. Underreporting may be more likely to be linked with mental health-related medications where the participants may feel stigmatized (Knudsen et al., 2002).

Claims and Dispensing Databases

The main strength in dispensing databases is the identification of medication exposure for large numbers of people, representing a specific population or even a nation, and the ability to follow them up on time. Medication use in these databases is not susceptible to recall, participation, or reporting bias. However, there are challenges in transforming data on dispensing events into periods when medications have been used (See section, Definition of Exposure from Prescription and Dispensing Databases). There is always uncertainty whether, when, and how dispensed medications are actually used. Some dispensing databases include data on dose but most databases include dose only in free text format or lack information on dose altogether (Furu et al. 2010). In addition, dispensing databases lack information of medicines obtained without prescription, particularly OTC medications. OTC medication use may be important for specific research questions, for example, in studies on nonsteroidal anti-inflammatory drugs that are often purchased without prescription.

Databases of various insurance schemes are restricted to medications covered by the specific insurance. For example, some Nordic nationwide or regional databases include only reimbursed medications (Furu et al., 2010). Canadian provincial drug claims

databases are subjected to restrictive drug coverage policies, which refer drugs not reimbursed by the insurance program, or their use is limited by requiring, for example, special authorization (Gamble et al. 2012). Changes in regulations and reimbursement practices in time may impact the usability of these databases for specific research questions. Medication coverage of an insurance may also impact the prevalence of medication use or prescribing (Amadio et al., 2015). Sometimes participants have more than one insurance, or private insurance in addition to public insurance and, thus, databases may lack some of their dispensing due to selective use of insurance (Allin et al., 2013). Medications may also be self-paid and not recorded in the database. Furthermore, medications may also be obtained from other sources, such as a family member, through the Internet, or purchased abroad. Data on medications used in hospitals, aged care services, or prisons may be lacking as some databases are restricted to outpatient medication use. Longitudinal follow-up of people in a database may be complicated by people changing insurance schemes, due to changes in employment or employers changing health plans for employees (Schneeweiss and Avorn, 2005). Instability of the population and lack of continuous enrolment are disadvantages of some insurance-based dispensing databases. In addition, changes may be selective if sick people drop out from their insurance scheme due to loss of job.

Claims and dispensing databases usually lack data on important confounding factors related to lifestyle, such as alcohol consumption and smoking. A limitation may also be that these databases do not include data on hospital care or diagnoses, and thus data on comorbid conditions or diseases severity cannot be obtained. Depending on the country, it may be possible to link claims or dispensing data with hospital care database to obtain diagnoses and possible outcomes of drug use.

Medical Record Databases

Medical record databases collect data on prescriptions from physicians' electronic prescribing and medical record system (Hennessy, 2006). The strengths of medical record databases include detailed data on prescribed medications, often including prescribed doses. Such databases also contain other information relevant for patient care, for example, data on comorbidities, body mass index, alcohol use, and smoking. They may also include data on laboratory test results. As with insurance-based dispensing databases, medical record databases may include unstable patient population which hinders longitudinal follow-up. Such databases include only medications prescribed within these systems and lack prescriptions from other sources (i.e., other clinics or hospitals). For specific patient populations, who are frequently hospitalized, or for specific diseases, which are often treated in specialised settings, this may be an important limitation. In traditional medical records, data may not be in a readily usable format and may require extensive text mining to extract, for example, data on smoking. In addition, information on lifestyle factors may not be recorded for all patients and there is a need to decide how to deal with missing data.

Definition of Exposure from Prescription and Dispensing Databases

Medication exposure from electronic databases includes either prescribed or dispensed medications. Databases consisting of prescribed medications are often called medical record databases as data are derived from physicians' electronic prescription systems. However, terminology may be confusing. For example, Nordic nationwide registers are named as "Prescription" or "Prescribed Drug" registers but actually these databases are based on dispensings from pharmacies. Dispensing databases are based on medications dispensed from pharmacies. This means that they lack data on medications that have been prescribed but never dispensed. Databases based on prescribed medications include also prescriptions that may have never been dispensed from pharmacy (Hennessy, 2006). Some more recent electronic systems combined both prescribed and dispensed drugs.

Prescribed and dispensed data do not readily indicate when a person has been exposed to the medication. However, pharmacoepidemiological research is most often focused on timing and/or duration of exposure. Electronic databases consist of dates of events, when medication has been prescribed or dispensed. Appropriate method for valid definition of exposure depends on various factors, including the research question, study design, the length of follow-up, specific data included in the data source, and whether the assumed association between exposure and outcome is acute or long term.

Correctly defined exposure to medications is crucially important, as misclassification of exposure may lead to biased or spurious results. Cross-sectional measure of exposure is defined at one point in time and is assumed to remain constant during follow-up. For medications used on a "when needed" basis or for symptomatic treatment, baseline users use the medication only on those days when they experience symptoms and baseline nonusers may initiate medication use during follow-up. For example, a previous study showed that baseline benzodiazepine users were exposed to 44.6% of person-days during follow-up as compared to baseline nonusers to 3.7% of days (Ray et al., 2002). This misclassification increased with time. In this study, misclassification led to substantial underestimation of the association between benzodiazepine use and falls risk, compared with exposure status modeled time-dependently on a day-by-day basis (Ray et al., 2002). The changes in who is a "user" and who is a "nonuser" are shown to change in time also for medications meant for long-term regular use (Beiderbeck et al., 2004).

Various methods for deriving medication exposure periods (i.e., when medication use started and ended based on dates of prescriptions or dispensings) have been developed. Applicability of these methods depends on the content in the database. Duration of use may be determined with prescribed doses and prescribed or dispensed amounts of the medication, by dividing the amount with the prescribed dose resulting in the number of treatment days (Lau et al., 1997). Another possibility is the days' supply of medications recorded in each dispensing event in some databases. Recording and validity of the days' supply measure may be supported by a rigorous 30-day refill requirement stated by some insurance plans (Schneeweiss and Avorn, 2005).

If the prescribed dose is not recorded in a separate, readily usable format for research purposes, it may be derived from free text fields included in the prescriptions. This requires enhanced text-mining algorithms and careful consideration of validity of their

results (McTaggart et al., 2018; Shah and Martinez, 2006). However, prescribed doses may include a range of dose and/or frequency of use. In these cases, researcher must choose whether minimum, maximum, or median dose is considered as the "prescribed dose" (Karystianis et al., 2016). Prescribed doses may also include adjustment according to symptoms, for example, extra inhalations of respiratory medications during infections. In addition, not all prescriptions include dosing instructions and researchers must decide how to handle prescriptions such as "use as instructed" and "according to previous instructions." In some databases, a significant proportion (one out of three or four) of exact dosing instructions may be missing from prescriptions (Lum et al., 2017). Similar considerations may apply to measures of days' supply (Gross et al., 2008).

When prescribed doses, free text instructions, or days' supplied are not included in the database, basic methods for deriving medication exposure periods may be categorized into "fixed assumptions" of daily doses and "time window" methods. Time window methods refer to assumptions that a medication is prescribed or dispensed every, for example, 30, 90, or 180 days (Andrade et al., 2006). The dispensing regulations impact on the width of the time window as maximum allowance for medication supply varies between countries, usually from 1–3 months. Waiting time distribution may be described as a form of the time window method. The waiting time estimates how frequently users of a specific medication refill their prescriptions (Pottegård and Hallas, 2013; Stovring et al., 2016). Researchers may choose to use a time window based on the waiting time distribution. One example of this is the number of days when 80% of users have refilled their prescription.

Fixed assumptions of daily doses are frequently used in pharmacoepidemiological research. One of the most commonly used is the assumption that a medication is used as one Defined Daily Dose (DDD). WHO defines DDD as "the assumed average maintenance dose per day for a medication used for its main indication in adults" (WHO, 2018). Even the definition of DDD implies to several disadvantages of this assumption, as medications may be used for multiple indications (possibly with a different dose) and by other than adult users. Another commonly used method is the assumption of "one unit per day," the unit usually referring to tablets. For other formulations than tablets or capsules, such as injections, creams, and patches, this assumption may not be applicable (Tanskanen et al., 2014). These assumptions may be valid for specific medication classes but not for others, even within the same therapeutic area (Rikala et al., 2010). Statins are an example of a medication class that is often used as 1 tablet per day (but almost never as 1 DDD per day) (Romppainen et al., 2014).

All basic methods, especially fixed assumptions of the daily dose, are often accompanied with grace periods (Schneeweiss and Avorn, 2005). Calculated days' supply or duration of use based on a fixed assumption is extended with a grace period which allows some irregularity or nonadherence between refills, or lower than prescribed use. Grace period is needed because in clinical practice, patients may refill their prescription earlier (which results in overlap of two dispensed prescriptions) or later when a gap between two dispensed prescriptions is formed (Gardarsdottir et al., 2010). To balance these irregularities, a grace period (a prespecified gap length) is allowed between dispensing events. The grace period may be a fixed number of days added to the duration of each drug use period, or the calculated duration is multiplied by some fraction (such as 50%). Grace periods are applied to avoid misclassification of use and unrealistically short (1–2 days') breaks between the exposure periods. The length of grace periods may vary from 7 days to 180 days (Andrade et al., 2006; Gardarsdottir et al., 2010).

It is important to note that adding a fixed number of days to each dispensing event disregards the fact that medications may be dispensed in different package sizes, and adding a 30 days' grace period has larger impact when it is added to a 30 days' package than into a 90 days' package. If the grace period is too long, it increases the risk of misclassification of exposure as patients discontinuing use are categorized as users. In contrast, a too short grace period will result in false discontinuation and misclassifies users as nonusers. Gaps can be filled either prospectively (grace period is always added) or retrospectively (grace period is added only if there is a next purchase within the duration of use plus the allowed gap) (Nielsen et al., 2008). This basically means that researchers must decide whether a grace period is always or never added to the last purchase. It has been pointed out that retrospective filling of gaps may lead to biased results (Nielsen et al., 2008). The appropriate length of the grace period depends on the nature of treatment (short-term, intermittent, chronic or episodic), and it should be carefully considered as it will have impact on the results (Gardarsdottir et al., 2010).

Stockpiling of medications means a situation when a patient refills a prescription while there is medication left from the previous dispensing event. Some stockpiling usually happens in each dispensing activity as medications are often dispensed before the last dose has been consumed. Major stockpiling may be introduced due to reimbursement regulations, such as fulfilment of annual limit for medication costs (safety-net), although reimbursement systems usually try to limit stockpiling. Two basic ways to handle stockpiling are ignoring any overlaps or add the overlapped amount to the following dispensing (Mantel-Teeuwisse et al., 2001). Some researchers have also suggested that a part (e.g., 50%) of stockpiling can be assumed (i.e., that a patient uses half of tablets later that were left when the prescription was refilled) (Greevy et al., 2011). Another possibility is to calculate a cumulative stock (assuming that all tablets are used later) during the medication use period. In exposure periods lasting for years, this may not be feasible approach as it is unlikely that large amount of drugs stocked years before would actually be used later.

More recent methods aim to consider individual variation in medication use patterns, such as personal regularity of refilling prescriptions and stockpiling. The estimation of drug coverage (COV) method divides the number of dispensed units by the estimate of averaged dose for each person (Meid et al., 2016). The prescription drug purchases to drug use periods (PRE2DUP) method is based on mathematical modeling of daily doses for each person and each drug (Tanskanen et al., 2015). It takes into account regularity of dispensings, stockpiling of medications, and hospital care periods when medications dispensed from pharmacies are not used. Prescription drug purchases to drug use periods or PRE2DUP does not assume any fixed dose for medications but allows individual variation in dose within limits of normal medication use specific for each medication package.

Individually tailored medication use modeling results in higher accuracy in estimating medication use (Taipale et al., 2016; Tanskanen et al., 2017).

When reading or conducting pharmacoepidemiological studies one must keep in mind the possibility of exposure misclassification and assess whether it may lead to biased results. Especially when the method assumes certain medication use behavior, the researchers and readers of the scientific articles must critically assess whether the actual medication use patterns in the population deviate from the applied assumption. In addition, the coverage of the data sources should be critically evaluated as they may be restricted to a selected population or may not cover all medications. Medications used during hospital care are often not recorded in claims or dispensing databases, which may cause exposure misclassification due to immeasurable time bias (Palmaro et al., 2017; Suissa, 2008). If this unobservable exposure time is not accounted for in the analyses, it may bias the association between exposure and outcome.

Definition of Medication Adherence

The World Health Organization (WHO) has defined adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabate, 2003). When talking about medication adherence, it has been defined as "the extent to which patients take medications as prescribed by their health care providers" (Osterberg and Blaschke, 2005). Medication adherence has been proposed to consist of three components: initiation, implementation, and discontinuation (Vrijens et al., 2012).

Medication adherence can be studied directly or indirectly (Osterberg and Blaschke, 2005). Direct methods (e.g., blood tests, direct observation, or electronic monitoring of medication-taking) are expensive and impractical in large populations. Indirect methods (e.g., data on medication dispensings, participant interviews, pill counts) are more suitable for large adherence studies. Indeed, dispensing databases are often used to study medication adherence (Raebel et al., 2013).

To study primary adherence (i.e., are prescribed medications initiated), data are needed on both prescriptions and dispensings (Raebel et al., 2013). To measure secondary adherence (i.e., adherence to initiated medications) from databases, dates of dispensings and dispensed quantities of the studied medications need to be identified (Peterson et al., 2007). Based on these, it is possible to calculate different metrics to evaluate adherence. Examples of these measures are the medication possession ratio (MPR) and proportion of days covered (PDC). MPR is derived by dividing the number of days of medication supplied with the number of days in the considered interval. PDC is derived by dividing the number of days with medication available with the number of days in the considered interval. Persistence (i.e., time from initiation to discontinuation of medication) can be measured, for example, as days to discontinuation. It is preferable to differentiate between new and prevalent users as adherence estimates most likely differ between these groups (Andrade et al., 2006).

The lack of consistency in the used terminology constitutes a challenge in adherence studies (Raebel et al., 2013). There is also large variability in the applied measures of adherence. Adherence defined as 80% MRP/PDC is often used; however, the clinical meaningfulness of this categorization is not certain (Peterson et al., 2007; Raebel et al., 2013). Adherence studies based on dispensing databases have many limitations, including that the actual consumption of medications is uncertain (Andrade et al., 2006). In addition, information on dosages is not always available leading to the use of assumptions such as fixed dosing to calculate medication availability.

Approaches for Controlling Bias and Confounding in Pharmacoepidemiological Studies

Approaches in Study Design Phase

Restriction of the study population is one commonly used approach in pharmacoepidemiology to reduce both confounding and bias (Schneeweiss et al., 2007). For example, restricting the cohort to new users has several advantages over designs that follow prevalent users (Johnson et al., 2013; Ray, 2003; Schneeweiss, 2010). In the new-user cohort design, follow-up is started from the initiation of medication use and prevalent users are excluded by applying a washout period for previous medication use. Starting the follow-up from initiation of medication use enables studying both the incidence of early and late outcome events and assessing the hazard function over the duration of medication use. If prevalent users were included, the results could be biased as prevalent users often represent "survivors" that are able to tolerate the medication and potentially benefit from the medication use. Therefore, studies that follow prevalent users may ignore outcome events that occur soon after the treatment initiation and result in biased estimate of the risks associated especially with the short-term use of the medicine. In addition, the temporal ordering of events is more explicit in the new-user design and, thus, it enables measuring confounders before the initiation of medication use. This decreases the risk of adjusting for intermediate variables that medication use may already have altered and which may be a part of the causal pathway between the medication exposure and the outcome event.

To be classified as new users, individuals should not have used the medication in question during a washout period (Schneeweiss, 2010). A washout period refers to a predefined time period (e.g., 6 or 12 months) preceding the initiation of medication use that is required to be free from the medication use. The longer the washout period, the higher the certainty that new users are truly treatment naïve. However, longer washout periods reduce the study sample size as higher number of previous users are excluded from the study cohort. Varying the length of the washout period can lead to misclassification of new users and substantial differences in the estimated incidence of medication use as well as impact on the characteristics (e.g., age and sex

distribution) of the included medication users (Gardarsdottir et al., 2006; Riis et al., 2015). Thus, the length of the washout period should be decided by considering the medication and outcome being studied, and it has also been recommended that the effects of different washout periods should be tested in sensitivity analyses.

The new-user design mimics the design of randomized controlled trials (RCTs) (Schneeweiss, 2010). However, in observational studies, the initiation of the study medication is never randomized, and medication users typically differ from nonusers as there is always a reason for initiating the medication (Johnson et al., 2013; Schneeweiss et al., 2007). If the indication for the medication or other characteristics of the patient affect the treatment decision and the same factors affect the risk of outcome, confounding may bias the results. Confounding by indication is especially problematic when studying comparative effectiveness in observational studies because the indication is closely related to the desired effect (Schneeweiss et al., 2007). The comparison group in the new-user design can be nonusers or new users of other medications. Restricting the cohort to new drug users and carefully chosen active comparator may reduce confounding. However, selecting the optimal comparator group is often difficult and confounding by indication may still remain. This is because even medications from the same therapeutic group can have various indications and contraindications, and the factors affecting treatment choices are often unknown.

New-user design with an active comparator group can be used as one approach to reduce the effects of healthy user bias (Schneeweiss et al., 2007). An active comparator could be a drug group with similar indication or another preventive drug group with no known association with the outcome.

Individuals that are adherent to use of preventive drugs (e.g., statins) are often healthier than nonusers of these drugs (Brookhart et al., 2007; Dormuth et al., 2009). It has been reported that individuals who have better adherence to medicines are also more likely to seek preventive treatment, receive vaccinations, attend cancer screenings, follow a healthier lifestyle, and less likely to be frail. Therefore, all or part of the positive effects associated with drug use may not be due to the drug but instead caused by the health seeking behavior. For example, it has been demonstrated that more adherent statin users are less likely to have motor vehicle and work place accidents than less adherent users (Dormuth et al., 2009). These are unlikely related to statins' biological effects. Healthy user bias may cause artificial positive effect, strengthen true positive effect or, on the other hand, diminish negative effects of drugs. In a similar phenomenon, individuals who are frail may be more likely to stop the use of preventive drugs and physicians are also less likely to prescribe preventive drugs for frail individuals near end of life (Glynn et al., 2001). This selective underuse of drugs may also bias results so that drug use may seem to protect from negative outcomes and death.

When studying second-line treatment options, restricting analyses to naïve new users is often not feasible as most patients have switched from the first-line drug to another drug (Schneeweiss, 2010; Suissa et al., 2017). Therefore, it has been suggested that a prevalent new-user cohort design could be applied when comparing the effects of drugs that have newly entered the market with older medications (Suissa et al., 2017). In this modification of the new-user design, the comparator medication user is selected time-dependently so that the history of previous medication use (i.e., time since the first comparator prescription or the number of comparator prescriptions) is similar to the patients who switched to the newer medication. This design has its own limitations and researchers need to consider several methodological issues, such as how to distinguish a switch of a medication from start of a concomitant second medication.

One advantage of using an active comparator is a decreased risk of immortal time bias as follow-up can start from the same time point (i.e., first date of drug use) for both groups (Johnson et al., 2013; Schneeweiss, 2010). When new users are compared with nonusers, researchers need to consider more carefully how to avoid immortal time bias. Immortal time bias refers to a period of follow-up when individual cannot die or experience the outcome event due to the study design that was chosen (Lévesque et al., 2010; Suissa, 2007). For example, if follow-up starts from the diagnosis of a certain disease and exposure status is defined based on the first date of dispensation of the drug after the diagnosis, the time from the diagnosis until the first dispensing is considered immortal time. This is because to be classified as exposed one must survive (i.e., stay alive and without the outcome event) until the first dispensing of the drug. In this situation, immortal time bias may occur if the immortal time is counted as exposed time (misclassification) or if it is excluded (selection) (Lévesque et al., 2010; Suissa, 2007). If immortal time is not properly accounted for, medication users will have apparently better survival. The longer the immortal time, the larger the error. One option to avoid this bias is to conduct the analyses with time-dependent exposure, which is to classify the person-time to exposed and nonexposed time at each day of the follow-up.

Another approach to reduce immortal time bias is to use exposure-matched design where each user is matched (based on, e.g., age, sex, and disease duration) to nonusers and the date of initiation of medication use serves as the index date for the matched nonusers. Applying the new-user design and avoiding immortal time bias are easier in studies that utilize electronic databases as information source for medication exposure (Ray, 2003) than, in for example, cross-sectional interviews.

The new-user design may be conducted with the intention-to-treat (ITT) approach or as-treated or both if one wants to test whether these different approaches lead to different results (Schneeweiss, 2010). In the ITT approach, exposure status is defined at baseline, and all patients are followed for a fixed time period (e.g., 180 days), regardless of changes in drug use over time. In the as-treated approach, follow-up is censored if a patient discontinues medication use or switches to a different medication. The ITT approach may lead to misclassification of exposure time as users may discontinue drug use and nonusers may initiate medication use. The longer the follow-up, the higher the possibility of misclassification bias. On the other hand, the as-treated approach may lead to selection bias if, for example, switching or discontinuation of drug use is due to lack of efficacy or early signs of adverse effects that ultimately would lead to the outcome. In this situation, censoring the follow-up at discontinuation of use underestimates the risk of outcome associated with the drug exposure (i.e., informative censoring). Thus, both ITT and as-treated approaches have their own limitations, and these approaches can be used to complement one another.

A limitation of the new-user design is that it reduces sample size limiting the power of the study (Johnson et al., 2013; Ray, 2003; Schneeweiss, 2010). However, the new-user design has several advantages, and it has been argued that a more valid estimate is better than a more precise but biased estimate. Recently, there has been debate on whether the new-user design should be preferred by default or not in pharmacoepidemiological studies (Brookhart, 2015; Hernán, 2015; Vandenbroucke and Pearce, 2015).

Concerns have been raised that if there is a limited follow-up, this design may decrease the ability to observe outcomes during long-term use and give less information on the risks during cumulative or long-term use (Vandenbroucke and Pearce, 2015). Of course, when choosing or evaluating study designs, we need to consider, for example, what type of effect we are interested in (acute/transient/constant/cumulative) and whether the outcome is rare or has a long latency period. Biases can be avoided or diminished with rigorous selection and application of the most optimal study design and methods for the specific study question. However, the available data source may complicate and limit the choice of appropriate methods. Therefore, all researchers as well as readers must critically evaluate the direction and amount of bias in the results.

Approaches to Confounding Control in Analysis Phase

In addition to controlling confounding by study design, it can be reduced by various statistical approaches in analysis phase (Table 1).

Nowadays, it is common to use propensity score methods to reduce confounding instead of traditional multivariable regression models. Propensity score refers to estimated probability of initiating the drug conditional on patient's baseline characteristics (Glynn et al., 2006). The idea is that conditioning on the propensity scores will balance the distribution of baseline covariates between the drug users and nonusers/comparator drug users. Propensity score can be easily estimated with logistic regression, and it combines all the measured confounders into a single score. Therefore, one important advantage of using propensity score methods against traditional multivariable adjusting is the ability to control vast number of confounders effectively even though the outcome was rare. It is important to plot and compare the distribution of propensity scores for exposed and unexposed individuals (Schneeweiss and Avorn, 2005). The amount of non-overlap of curves for exposed and unexposed on the extreme ends of distribution indicate patients who have a very low probability of treatment (i.e., never treated) and patients who would be expected to always receive treatment. It is also important to check covariate distributions before and after propensity score matching or weighting, for example with standardized differences or other balance diagnostics (Austin, 2008).

Propensity score methods are often considered better in controlling confounding by indication compared with traditional multivariable adjusting (Glynn et al., 2006). However, propensity scores cannot control for unmeasured confounders, and therefore, their applicability and effectiveness at reducing confounding depend on how well important confounders have been identified and measured from the data. As described in Chapter 205 (Methodological challenges in epidemiological studies), the selection of confounding variables should be based on subject matter knowledge. This also applies to covariates included in the calculation of propensity score (Brookhart et al., 2006). True confounders as well as variables that are unrelated to the exposure but related to the outcome should be included in the propensity score model. However, variables that are unrelated to the outcome but related to the exposure increase variance of the effect estimate without decreasing bias.

Table 1 Approaches to control confounding in analyses

Approach	*Considerations*
Standardization	• for example, incidence rates may be standardized by age and sex • difficult to apply otherwise as there are often multiple confounders
Stratification	• the association between drug exposure and outcome can be analyzed separately in different categories of the confounder (e.g., separately among male and female), and these stratified results are then pooled • usefulness is limited as there are often multiple confounders • stratification can be used to investigate effect modification more closely (if an statistical interaction between the exposure and potential effect modifier has been found)
Adjusting in multivariable regression models	• the measured confounders are included into the statistical model • the assumptions of the statistical model must hold • the number of included confounders is limited as there should be enough events per included variable
Propensity score methods	• a measure of likelihood that an individual would have initiated drug use considering the baseline covariates • combines vast number of confounders in a single score • can be used in several ways including adjusting, matching, restriction, stratification or weighting
Disease risk scores	• a measure of likelihood that an individual will have an outcome (disease) by summarizing the predictive information of potential confounders • can be used as a summary confounder in a multivariable statistical model or in stratification

Pharmacovigilance

The WHO defines pharmacovigilance or drug safety as the "science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" (World Health Organization, 2018). Traditionally, pharmacovigilance means almost exclusively spontaneous adverse drug event reporting (ADER). However, recently the availability of near real-time access to large medication claims databases has provided opportunities for postmarketing surveillance with methodologies that can offer quick answers to medication safety questions (Lai et al., 2017).

Most countries maintain their own ADER system via national medicines regulatory authorities. Of these countries, more than 120 submit their ADERs to the Uppsala Monitoring Centre in Sweden as part of the WHO Programme for International Drug Monitoring. To date, over 16 million ADERs have been submitted which now form the "Vigibase" (World Health Organization, 2018).

ADERs is a common source for pharmacovigilance studies. However, utilizing this data requires some considerations on data quality. First, submitted reports may not be complete. If crucial information is missing, the causality assessment between the suspected medication and the adverse drug event (ADE) will be difficult. Tools have been developed to assess the potential causality. These tools include, for example, the Naranjo Algorithm (Naranjo et al., 1981) and the WHO-UMC system (The Uppsala Monitoring Centre, 2018).

Another challenge in analyzing ADERS is the lack of a denominator—the number of people who are at risk of the ADE is not known. New medications are more likely to lead to ADERs as it is mandatory for pharmaceutical companies to report ADEs occurred in clinical trials. Prescribers and pharmacists are also more likely to report unpredictable and largely unknown ADEs, which occur more likely in new medications than in older ones. This means that when comparing ADE rates across two medications or medication classes, the rates will be overrepresented in the newer medication. Another prompts for ADERs are new studies reporting on a possible ADE or any ADE attracting media interest. Overall, ADEs are underreported in any reporting system so the actual rates of the ADEs cannot be detected using ADERs. When conducting a pharmacovigilance study using ADERs, the issues around reporting need to be carefully considered.

There are guidance published on the best practices of summarizing ADERs and determining associations (e.g., European Network of Centres in Pharmacoepidemiology and Pharmacovigilance, 2018). These are important sources when conducting a study utilizing ADERs. FDA provides all their ADE data reported via their Adverse Event Reporting System on their website (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm082193.htm). These data can be utilized for research purposes with sufficient skills understanding these data and in data management and analysis.

Conclusion

Pharmacoepidemiological studies face methodological challenges; however, the discipline has grown rapidly during the past decades and is still evolving. With robust methodologies and good quality data, real-world evidence on harms and benefits of medications can be produced. This includes pharmacovigilance studies where evidence is created utilizing ADER reports.

Additional Reading

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 7). http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

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Application of Pharmacoepidemiology and Pharmacovigilance Studies

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Introduction

Pharmacoepidemiology is the study of use and effects of medicines in large populations, and pharmacovigilance assesses the safety of medications and adverse outcomes related to drug therapy (Strom, 2012). Pharmacoepidemiology has broad applications in research and practice including evaluating patterns and appropriateness of drug utilization, measuring nonadherence, promoting postmarketing surveillance, and has been critical in the evaluation of health interventions to improve drug use and outcomes.

In recent decades, automated datasets have provided a unique platform to follow large populations over a long period to answer key research questions quickly and cost-effectively. Randomized controlled trials (RCTs) often exclude the elderly, pregnant women and children and observational studies utilizing big data have the potential to complement findings from clinical studies by assessing treatment effectiveness in underrepresented groups often encountered in routine clinical practice.

Well-designed studies in pharmacoepidemiology are useful for signal detection and postmarketing surveillance. Disease surveillance and needs analysis can map trends in populations over time and identify prevalent or incident clinical population. Additionally, data from various sources such as hospitalization and medicine claims are useful for identifying health outcomes or estimate economic implications such as costs associated with duration of care provided. Differences in patterns of care in special populations, rare adverse outcomes, or impact of policy implementation can also be measured using pharmacoepidemiology or pharmacovigilance studies.

This chapter outlines the practical applications of pharmacoepidemiology and pharmacovigilance studies in clinical and pharmacy practice, which are related disciplines of the same field of research and focus on improving prescribing and understanding medication safety. In the next section, we focus on studies, such as drug utilization, assessment of medication adherence, and assessment of medication errors that have made a massive impact on improving clinical and pharmacy practice.

First, we describe the impact of drug utilization studies in clinical practice and health services research. The chapter further explains some standardized methods used to measure drug utilization and how to compare results across various health-care studies conducted globally. Drug utilization studies also enhance postmarketing surveillance for the safe and effective use of medicines by monitoring medication adherence and errors, such as prescription or dispensing errors. Second, we discuss the assessment of population-level prescribing by examples of preventive medicines use in specific population and addressing increasing health concerns such as polypharmacy and hyperpolypharmacy in the general population.

Third, we shift the focus to opportunities provided by pharmacoepidemiology studies to monitor the quality use of medicines, assessment of medication adherence, and identification of medication errors.

Finally, we discuss the policy implications of pharmacoepidemiology research how it informs clinical and pharmacy practice. We briefly further deliberate on the advantages of social media platforms to influence policies. The conclusion provides a brief glimpse of future opportunities for pharmacoepidemiology research likely to influence clinical pharmacy and practice.

Pharmacoepidemiology: Impact on Clinical Practice

Drug Utilization Research

In 1977, the World Health Organization defined drug utilization research as the marketing, distribution, prescription, and use of drugs in a society, with particular emphasis on the resulting medical, social, and economic consequences. Drug utilization studies are either descriptive or analytical. Descriptive drug utilization studies using routinely collected automated dispensing or pharmaceutical claims data describe patterns of drug use, estimate under- or overutilization and regulate medicine use.

Drug utilization studies can inform clinical and pharmacy practice by identifying prescribing practices, assessing factors influencing prescribing practices, examining incidence of adverse drug reactions, examining nonadherence to treatment regimens, and cost-effectiveness of drugs. The information derived from drug utilization studies can also inform drug formularies and guidelines.

Monitoring medication use against standard treatment guidelines and evidence-based recommendations provide insight into the evolving prescribing trends. A population-level study (N = 56,026) conducted in the Netherlands found that a significant proportion of women (30%) and men (47%) with hypertension and coexisting cardiovascular disease were undertreated for hypertension as per the guidelines (Klungel et al., 1998). Overall prescribing trends can indicate the appropriateness of medicine use against a backdrop of evolving guidelines (Narayan and Nishtala, 2017). Additionally, drug utilization trends can provide a pathway for regulating the use of controlled medicines or examine the impact of specific quality-driven programs or the impact of interventions. Furthermore, drug utilization trends can be used as a proxy to educate prescribers on the appropriateness of medicines in special populations, for example, elderly with renal or hepatic impairment or geriatric syndromes and with multiple chronic diseases (Hennessy, 2006).

Drug utilization studies have also been employed to understand drug exposure patterns in pregnant women and children. Drug utilization studies done on pregnant women relay vital information on the timing (trimester), dose, and duration of medicine use in pregnancy, which are important variables that influence fetal toxicity.

Drug utilization studies in children have received special attention from both the US Food and Drug Administration and the European Medicines Agency (EMA) in light of growing concerns about the lack of research for the efficacy and safety of medicines use in children. A retrospective cohort study conducted in Europe analyzed primary care data in the Netherlands, the United Kingdom, and Italy to examine prescription patterns in children aged up to 18 years (Sturkenboom et al., 2008). The findings of this study have the potential in informing prioritization of research into the long-term safety of pediatric drugs, as well as inform effectiveness studies in the pediatric population.

Assessment of Medication Adherence

In recent years, there has been increasing use of pharmacy databases including claims and insurance databases to understand medication adherence and persistence in large populations. The findings from these real-world populations present tremendous opportunities to improve patient adherence to chronic medications in pharmacy practice.

Medication nonadherence is high in people living with chronic conditions such as hypertension, diabetes, and hyperlipidemia (Lehmann et al., 2014). Several studies in pharmacoepidemiology have shown high levels of nonadherence to antihypertensive and medications for dyslipidemia contributing to negative health outcomes (Hess et al., 2006; Meddings et al., 2012; Stroupe et al., 2006). Similarly, studies have identified nonadherence to psychotropic medicines such as antidepressants. A large retrospective cohort study (N = 27,865) using the French National Health Insurance reimbursement database found that only 26.9% of patients were adherent to antidepressants as recommended by international guidelines (Braunstein et al., 2017). Another retrospective study conducted using the UK Clinical Practice Research Datalink found patients with gout starting allopurinol were nonadherent to therapy particularly the younger age groups and females. Both studies highlight the importance of training clinical pharmacists to counsel patients on the continuation period for treatments for better health outcomes.

Adherence to medication can be measured using direct or indirect measures such as pill counts, patient reports, questionnaires, interviews, and electronic pill caps (Parker et al., 2007). However, these methods can be very time-consuming. Studies in pharmacoepidemiology employ alternative methods, among which the most commonly used and validated are the proportion of days covered (PDC) and medication possession ratio (MPR) (Karve et al., 2009). There is a considerable body of evidence derived from pharmacoepidemiology showing nonadherence to medications in asthma and chronic pulmonary obstructive disease (COPD). A retrospective cohort study conducted using the prescription database from a network of general practitioner surgeries in Scotland calculated adherence using the MPR and found it was relatively low in this UK population (Covvey et al., 2014). The role of healthcare professionals particularly community pharmacists in improving medication adherence is well established. There is a large body of research conducted in Australia, New Zealand, United Kingdom, and the United States demonstrating that community pharmacists have played a significant role in the improvement of COPD and asthma management via collaborative services and shared decision-making including medicine use services, implementation of asthma management plans, advice on optimal selection and use of pharmacotherapy, and distribution of medicines for asthma.

Given the clinical and economic consequences of nonadherence to chronic medicines, the findings from pharmacoepidemiology can improve pharmacy practice by proposing tailored interventions, such as medication adherence aids, medication management plans, health literacy, and patient education (Brown and Bussell, 2011; Stroupe et al., 2006).

Assessment of Adverse Drug Reactions and Medication Errors

In recent years, there has been increasing use of national pharmacovigilance systems to collate and report patterns of adverse drug events and medication errors. The European Union has legislated reporting of medication errors, and the European Medicines Agency has published guidelines to improve medication error reporting practices.

In Europe, a centralized database, the EudraVigilance, was established for reporting and evaluating suspected adverse reactions of medicines (Postigo et al., 2018). Similarly, National Poison control centers established worldwide are an invaluable surveillance tool for identifying medication errors on a national or regional scale. These centers report medication errors with detailed clinical and biological data, which is particularly relevant to clinical and pharmacy practice. A classic example is the reporting of methotrexate toxicity by national pharmacovigilance and Poison centers (Bebarta et al., 2014; Perregaard et al., 2015). Regulatory agencies can use such surveillance data to improve and update product information. At practice level, pharmacists can follow good dispensing practices to avoid dosing errors, including provision of consumer medication information. Surveillance registers can identify common medicine errors and help implement policies to reduce recurring errors (Antonow et al., 2000).

A retrospective analysis of the FDA Adverse Event Reporting System Database from 2006 to 2014 reported 902,323 serious outcomes including 244,408 deaths, 72,141 disabilities, and 585,774 other serious outcomes (Sonawane et al., 2018). Manufacturers submitted majority (approximately more than 70%) of the expedited reports on serious ADEs. Health professionals (47.3%) followed by consumers (36.1%) and other sources (16.6%) contributed to these reports. Interestingly, there was a bimodal age distribution of ADEs represented by patients aged 45–64 years (40%) and ≥65 years (approximately 33.0%). This is another good example of the contribution made by the field of pharmacoepidemiology in guiding postmarketing surveillance and examining the public health burden of ADEs.

Assessment of Population-level Prescribing

Polypharmacy and Hyperpolypharmacy Trends

The use of multiple medicines increases with the prevalence of chronic diseases and increasing age. Polypharmacy (use of five or more medicines) and hyperpolypharmacy (use of ten or more medicines) are proxy indicators for inappropriate medicine use that lead to adverse clinical outcomes, particularly in the older population (Nishtala and Salahudeen, 2015). Studies that examined the trends of polypharmacy and related clinical outcomes identified that older adults who are prescribed multiple medications may be twice as likely to become frail in a relatively short period (3 years) compared to those who take fewer medications (Saum et al., 2017). The information gathered from these studies serve as a feedback for the development of guidance documents focused specifically on the management rational use of medicines.

A recent position statement from the International Group for Reducing Inappropriate Medication Use and Polypharmacy (IGRIMUP) advocates ten recommendations for action to combat polypharmacy (Mangin et al., 2018). The position statement outlined the global problem of polypharmacy and provided a framework to reduce polypharmacy in the context of multimorbidity.

Evidence of the high prevalence of polypharmacy and potentially inappropriate medicines has also led to the development of medicines optimization services. Medicines optimization services delivered by specialized clinical pharmacists are recognized as a core clinical pharmacy service to address the global challenge of polypharmacy.

Pharmacoepidemiology: Opportunities to Inform Evidence on Prescribing Practices and Medicines Optimization

Inappropriate Prescribing

Pharmacological therapy is necessary to manage acute illness, maintain current health and prevent further deterioration; however, prescribing for populations such as multimorbid individuals or older patients is challenging, and sometimes, medicines can do more harm than good. This also extends to other populations such as children as the WHO estimates that >50% of all medicines prescribed and purchased for children may be inappropriately prescribed (Reidenberg, 2009). In recent decades, drug utilization review tools have been developed to highlight instances of potentially inappropriate prescribing. Among these tools, one of the most widely used, particularly for older people, is the Beers criteria, which were developed in 1991 and had been modified since (American Geriatrics Society Beers Criteria Update Expert, 2012; Beers et al., 1991). International studies and reviews have shown evidence that identifying inappropriate medicines using the Beers' criteria has been associated with adverse health outcomes in community-dwelling middle-aged and older people (Chang et al., 2005; Fick et al., 2008; Jano and Aparasu, 2007; Moriarty et al., 2017).

Similarly, the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria developed by researchers from Ireland are now increasingly used to screen for inappropriate prescribing on large prescription databases (O'Mahony et al., 2015). Importantly, screening tools such as the STOPP-START have shown utility as decision support tools to reduce inappropriate prescribing and improve patient safety. A recent study validated a computerized application of the STOPP/START criteria to electronic medical record data to assess prescribing for older patients (Nauta et al., 2017). The study highlighted not all domains of the criteria can be applied by means of algorithms. Nevertheless, with rapid development of

technology and advancement of artificial intelligence, it is a matter of time before these tools will have massive implications for changing clinical practice.

In summary, health-care professionals including clinical pharmacists have an opportunity to integrate such decision support tools into their dispensing software and correct inappropriate prescribing where necessary either by initiating a medicine review or a clinical intervention with the prescriber.

Comparative Effectiveness Studies

An important application of pharmacoepidemiology is to conduct comparative effectiveness studies, examining the differences in efficacy demonstrated in RCTs and effectiveness of a medicine when used in large real-world populations. RCTs are considered the "gold standard" for producing evidence relating to the comparative risks and benefits of pharmaceuticals; however, RCTs have their own limitations. First, they lack external validity, since the conditions under which they are conducted may not be reflective of real-world experience. Second, for operational or ethical reasons, it may not be feasible to conduct RCTs over a long enough period to capture all adverse drug events. Moreover, RCTs are not representative of patients prescribed medicines and often exclude vulnerable and multimorbid populations, hence their findings may not be generalizable to these subgroups. Consequently, there is a growing interest in bolstering evidence from RCTs using data from other sources, including population-level data.

Efficacy and Effectiveness

Efficacy is defined as the performance of an intervention under ideal and controlled circumstances, such as during development of a drug therapy, whereas effectiveness is its performance under real-world conditions (Singal et al., 2014). During the drug development process, there is inadequate information on how real-world population will respond to a medicine. In addition, the inclusion of an ideal population in clinical trials does not benefit the increasing number of individuals living with multiple morbidities (Barreto, 2005; Hilmer et al., 2012).

Evidence drawn from comparative effectiveness research is important to patients, physicians, payers, and policymakers in making "real-world" choices among the treatment options that are available. In summary, comparative effectiveness, research can inform evidence base for drug committees and formularies as well as provide the evidence base for pharmacists in applying evidence information at a patient level.

Health Economics and Pharmacoepidemiology

Pharmacoepidemiology provide the evidence on the cost-effectiveness of medicines that could potentially influence policy and decision-making. Additionally, they provide evidence on the costs of inappropriate or suboptimal prescribing on healthcare budgets. A longitudinal study conducted on a large German database measured inappropriate prescribing using the PRISCUS list (Helder et al., 2018). The study included 3,860,842 individuals with no exposure to PIM matched to 508,212 exposed individuals within the same study period. After controlling for confounders, they found that the average effect of one additionally prescribed substance on total health-care costs was increased by an amount of 137 € for individuals exposed to a PIM.

Previous international studies estimating the costs associated with discontinuing a preventive medicine such as statins has yielded positive outcomes and influenced further discontinuation of other medicines hence amplifying these savings (Kutner et al., 2015; Tjia et al., 2014). Furthermore, noticeable findings of a reduction in health-care costs will enable individuals and health-care funders to better allocate their resources.

Pharmacoepidemiology and Medicines Policy

Pharmacoepidemiology research informs and influence policies in improving professional practice and the rational use of medicines (Hogerzeil et al., 1989). Rational use of medicines infers patients receive the appropriate medicines, in doses that meet their requirements, for an adequate period of time, and at the lowest cost both to them and their community (Garattini et al., 2008). Suboptimal prescribing patterns contribute to the high cost of medications for patients as well as the difficulty in providing affordable prescription drug benefit. Studies examining variations from guideline-based prescribing provide real-world evidence on the implications and adverse outcomes related to irrational medicine use to influence policymakers (Fischer and Avorn, 2004; Radley et al., 2006).

Pharmacoepidemiology and Pharmacovigilance in Pharmacy Practice

This chapter discussed the application of pharmacoepidemiology concepts and methodology in clinical and pharmacy practices including drug utilization evaluations, pharmacoeconomics evaluations, comparative effectiveness research, and adverse drug reaction surveillance.

The best drug therapy decisions are based on up-to-date evidence provided by everyday consumers of medicines (Jill and David, 2005). Pharmacoepidemiology provides real-world evidence since assessment of safety of medicines based on clinical trial

data is often inadequate, and big data with larger follow-up periods are essential for signal detection that are often missed during a clinical trial due to small sample sizes, sample selection bias, and limited drug exposure periods. Hence, pharmacoepidemiology delivers a stronger scientific base for making clinically relevant decisions and promoting the rational use of medicines (Chant, 2017; Toklu, 2015). Pharmacovigilance studies employ several methodological designs on big data to detect, analyze, and understand safety signals are also essential to inform clinical and pharmacy practice.

Social Media Platforms

Social media platforms that share health-related information are a potential source for postmarketing surveillance. Data from social media platforms are used to assess smoking cessation patterns, monitor drug abuse, and infectious disease spread (Leaman et al., 2010). A recent study examined Twitter accounts of pregnant women to analyze trends of drug exposure and birth defects during pregnancy (Golder et al., 2018). The study reported a 0.44% rate of birth defects in pregnant women. The authors acknowledge several methodological challenges including difficulty in defining cases and finding matched controls. However, their study highlighted the potential future role of social media platforms in postmarketing surveillance particularly in populations underrepresented (i.e., pregnant women) in clinical trials.

In the current scenario, data extraction from social media platforms is laced with several challenges including limitations of existing tools to mine data accurately and ethical considerations of using private data publicly available. However, in the technological advancement era, the possibility of mining vast amounts of private health data available publicly has the potential to advance pharmacovigilance.

Conclusion and Future Opportunities

Pharmacoepidemiology and pharmacovigilance studies can answer clinically important outcomes; however; the benefits from such observational studies can only be optimized, if they have an impact on clinical practice.

Pharmacoepidemiology provides population-level risk estimates and is useful in understanding adverse drug events and helpful in risk assessment and minimization. The challenge for policymakers is to develop strategies that can be implemented at a practice level in risk minimization.

Pharmacoepidemiology studies have made an immense contribution toward pharmacy practice in a clinical setting and as a health-care discipline, particularly focusing on improving prescribing and understanding medicine safety. The growth in the magnitude, diversity, and availability of electronic patient data has presented unparalleled opportunities for expeditious assessment of drug safety, monitoring pharmaceutical policies, health-care utilization, and decision support relevant to all individuals accessing health care. The opportunity to link patient-level data to hospital admissions, laboratory tests data, and sociodemographic data will facilitate the growth of big health-care data. Research founded on big real-world patient level linked data can produce evidence that is critical to optimizing health-care delivery, health outcomes, and to facilitate better monitoring of pharmaceutical policy.

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CONTENTS OF ALL VOLUMES

VOLUME 2

VOLUME 3A

VOLUME 3B

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Zaheer-Ud-Din Babar is Professor in Medicines and Healthcare and the Director of Centre of Pharmaceutical Policy and Practice Research at the University of Huddersfield, United Kingdom. He has worked as an academic in Pakistan, Malaysia, New Zealand, and in the United Kingdom, and understands the health systems and pharmacy globally. He is known for his work in pharmaceutical policy and practice, including quality use of medicines, clinical pharmacy practice, access to medicines, and issues related to pharmacoeconomics. Previously, he was the Head of Pharmacy Practice at the University of Auckland and received Vice Chancellor's Research Excellence Award from the University. He has published in high impact journals, such as *PLoS Medicine* and *Lancet* and has acted as a consultant for World Health Organization, Royal Pharmaceutical Society, Health Action International, International Union Against Tuberculosis and Lung Disease, World Bank, International Pharmaceutical Federation (FIP), and for the Pharmaceutical Management Agency of New Zealand.

His other work includes *Economic Evaluation of Pharmacy Services*, *Pharmaceutical Prices in the 21st Century*, *Pharmaceutical Policies in Countries With Developing Healthcare Systems*, and *Pharmacy Practice Research Methods*. Published by Elsevier and Adis/Springer, the books are used in curriculum design, policy development, and for referral all around the globe. Professor Babar is also the Editor-in-Chief of *BMC Journal of Pharmaceutical Policy and Practice* and can be contacted at z.babar@hud.ac.uk.

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Zubin Austin BScPhm MBA MISc PhD FCAHS is Professor and Koffler Chair in Management at the Leslie Dan Faculty of Pharmacy and the Institute for Health Policy, Management, and Evaluation—Faculty of Medicine at the University of Toronto. His research focuses on the professional and personal development of the health workforce. He has published over 160 peer-reviewed manuscripts and authored four reference texts. In 2017, he was installed as a Fellow of the Canadian Academy of the Health Sciences, the highest award for health services researchers in Canada. He is the only faculty member of University of Toronto to have ever received both the President's Teaching Award for excellence in education and the President's Research Impact Award for the societal significance of his work. He has also been named undergraduate Professor of the Year by students on 18 separate occasions.

Ahmed Awaisu

Dr. Ahmed Awaisu is an Associate Professor of Clinical Pharmacy and Practice in the College of Pharmacy at Qatar University. He received his Bachelor of Pharmacy degree from Ahmadu Bello University Zaria, Nigeria in 1999, his masters and PhD degrees in Clinical Pharmacy from Universiti Sains Malaysia (USM) in 2004 and 2009, respectively. He is also a licensed pharmacist and has practiced in the hospital setting since 1999. Dr. Awaisu has a unique privilege of past academic experiences in international pharmacy degree programs. He has made substantial and tremendous contributions that impact teaching and learning, research, curriculum design, as well as professional development of students and healthcare practitioners in Qatar and other countries. He received the Qatar University Merit Award for Outstanding Faculty for 2016–17 Academic Year. He is a member of the American College of Clinical Pharmacy (ACCP), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), among others.

Professor Awaisu has extensive experience in the conduct of pharmacy practice and clinical research involving various types of study designs including case-control and cohort studies, quantitative surveys, mixed-methods designs, randomized control trials, and systematic reviews mostly on diabetes, cardiovascular diseases, tobacco dependence, and other chronic diseases. He has published over 100 peer-reviewed articles in internationally reputable pharmacy and healthcare journals and 10 book chapters related to the field of pharmacy. He has successfully supervised several postgraduate and undergraduate research projects, including MSc and PhD.

His research interest includes pharmacy practice especially pharmacists' expanded scope of practice, outcome-based research, pharmacoepidemiology and medication safety, and health promotion. Dr. Ahmed Awaisu has conducted training sessions and workshops on research methodology and biostatistics, drugs in sports, developing cognitive pharmacy services, and responding to symptoms in pharmacy practice. He presents regularly at continuing professional development programs for healthcare professionals in Qatar and other countries.

Timothy Chen

Professor Timothy Chen is a registered pharmacist and Professor of Medication Management, School of Pharmacy, The University of Sydney, Australia. Tim is nationally and internationally renowned for his research in medication management review and strategies to reduce medication related harm. Tim's research directly informed the Australian Government funded Home Medicines Review programme (MBS Item 903). Tim is an experienced educator and health services researcher, with experience in both community pharmacy and hospital pharmacy practice. Tim leads a productive research team (>160 peer-reviewed papers) and has completed main supervision of 15 PhDs, amongst other postgraduates. Tim has delivered >70 invited presentations at conferences and meetings across the globe. Tim has received university and national awards (Australian Government) for teaching, is an International Pharmaceutical Federation (FIP) Fellow (2016), and is President of the Social and Administrative Pharmacy Section, FIP.

Louise Curley

Louise Curley is a pharmacist and Senior Lecturer in Pharmacy practice at the School of Pharmacy. Louise's area of research focuses on the effects of recreational drug use in humans. She began her research as an undergraduate by investigating the subjective and electrophysiological effects of the Party Pill drugs using electroencephalography (EEG) and graduated with a PhD in pharmacy in 2012. Her thesis investigated the effects of the main constituents of "Party Pills" benzylpiperazine (BZP) and trifluromethylphenylpiperazine (TFMPP) on executive functioning and reward using functional magnetic resonance imaging (fMRI). Currently, her focus is developing new fMRI paradigms to investigate different aspects of risk, specifically by comparing populations of dependent versus non-dependent participants. Louise also has an interest in pharmacy practice research including innovative methods of teaching undergraduate students using different technologies and evaluating the effects of these innovations. She has recently been awarded the Butland Teaching Award: Innovation in Teaching.

Danijela Gnjidic

Dr. Danijela Gnjidic (BSc PhD MPH) is an NHMRC Dementia Leadership Fellow and Senior Lecturer at the School of Pharmacy, Faculty of Medicine and Health, University of Sydney. Her research expertise is in clinical and geriatric pharmacology, clinical studies on polypharmacy, high risk prescribing, and deprescribing in older people, pharmacoepidemiology, and the quality use of medicines. Danijela's academic track record includes 115 publications, 3-book chapters, with over 2500 citations on Scopus and $4M in research funding. Danijela was awarded the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Denis Wade Johnson & Johnson New Investigator Award in 2012. Internationally, Danijela's contribution to the filed was recognized with the 2018 American Society of Clinical Pharmacology and Therapeutics William B. Abrams award in Geriatric Clinical Pharmacology. Danijela is an Associate Editor of the *Journal of Alzheimer's Disease* and Academic Editor of the *PloS One Journal*.

Arijana Meštrović

Dr. sc Arijana Meštrović, MPharm, FFIP has been working as a community pharmacist and she was responsible for education, services, and competency development in the biggest pharmacy chain in Croatia. She is now independent consultant and educator in Pharma Expert international agency, providing lectures and workshops in CPD programs for pharmacists, pharmacy technicians, medical representatives, implementing new services in pharmacy chains, and teaching Social Pharmacy and Pharmaceutical Care at universities in Croatia and Cyprus as Assistant Professor. Her Doctor's degree is in biomedical sciences—competency development in pharmacy. Arijana serves as member of the International Services Program Advisory Group the Accreditation Council for Pharmacy Education (ACPE, USA), member of PCNE (Pharmaceutical Care Network of Europe), ExCo member of FIP (Pharmaceutical International Federation) Academic section, and WHO international expert consultant in Pharmaceutical care field. She used to serve as Co-Chair of the FIP World Congress Programme Committee, Expert Member of the Board of Pharmacy Practice at FIP. In Croatia, she is a leader in Croatian Pharmaceutical Society and Croatian Chamber of Pharmacist as a Lecturer and Co-author of New services model in community pharmacy practice. Arijana is dedicated to promoting competency-based education in CPD cycle, so her teaching usually addresses all components of competencies—knowledge, experience, and motivation. In collaboration with ACPE International Services, she has founded and implemented SMART Pharmacy CPD model for pharmacists in more than 12 countries all over the world. She was invited speaker and consultant in more than 40 countries.

Kath Ryan

Kath is Professor of Social Pharmacy at the University of Reading, and Visiting Professor at Bournemouth University, United Kingdom. She has 45 years of experience as a pharmacist in the pharmaceutical industry, community practice, and academia. She has held posts at the University of Otago, New Zealand; Bournemouth University, United Kingdom; La Trobe University, Melbourne, Australia; and the University of Reading, United Kingdom. She also has experience in academic nursing and midwifery. Her research interests include extended roles for pharmacists, especially in general practice; application of the behavioral sciences to pharmacy practice; personal experiences of health and illness; and public and patient involvement, engagement and participation in research, and the education of health professionals. She has expertise in quantitative, qualitative, and mixed methods research. She also has an interest in infant feeding,

particularly breastfeeding research, promotion and support, from lay, professional, and academic perspectives. She has been a health advisor to La Leche League International and La Leche League New Zealand. Kath has been on Scientific Committees for the International Social Pharmacy Workshops and the Australasian Pharmaceutical Sciences Association. She has consulted for the National Institutes of Health, USA; Canadian Forces; Health Technology Assessment, NHS UK; and the NZ Ministry of Health.

Kath has over 100 publications in peer-reviewed journals and several book chapters and reports. She produced two multimedia, online resources for Health Talk: women's experiences of breastfeeding in the United Kingdom, and people's experiences of ageing in Australia. She was a Founding Co-Director of Health Talk Australia.

FOREWORD

This first edition of the Encyclopedia of Pharmacy Practice and Clinical Pharmacy is one-of-a-kind and the most comprehensive amalgamation of an inclusive range of topics relevant to the pharmacy profession brought together to ensure safe and effective provision of pharmaceutical care across the world. Professor Zaheer Babar is a Professor in Medicines and Healthcare at the University of Huddersfield and also a global expert in pharmacy practice and pharmaceutical policy. He has united over hundreds of researchers and practitioners from across the world in a collaborative endeavor to provide a unique insight into current best practice and strategies for the future for the profession of pharmacy and its practice.

As patient care becomes more complex with advances in medicines and new developments in practice, including pharmacogenomics and pharmacoeconomics, there is an ever-evolving demand for practice and policy to keep pace. This encyclopedia contains 180 chapters, from all fields of pharmacy practice and clinical pharmacy, providing an in-depth coverage of modern approaches to the practice of pharmacy and highlighting the directions that will enable advancement to continue.

This encyclopedia includes definitions, concepts, theories, and applications of clinical pharmacy and pharmacy practice, providing background knowledge of the area that will provide valuable information for students of pharmacy practice. By providing relevant and topical summaries on a broad range of subjects, this book is also an excellent resource for those seeking information beyond their specific areas of expertise. In addition, the information contained in this book and its communication is of importance to a range of stakeholders, such as physicians and other healthcare professionals, health regulatory authorities, and the pharmaceutical and health industry, in addition to patients and their caregivers.

This encyclopedia also provides an excellent insight into pharmacy practice research and methods, as well as pharmacovigilance, pharmacoeconomics, social and administrative pharmacy, public health pharmacy, pharmaceutical systems research, the future of pharmacy, and new interventional models of pharmaceutical care. In addition, new treatments, algorithms, standard treatment guidelines, and pharmacotherapies regarding diseases and disorders are also covered.

The six key strands around which this encyclopedia is arranged pay testament to the complex and broad nature of the topic and are key topics of interest in pharmacy today and drivers of change for the future, for the benefit of public health across the world.

1. Pharmacy practice
2. Pharmacy practice research methods
3. Clinical pharmacy education, professional standards, and workforce
4. Clinical pharmacy and pharmacotherapy
5. Pharmacoepidemiology and pharmacovigilance
6. Socio-behavioral and administrative pharmacy

Topics range from the education and training of pharmacists, technicians and assistants to counterfeit medicines, pharmaceutical pricing policies, and implementation of change. As pharmacy practice evolves to meet the ever-more-complex health and medicines needs of patients, practitioners need an understanding of the social, political, and economic contexts across the world, noting particular highlights and challenges in developing countries to reach high standards. While it is acknowledged that there are differences between countries in terms of legislation, regulations, and guidelines (as detailed in individual chapters), the vision for the profession must be for a world in which everyone can access safe, effective, and affordable medicines and pharmaceutical care. The chapters include many examples of innovation and best practice in delivering health

services for the future, embracing additional roles beyond the supply of medicines in a robust manner underpinned by scientific and evidenced practice. Quantitative, qualitative, and mixed methods of pharmacy practice research are presented alongside expanded and evolving roles for pharmacists and where technology may take us. More quality research and coordinating efforts will bring a range of theoretical concepts and an evidence-based practice to the forefront of our activities, to focus a global workforce to meet the challenges of this exciting new era for pharmacy practice. This timely volume exemplifies the willingness and ability of the profession to work collaboratively on global issues, representing an unprecedented opportunity to shape the future of pharmacy practice.

With ever-increasing demands on healthcare systems, alongside growing financial pressures, it is essential that we work collaboratively with other pharmacists and the wider public health workforce who have the expertise, opportunity, and capacity to support and inform development.

In this context, this encyclopedia is an important resource with far-reaching impact on global healthcare community, and I hope this will be well liked by students, researchers, and academics.

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March 2019

PREFACE

Encyclopedia of Pharmacy Practice and Clinical Pharmacy

This encyclopedia has 180 chapters in total and it covers all domains of pharmacy practice and clinical pharmacy, including pharmacy practice research, socio-administrative and behavioral pharmacy, pharmacy education, pharmacoepidemiology, and the pharmacotherapy. One main question being asked is the need for this work. *What encyclopedia of pharmacy practice and clinical pharmacy adds to the current body of literature and what it means for global pharmacy community?* The answer to that is, though there were a number of books available on pharmacotherapy, however, current landscape lacks material comprehensively covering aspects, such as pharmacy practice, pharmacy practice research, social pharmacy, pharmacoepidemiology, pharmacy education, and the linking of clinical pharmacy with the health system. This encyclopedia aims to provide a collection of chapters on the above-mentioned areas. It also developed, synthesized knowledge, and provided policy guidance in the areas where there were gaps in the literature. For example, filling the gaps and including chapters on health systems, pharmaceutical policy, evidence and impact in pharmacy practice research, and on pharmacy education.

Here is a brief summary of what is being covered in its three volumes: Volume 1, 2, and 3.

Volume 1 includes chapters on pharmacy practice and pharmacy practice research. The pharmacy practice section starts with the historical evolution of pharmacy practice, medicines management, expanded roles of pharmacists, cognitive pharmacy services, community, and ambulatory pharmacy practice, ethics and regulation, and the new models of pharmaceutical care. There are also chapters on prescribing standards, practices, and competencies, interpersonal communication, evidence-based medicine, models on patient counseling, innovative pharmacy services, technology in pharmacy practice, and the pharmacist's role in substance misuse. The case studies chapters include pharmacy practice in high, low, and middle-income countries; United Kingdom, Western Europe, Australia, New Zealand, China, India, Gulf States, Philippines, and Portugal.

It is vital to understand and discuss the quality of evidence in pharmacy practice research, for example, how the evidence is produced and how it could impact on health outcomes. This is a niche section in the encyclopedia covering chapters on quantitative and qualitative methods in pharmacy practice research, quality of qualitative research, philosophical perspective and theories applied in pharmacy practice research, meta-synthesis, mixed methods research, discrete choice experiments, and the use of network meta-analysis in pharmacy practice. There are also chapters on evolution and definition of practice research, evidence, impact, and gaps in pharmacy practice research in low- and middle- and high-income countries.

Volume 2 covers pharmacovigilance, pharmacoepidemiology, and the socio-behavioral and administrative aspects of pharmacy and medicines use. The knowledge regarding pharmacoepidemiology and pharmacovigilance significantly impacts on medicines safety. The chapters included are on definitions, principles, and application of pharmacoepidemiology, descriptive and drug utilization studies, case-control and cohort studies, methodological challenges in epidemiological studies, data sources, and the issues related to medicines safety and comparative effectiveness research.

The socio-administrative and behavioral pharmacy section covers two broad aspects, namely, social pharmacy and pharmacy administration. Social pharmacy section covers concepts, development, and theories related to social pharmacy, public and patient engagement, sociology for pharmacists, implementation of change in pharmacy practice, and the social perspectives in addiction. There are also chapters on medicines adherence, compliance, and concordance, medication narratives, investigating medicines use among elderly

from a sociological perspective, changing nature of pharmacy as a profession, the impact of culture and religion on medicine use, and the issues related to disease mongering.

The understanding of health system is vital when promoting access and the use of medicines, hence in this context understanding administrative aspects of pharmacy are crucial. This section explores the dynamics between public policy, pharmaceutical policy, pharmacy practice, health systems, and patient-health outcomes. It covers a range of pharmaceutical policy and health system issues including access to biosimilars, access to high-cost medicines, counterfeit medicines, factors influencing pharmaceutical policy implementation, funding mechanisms for community pharmacy services, generic drug policies, national medicine policies, essential medicines list, pharmaceutical company sponsored medication assistance programs, and the pharmaceutical pricing policies.

Volume 3 covers clinical pharmacy education and pharmacotherapy. Pharmacy education training and the workforce have a great impact on global health. There are 25 chapters or more on pharmacists' training, and certification exploring the relationship between education, regulation, and practice. This is one of the largest collection of chapters covering pharmacy education and regulation at the global level. This includes chapters on pharmacist workforce, competency standards for clinical pharmacists, quality assurance in the pharmacy education, developing and evaluating clinical skills, continuing professional development, experiential education, inter-professional learning, leadership in pharmacy education, and the needs-based education. There are also case studies chapters on clinical pharmacy professional standards in the United States of America, Canada, the European Union, and in the low- and middle-income countries.

The pharmacotherapy section covers over 70 chapters discussing standard treatment guidelines, pharmacist's role in the central nervous system, infectious diseases, cardiovascular disorders, skin and endocrine disorders, musculoskeletal disorders, neurology, gastrointestinal disorders, and the respiratory disorders. The other key chapters include clinical pharmacy concepts, history, and development, clinical governance principles, pharmacokinetics, therapeutic guidelines, end of life care, palliative care, long-term care, fundamentals of pharmaceutical care planning, health outcomes and quality of life, the role of the pharmacist in the military and prisons, and the pharmacotherapy and deprescribing.

It has been a challenging task to complete this encyclopedia within a short span of 2 years. However, I am very thankful to the support of my section editors, reviewers, and hundreds of authors from all over of the world to come together and to contribute to this exciting project.

I hope you will like this effort and it will serve its purpose.

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To Danyal Zaheer

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Professional Ethics in Pharmacy Clinical Governance

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Introduction

Clinical governance provides a scaffolding structure for a shared professional dedication to developing and attaining highest standards of patient care. It is a commitment to providing quality services through good clinical practice entwined with high ethical standards of patient care. Clinical governance relies on good processes and an environment where continuous improvement is advocated to allow excellence in the provision of care and services to flourish for patients. Integral to the delivery of high-quality patient-centered care is ensuring professional governance and high ethical standards. The main requirement for any health-care service is patient safety and quality improvement (Flynn Maureen et al., 2015). The provision of pharmacy services is no exception. The patient is afforded the right to have pharmacy services delivered to an appropriate quality and standard. Pharmacy is governed and guided by codes, ethical obligations, regulatory authorities, legislation, professional organizations, corporations, and central agencies, ministries, and consumer advocates. A fundamental tenet of ensuring a high standard of service is through embracing ethical leadership and ethical obligations that bind the profession. This chapter explores the topic of professional ethics in pharmacy as a pillar of patient-centered care and consequently the premise of good clinical governance. This chapter explores a history of ethics in pharmacy, emergence of bioethics, professional governance, reasoning, and decision-making.

Ethics in Pharmacy—A Brief History

In ancient times, medicine and pharmacy were merged in one body of practice, interwoven and tightly bound in religious practices. Pharmacy always played a prominent role in the history of civilization. Even in the age of Hippocrates (c.400 BC), physicians knew that disease was not an act of divine providence as much as it was a condition that an experienced doctor could diagnose, and with the help of natural medicines, relieve or cure (Pötzsch, 1996).

The foundations of pharmacy were laid centuries ago by a series of many civilizations; but it was not until the 9th century AD in Baghdad that the first pharmacy was ever established and where pharmaceutical literature in Arabic began to proliferate. This historical event marked the first separation of roles of physicians and pharmacists, and recognition of governmental responsibility for peoples' health, which later spread to Europe (Pötzsch, 1996). Pharmacy as a separate profession from medicine began to emerge in Great Britain in the 17th century.

Ethics in health care as we know it today in the Western world has its roots in history from the time of Hippocrates (Edelstein, 1967). The paradigm of this ethical foundation of health care is the Hippocratic Oath, which, according to some scholars, emerged not from the general milieu of the Greek philosophers in medicine but even further back in history, to the philosophical–religious cult of the Pythagoreans (Carrick, 1985; Edelstein, 1967; Jonsen, 1998).

Although ethics in health care is not necessarily all about codes of ethics (Kerridge et al., 2009), the Hippocratic Oath is generally acknowledged as the first code of ethics in health care and the foundation for medical ethics in the Western world. The

Oath itself is divided into two parts: The first, the opening covenant, relating to the relationship between teacher and scholar. The second part, often referred to as ***the*** "code of ethics," is subdivided into three areas of medicine: dietetics, pharmacology, and surgery, offering detailed statements and instruction on principles of patient care.

The Oath served a number of purposes, including the binding together of professionals into a cohesive and effective social force. However, in relation to medical ethics, the Oath has had the "***most significant influence***" and with only minor amendments, has remained over the millennia central to the ethics of physicians to the present day (Kerridge et al., 2009).

The main reason for the longevity of this code is the patient-centered values it represents. For example, on dietetics, the pledge was to apply measures "*for the benefit of the sick according to my ability and judgment.*" Often referred to as the principle of "*beneficence*" (to do good), this core principle in health care still stands strong today. This one line is considered to be the most important line in the *Oath.* Another long standing principle handed down from the Oath is the principle of *non-maleficence* (to do no harm). These two mainstays of medical ethics have been extended to include all health-care ethics relating to the patient throughout the centuries after it was written, including pharmacy (Veatch, 1989).

Profound issues and perspectives about health-care ethics have come to the forefront over the last decades. In particular, post-World War II, the emergence of human rights as a driving social and political agenda in the Western world—generating movements such as consumerism, feminism, and the rights movements, have immensely influenced ethics in health care (Darvall, 1993). The tradition of representing health-care ethics by reference to the Oath is slowly waning in the face of substantial change in practice as a result of both technological/scientific advances and major changes in societal expectations after the war. Over time, the four major principles of *bioethics* have emerged: (1) Respect for patient autonomy; (2) to do good; (3) to avoid harm; and (4) justice. Along with profession-specific values complementing these principles, most health-care professions today, including pharmacists, recognize the principles of bioethics as fundamental in the practice of health care.

Deliberation and acceptance of ethical principles are often the precursors for the development of regulations and codes. Bioethical principles have been recognized and heavily underpin laws and codes pertaining to patient protections. These patient-centered values that have emerged from principles of bioethics have been enveloped in codes that prescribe the fact that every consumer can expect a high standard of care with respect to their privacy, dignity, and independence.

Patient Rights and Legislation

Codes and legislation governing the rights of particularly vulnerable patients, such as those receiving health and disability services, are prominent in health care and enforced by most health organizations. These regulations prescribe the rights that every health and disability service consumer can expect and impose corresponding duties on the health-care provider to fulfil these obligations (Manning, 2004).

Similarly, the privacy of the patient is today, and around the world, strongly protected through privacy legislation and health information privacy codes, as it is accepted that due to the sensitive nature of health information, it should be treated differently and assumes a need for greater level of privacy. These ethical principles embodied in regulations around the world, help further the creation of a culture, which embraces the aims of clinical governance. The aims of clinical governance are enabled by a focus on quality and safety through quality improvement methodologies as well as good ethical leadership (Goona et al., 2014).

The Emergence of Bioethics

Bioethics has been an area of major growth in moral philosophy since the 1960s (Frey, 1998). Bioethics is principle-based ethics, that is, specifies general principles to guide moral actions and more specific rules to provide clear applicable guides (Kerridge et al., 2009). The concepts of bioethics began to take shape in the decades immediately post-World War II during which the conceptual foundation for evaluating outcomes within tenets of consequentialism was expanded to include other ethical principles beyond *beneficence* and *non-maleficence* (Savulescu, 2003). These newer principles press the practitioner–patient relationship beyond traditional ethical guidelines to include additional principles such as *justice* (strategies or acts that ensure fair allocation of goods and services) and *respect for autonomy* (strategies or acts that respect the self-determination of others) (Buerki and Vottero, 1994).

These four principles, the so-called pillars of bioethics, are at the core of most medical ethics curricula in English speaking world, presented to readers with detailed descriptions of the physician–patient or nurse–patient relationship (Beauchamp and Childress, 2009; Kerridge et al., 2009). Scholars have, however, rarely extended this analysis to the profession of pharmacy or explored the underlying nature of the pharmacist–patient relationship (Buerki, 1994). We explore this extension further in the next section.

There is in fact far more literature available in the philosophy of health professions, such as medicine and nursing, than in pharmacy (APPLET: Pharmacy Law and Ethics, 2006; Morley, 1993; Wingfield et al., 2004). While differences exist between the health care professions in practice, they do have much in common, however, particularly in sharing common values and principles concerning their duties toward patients (Merrills et al., 2002).

Nevertheless, each profession is distinguished by its specific role and duties, necessitating some degree of specificity in ethical principles applicable to practitioners of each health-care profession. For instance, in a case where decision-making relates to the institutionalizing of an aged patient to a nursing home, primary ethical responsibility lies with the physician, not the nurse or pharmacist. Not all principles of professional ethics applicable to medical practitioners are relevant to other health-care providers.

Hence, there is bound to be a specific scope of ethics particular to pharmacy. It may be beneficial at this point therefore to examine ethics relating specifically to the profession of pharmacy.

Professional Governance

While the primary role of a professional code of ethics is to espouse the standards of conduct, the requirements for ensuring competence in the discipline of pharmacy are often emulated by the requirement for registration. Accountability and continuous quality improvement of processes, as well as within professional development, are fundamental tenets of clinical governance (Flynn Maureen et al., 2015). Having a consistent, accountable regime to ensure all health practitioners are working to a set of standards is often embodied in legislation. Regulating health-care professions ensures that practitioners are competent and fit to practice their professions, hence protecting the patient's right to receive care commensurate with an appropriate standard (Manning, 2015). These regulations also serve an essential regulatory function as it provides a framework against which breaches of appropriate standards can be assessed.

Theoretical Foundations in Pharmacy Ethics

Ethics as it applies to the practice of pharmacy has, with only a few exceptions, mainly been articulated in codes or pronouncements from professional bodies, opinions in textbooks or debates, rather than derived on the basis of philosophical analysis of the core values in the profession (Dessing, 2000, 2002; Dorey, 1997; Wingfield et al., 2004).

An endeavor to examine the philosophical foundations of pharmacy ethics has been made in the United States over the past few decades, particularly in the works of Robert Veatch, a renowned ethicist in health care, Robert Buerki, Louis Vottero, and Amy Haddad, who specialized in pharmacy ethics, Charles Hepler, co-founder of the conceptualization of pharmaceutical care, and Joseph Fink among many others. Some research has also been conducted on moral reasoning capabilities of pharmacists in the United States (Buerki and Vottero, 1994; Buerki, 1985; Edgar, 2002; Fink, 1985; Haddad and Buerki, 1996; Haddad, 1991; Knapp, 1985; Latif, 2000a, 2000b, 2001, 2004; Salek and Edgar, 2002; Smith et al., 1991; Veatch, 1985; Vottero, 1995).

Over 20 years ago, in a conference in the United States entitled *"The Challenge of Ethics in Pharmacy Practice,"* the importance of codes and the role of society in pharmacy ethics were examined. Principles such as *beneficence*, *respect for patient autonomy*, *veracity*, *promise keeping*, *non-maleficence*, and *justice* were identified as pertinent to the practice of pharmacy. Moreover, it was observed that with the advent of contemporary patient-focused health care, a shift in ethical orientation in pharmacy practice had taken place rendering traditional paternalism (an approach in which the desire to help, advise, and protect may neglect individual choice) no longer acceptable.

That conference was a pivotal forum for the inaugural discussion of ethics in contemporary pharmacy practice, in which many ethicists presented their interpretations and perspectives. Robert Veatch analyzed the origins of some relatively newer concepts and principles in terms of fundamental theories of utilitarianism and deontology, and the relevance of these principles to pharmacy (Veatch, 1985). The challenge to the Hippocratic principle, according to Veatch, started with changes in the source of moral authority shifting from the professional as articulated in a code of professional ethics, to a broader source, which included the most important stakeholder in the health-care forum: the patient. Other challenges were the lack of training of those who wrote the codes; freedom of speech and the benefits versus risks of advertising, in their role in educating the public.

Flowing on from that, it was also highlighted that ***individualism*** (in health-care manifesting as *patient autonomy*), an essential aspect of Kant's deontology, was the second major challenge to the Hippocratic tradition, calling for changes in practice and the ethical framework within pharmacists to serve the public. The Kantian approach to applied ethics, however, does not address problems associated with fair allocation of resources among patients (*justice of distribution*), an often ignored dimension of pharmacy ethics, or of conflict between the patient's interests and society's interests—a utilitarian approach *(the greater good for the greater number)* might serve better for these issues. The deontology of Kant does, however, raise serious questions with respect to pharmacists' roles in clinical trials, about the well-being of the individual patient participating in a double-blinded placebo controlled trial (a clinical trial in which neither the subjects nor the researchers know which subjects receive active treatment, or placebo-pseudo-treatment, innocuous or inert substance).

Pharmacists' role in medical research, which is designed to increase scientific knowledge and ultimately benefit the general public, would, however, be considered unethical if the moral mandate is stated to be the benefit of the individual patient. Veatch stated that a utilitarian approach would then be the only "corrective" ethical stance. The problem with that approach would be the risk of swamping the patient in a "sea of social considerations" radically sacrificing the welfare of the patient for the benefit to society.

Veatch highlighted in addition to *autonomy*, and *justice*, the relevance in pharmacy of *veracity* and *promise keeping*, derived from the principle of respect for the individual. Interestingly, he also regarded *avoidance of killing*, albeit under the banner of *non-maleficence*, as a stand-alone principle that must be given separate attention. It would prohibit, for example, hospital pharmacists from dispensing medication in quantity and quality that could cause death of a patient; or a pharmacist from dispensing lethal doses of medication used for capital punishment or euthanasia, if the legislation so allowed (Veatch). This may now be considered slightly outdated, as countries around the world endeavor to legislate the right of patients to euthanasia and the profession of pharmacy in its capacity as

"gatekeepers of medicines" is beginning to grapple with implications of this kind of legislation, which has been in place in countries like the Netherlands, Belgium, Switzerland, some states of the United States, and recently Canada.

These analytical perceptions have enriched the tapestry of ethical reflection in pharmacy, and adequately set the scene for further discussion of some of the ethical challenges yet to be resolved, which pharmacists face on a day-to-day basis.

Ethical Concerns in the Practice of Pharmacy Today

As in any profession, pharmacists face an array of ethical dilemmas in the course of their work. Some are related to the details of a task at hand and others are broader in scope. For example, it is not uncommon for a pharmacist to be called upon to provide a medicine late at night, desperately needed to relieve the pain of an elderly patient, but without a legal prescription. The dilemma is every pharmacist's nightmare. There is every chance that compassion for the sick could lead to serious consequence for the pharmacist. As custodians of all restricted medicines, the penalty for misappropriating addictive substances in pharmacy is nothing less than suspension of license or deregistration. This ethical dilemma is clearly a practice-based example of an issue where a critical decision must be made, with little time to deliberate carefully.

Direct to Consumer Advertising

There are also ethical issues related to pharmacy, of a larger scope and/or of greater concern, than an individual pharmacist's perspective. A case in point is the role of advertising medicines generally, particularly Direct-to-Consumer-Advertising (DTCA) of prescription medicines. Although the issue is a marketing one, and of concern to the pharmaceutical industry more than the community pharmacist, its impact is, broadly speaking, one that touches most human beings' lives in one way or another. Commercial promotion of medicines manifests not only in advertising per se but also in gifts to physicians, bonuses for pharmacists, promotions, and grants. Such promotions may be evident in advertisements in the various media outlets, and even on the street. The ethics of marketing pharmaceuticals, in terms of patients' best interests, has been questioned extensively in the literature and many research studies investigating the issue of DTCA have been conducted around the world.

For instance, many studies have explored the impact of DTCA on consumers (Chaar and Lee, 2012; Joseph et al., 2008; Mintzes, 2006; Rosenthal et al., 2002), and on health-care providers, including pharmacy (Chaar, 2010; Chaar and Kwong, 2010). Pharmacists generally perceive DTCA to be disempowering to them in their role as "gatekeepers" of medicines, and are particularly challenged when a patient demands a product as a result of DTCA, that would not be in their best interests to provide them with (the dilemma of best interests of the patient versus respect for patient autonomy). It is again symbolic of the contemporary shift of ethical and moral responsibility from the practitioner to the patient. This shift can be challenging if not frustrating when the practitioner has the knowledge to discern appropriateness, safety, and efficacy of the product based on expertise and the latest evidence.

Duality of Interest

Another unique aspect of pharmacy to consider is the duality of interest vested in the business of pharmacy, resulting from the actual sale of products. Although the pharmacist is the most accessible health-care provider, and can be consulted free of charge by any passer-by, there remains the thorny issue of viability of the business in balance with patient-centered care. Hence, while the pharmacist as a professional enjoys very high levels of social/community trust around the world, almost on an annual basis scoring in the top 10 most trusted professions, there is always a shadow hanging over the integrity of the pharmacist, as an owner of a business. To maintain viability of the business, the community pharmacist must employ marketing strategies, sustaining continuity of their career and livelihood. Some pharmacists unfortunately exacerbate the perception by adopting aggressively competitive marketing ploys, thereby heightening sensitivity to the integrity and trustworthiness of his or her advice. Whether the competitive model of community pharmacy, favored by many Western country governments, is a suitably ethical framework for the profession is quite a contentious issue. Some, more regulated Northern European models of pharmacy practice could exemplify good balance between business concerns and caring for the health and well-being of patients/clients. Another approach would be to train pharmacists not just in marketing and business management, but also in business ethics, which is generally absent from pharmacy curricula.

Other ethical concerns involving pharmacists are issues such as "*conscientious objection*", "*whistle blowing,*" and the most contemporary: what is known as "*social media*" and *privacy*.

Conscientious Objection

Conscientious objection is the right a pharmacist has to refuse supply of a medication or product, as a result of a moral, religious, or other belief. This right to refuse supply is sometimes invoked when a pharmacist is approached for supply of a medicine that might be abortive or contraceptive or a substance used in euthanasia, etc.; that is, those items that may be against one's religious or personal beliefs. In such cases, the best interests of a patient do not theoretically override pharmacists' right to refuse provision of a medicine. The situation is easier to overcome when the pharmacist works in urban areas and the patient may be directed to

another pharmacy close by. It is by far more difficult for those residing in rural areas to find an alternative, with pharmacies separated by many miles of travel.

Although this contentious issue has generated large forums of global debate, no clear resolution has been found. Some states in the United States have legislated supply regardless of the professional's objection, others continue to allow for pharmacists' right to conscientious objection. The world appears to remain divided. In most countries, it is the requirement of the pharmacist to clearly display his or her reasoning in signage easily seen and understood by clients, to avoid the perception of discrimination when the unknowing patient is declined service. In one study, it was found that up to 5% of practitioners in NSW, Australia fall into the category of those who claim conscientious objection to supply the emergency contraception pill (Queddeng et al., 2011). A similar situation exists in the United Kingdom (Aultman, 2008; Wingfield et al., 2004). Despite wide debate, and some legislative resolutions in some areas, little consensus has been achieved so far, as to how best to attend to patients' needs other than to refer the patient to another practitioner (whether within the premises or outside).

Whistle-Blowing

"Whistle-blowing" or mandatory reporting of colleagues is a relatively new dimension of ethical deliberation in the practice of pharmacy. Legislation has recently been passed in some countries, requiring pharmacists to report impaired (i.e., those affected by alcohol, illicit substances, or mental illness) colleagues (Chaar, 2010). Research, currently underway, has revealed that it is a challenge to most pharmacists to have to report a colleague, and to have to cope with a number of ethical and practical concerns. These include risk of loss of employment, or loss of friends/colleagues, being known as an informer, not knowing enough about impairment, and preferring not to have to report or harm anyone. The legislation is meant to protect the public, hence based in utilitarian intent, but difficult for the practitioner to follow. Research is continuing in this area.

Social Media

Social media and privacy is another intriguing contemporary ethical concern. Increasing evidence is becoming available about the incredible expansion of Internet technologies in the last few years in the newly coined domain of "*Social Media.*" Society, in general, has enthusiastically embraced user-generated content such as blogging, personal websites, and online social networking, including health-care practitioners. Research shows that use of social media by the medical profession is common and growing. In one 2010 study, 220 out of 338 (65%) medical students at the University of Otago, New Zealand, had a Facebook account (MacDonald et al., 2010).

As health-care providers and students are increasingly participating in online social media, evidence is now emerging from studies, legal cases, and media reports that the use of these media can pose serious risks and liability for health-care professionals. Inappropriate online behavior can potentially damage personal integrity, health-care provider–patient and interprofessional relationships, and future employment opportunities. Perceptions and regulations regarding professional behavior are evolving to encompass these new forms of media. Guidelines have been developed in some countries to help guide medical students, warning them to maintain patient confidentiality at all costs, to be aware of who is accessing personal sites, to be careful to choose wisely who to allow access, and to consistently consider the destiny of any information posted on the Internet (AMA et al., 2010). These guidelines are applicable to pharmacy.

Pharmacogenetics

Another topic warranting discussion on discerning between help or hype is the emerging interest in pharmacogenetics and direct to consumer genetic testing (DTCGT)? Genetic tests are provided directly to consumers, usually via the Internet (Saukko, 2013). Consumers are provided insight into their genetic makeup and predicted risk of disease, often by sending samples from either saliva or cheek swabs (Kimberly et al., 2012; Ram et al., 2012). A health-care professional is not always involved in accessing these tests, and as a result, misunderstanding of results and inadequate provision of information is perceived by medical practitioners and pharmacists to be one of the risks associated with DTCGT (Ram et al., 2012). While the results provided by some genetic tests have established utility, others have been described as lacking clinical usefulness (Hennen et al., 2010; Saukko, 2013). Furthermore, the onset of a disease results from a complex interplay between an individual's genes, environmental factors, and lifestyle choices and not solely by a person's genetic makeup (Kimberly et al., 2012; Scott, 2011).

Data Protection

It has also recently come to light that dispensing information containing very sensitive patient material may also be subject to storage on the "Cloud" for back up and remote data access (Bratuskins, 2011). This may become all the more pertinent an issue when and if an electronic health care card for every Australian citizen is introduced and accessible to health-care providers (with permission from the patient). The complexities are difficult to fathom. The profession of pharmacy must keep abreast of all new technologies and document all incidents, including social media. It is also essential that guidelines are developed and revised constantly.

Moral Reasoning and Decision-Making in Pharmacy

Good judgment, both clinical and moral, relies on moral reasoning capabilities (Cohen, 2004). These capabilities are acquired by family influences, social assimilation, and professional integration (Thomas, 1997b). The child, born amoral, learns to think in certain ways, according to the way he or she is raised, experiential exposure to external aspects of life, education, environment, and social network (Thomas, 1997b). Cognitive moral development occurs naturally as a result of the accumulation of these processes (Kohlberg, 1976). For those who pursue professional careers, this cognitive moral development is theoretically further expanded with professional skills and acquisition of expert knowledge.

Kohlberg and Rest developed and validated a survey to measure levels of cognitive moral development, called the Defining Issues Test (the DIT), and it has been used extensively as a surrogate measure of moral development in many cohorts of people, including professionals (Rest, 1979; Rest and Narvaez, 1994; Rest et al., 1997, 1999).

Pharmacists and pharmacy students were examined in numerous studies in the United States and in Australia. It was consistently found that they did not score as highly as expected on this measure of cognitive moral development, particularly when compared to medical school students and practitioners (Latif, 1998, 1999, 2000c, 2000d, 2002, 2003; Rest and Narvaez, 1994). This curious finding, repeated in many studies, is difficult to explain; so a number of further studies have been conducted to explore trends and reasons.

In one study, findings indicated that moral reasoning of older male pharmacists in particular was consistently lower than any other group of pharmacists (Chaar et al., 2009). It is hypothesized that older male pharmacists may be less amenable to professional development, and trained in days when it was the norm for a health-care professional to behave paternalistically, and therefore might be less flexible than other age groups for change. Training in pharmacy only a few decades ago required deciphering and dispensing prescriptions written in Latin, working behind an elevated dispensary bench, maintaining a professional elitism, and evading questions asked by the patient. If the questions became too complex, the pharmacist would direct patient to return to the physician for an explanation. It was almost unheard of that a pharmacist intervened or made a suggestion to the patient or the doctor for any reason whatsoever. Some practitioners still practice somewhat, if not completely, in that mind frame.

This finding emphasized the critical importance of continuous life-long learning and professional development. For today, a prescription written in Latin would be a puzzle, and the pharmacist would not be expected to wait for a question but offer proper counseling using clear, unpaternalistic communication techniques, careful not to discriminate or disrespect any client. A pharmacist in this day and age could be sued for *not* properly counseling a patient or warning of some adverse effect that could happen.

These issues in practice are based on ethical and moral norms of the current times. Norms change with time; it is always up to the professional to keep abreast of change and not succumb to an unthinking conformity to the law or to perfunctory performance of a technical skill without exercising moral reasoning.

It also falls on professional organizations to actively promote ethical discourse, consistently revise the Code of Ethics, and provide a platform for continuing education that relates to ethical practices in community pharmacy. Codes are ordinarily regarded as legally nonbinding; however, in the course of investigating a pharmacist for professional misconduct by the local Pharmacy Board in many countries around the world, it is the code of ethics that is referred to for guidance in judging whether the practitioner's behavior can be regarded as right or wrong. On a practical basis therefore, it is crucial that the code remains up to date with contemporary issues, and clearly understood by all practitioners; and not a token document to showcase in the pharmacy dispensary.

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Clinical Pharmacokinetic Principles and Therapeutic Drug Monitoring

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Introduction

The success of pharmacotherapy can be achieved by ensuring the five rights of the medication use that is the administration of right drug to the right patient in the right dose at the right time through right route of administration. These five rights are classically included in the clinical decision-making goals of the pharmacist (Reynolds and Rupp, 2017). The selection of the right drug for the right patient depends on the right diagnosis of the underlying disease. However, the selection of right dose for the right patient requires understanding of pharmacokinetics of the drug under the clinical situations of the patients. A properly designed dosage regimen is important to achieve the therapeutic success with minimal adverse drug reactions (Leon Shargel, 2015). Variation in the individuals demands the review of dose selection and initiates the need for clinical pharmacokinetic, a discipline involving application of pharmacokinetic methods for safe and effective use of drugs in man and it is a multidisciplinary approach to individualize dosing strategies based on the disease conditions of the patients (Leon Shargel, 2015). The relationship between drug concentration in biological fluids and pharmacological effects forms the basic principle of clinical pharmacokinetics (Goodman and Gilman, 2017). During the process of drug development, dosage regimens are determined on a large number of patients, and recommendations are made to achieve the desired pharmacological response in the majority of target population. However, inter and intraindividual variability in patients may result in either subtherapeutic drug concentration or toxic drug concentration leading to the need of dose adjustment (Leon Shargel, 2015). This phenomenon is well described by the term "precision medicine," as an innovative approach for the prevention and treatment of diseases by taking into account the variability among individuals based on genetic makeup, lifestyle, and environment (US Food and Drug Administration). The individualized dosage regimen is not necessary for all the drugs as many drugs exhibit a wide therapeutic window (e.g., ibuprofen, naproxen, omeprazole, loratadine, etc.), and dose variation does not influence the safety and effectiveness of these drugs against the labeled indication (Leon Shargel, 2015). However, dose optimization for individual patients is necessary for the drugs having small

difference between minimum effective and toxic concentrations. These drugs are called narrow therapeutic window and aminoglycosides, carbamazepine, digoxin, phenytoin, ciclosporin, phenobarbital, rifampicin, theophylline, and warfarin, etc., are some common examples (Blix et al., 2010). The purpose of individualized dosage regimen for narrow therapeutic index drugs is to keep the plasma drug concentration within the therapeutic window by avoiding the fluctuation of concentration due to variability among the individuals in absorption, distribution, or elimination of drugs. The monitoring of plasma drug concentrations is important only if there is a relationship between the plasma concentration and the clinical outcome or adverse effect of a drug. The pharmacodynamic parameters may also be monitored for drugs in which clinical effect is not related to plasma drug concentration. For example, measurement of clotting time may be used for observation of anticoagulant effect of warfarin. The dose optimization for individual patients may also depend on the ability of patient to tolerate the side effects as in the case of cancer chemotherapy (Leon Shargel, 2015).

The physiological and pathophysiological changes often result in the modification of pharmacokinetic parameters, which ultimately results in the need for dose adjustment. The most important pharmacokinetic parameters that govern the dosage adjustment are clearance (CL), volume of distribution (V_D), and elimination half-life ($t_{1/2}$).

Clearance

Clearance is the volume of plasma or blood that is cleared of drug per unit time. It is the measure of the extent of drug elimination from the body without identifying its mechanism, and it can be calculated by adding the clearance from all the drug eliminating organs (Leon Shargel, 2015) as shown in Eq. (1).

$$\mathrm{CL_{Total}} = \mathrm{CL_R} + \mathrm{CL_{NR}} \tag{1}$$

where $\mathrm{CL_R}$ is the renal clearance, and $\mathrm{CL_{NR}}$ is the clearance from the organs other than kidney, which may include liver, GI tract, etc.

Alternatively, clearance can be calculated by multiplying the rate of elimination k_e by volume of distribution V of the drug as shown in Eq. (2).

$$\mathrm{CL} = k_e * V \tag{2}$$

In case where the rate of elimination process is complex, clearance can be calculated directly from area under the plasma concentration–time curve as

$$\mathrm{CL} = \frac{\mathrm{Dose}}{\mathrm{AUC}} \tag{3}$$

Volume of distribution

The volume of distribution is the second fundamental parameter that is considered for understanding the processes of drug disposition, and it makes a relationship between the amount of total drug in the body and the drug concentration in plasma or blood. This volume does not refer to actual physiological volume, but it is the hypothetical volume of fluid, which will be required to contain the whole administered drug at the same concentration as observed in plasma (Goodman and Gilman, 2017). It can be calculated as

$$V_d = \frac{\mathrm{Dose}}{\mathrm{Cp}} \tag{4}$$

where Cp is the concentration of drug in plasma. A high volume of distribution indicates that the drug is present in extravascular tissues and not in plasma. For drugs that follow a multiple exponential decay, the volume of distribution can be described as

$$V_{\mathrm{area}} = \frac{\mathrm{CL}}{k} = \frac{\mathrm{Dose}}{k.\mathrm{AUC}} \tag{5}$$

where V_{area} is the volume of distribution based on AUC, and k is the elimination rate constant, which reflects the rate of fractional elimination of the drug.

Elimination half life

Half-life is the term used to describe the time required for the plasma concentration of drug to be reduced to its half (i.e., 50%). It can be calculated by simple equation 6.

$$t_{1/2} = \frac{0.693}{k} \tag{6}$$

The half-life changes as the clearance and volume of distribution changes. Therefore, an approximate relation between all these parameters can be described by combining Eqs. (5) and (6) as

$$t_{1/2} = \frac{0.693 \times V}{\mathrm{CL}} \tag{7}$$

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) can be described as dose adjustment based on the measurement of drug concentration in serum, plasma, or other biological fluids in order to maintain the drug level within the therapeutic range of minimum effective concentration (MEC) and minimum toxic concentration (MTC) (Kang and Lee, 2009). This is not the absolute range because some patients may respond to the concentration above and below this range, and some patients may have toxicity within this so-called therapeutic range. Clinical pharmacokinetics quantifies the relationship between dose and response of drug and also describes a framework for therapeutic drug monitoring (TDM) of the patient (Goodman and Gilman, 2017). The plasma concentration of narrow therapeutic index drugs is more closely associated with the therapeutic and toxic effects than the administered dose. As the plasma concentration varies in individuals based on the metabolism and excretion of drugs, this forms the basis for TDM (Hutchinson et al., 2018). In addition to therapeutic success and patient safety, the TDM may also decrease the financial toxicity to the patients by reducing the cost of therapy.

Biological Matrices used for TDM

Only a few biological fluids can be collected safely from the patients for quantification of drug concentration and subsequent TDM. The invasive methods are painful due to surgical intervention and require the services of expert personnel. These include collection of blood samples, synovial fluid, spinal fluid, and tissue biopsy. The noninvasive methods, on the other hand, do not require surgical intervention and can be self-collected by the patients, for example, urine, feces, saliva, etc.

Blood (Plasma/Serum)

Blood sample is obtained by vein puncture and collecting the blood in a vial containing an anticoagulant such as heparin or EDTA. However, the whole blood contains cellular components such as RBCs, WBCs, and platelets, as well as various proteins such as albumin, globulin, etc. The presence of cellular components makes the whole blood unsuitable for storage as freezing will lead to hemolysis of RBCs. Moreover, it is unstable and coagulates in few minutes (Montenarh et al., 2014). Therefore, serum and plasma are most commonly used matrices for therapeutic drug monitoring. There is difference in protein contents of plasma and serum; however, both matrices have been proved comparable in terms of bioanalysis (Montenarh et al., 2014). As the blood cells are removed from plasma or serum sample, the drug concentration in these matrices reflects the concentrations in blood cells as the drug is assumed to be in dynamic equilibrium between blood cells and plasma (Leon Shargel, 2015).

Dried Blood Spot

Plasma or serum samples are the primary choices for TDM; however, the collection of blood samples may be challenging from special populations, particularly neonates and infants; therefore, other less invasive sampling techniques are used for TDM such as dried blood spot (DBS). This involves the collection of blood on a filter paper after pricking the heel or fingertip of the patient and storage of sample as dried spot of blood (Kloosterboer et al., 2018). The DBS sampling was successfully applied for TDM, and pharmacokinetic studies of tacrolimus and mycophenolic acid (Zwart et al., 2018) for antituberculosis drugs including rifampicin and pyrazinamide (Martial et al., 2018). This DBS sampling technique was proved as a reliable alternative to venous blood collection for TDM of fluconazole, voriconazole, and posaconazole. Moreover, the satisfaction level of patients DBS was also documented where most of the patients preferred DBS sampling over venous blood collection (van der Elst et al., 2013). Despite of omission of venous blood collection and success stories, this technique has also some limitations and was not proved successful for the monitoring of antipsychotic drugs (Kloosterboer et al., 2018) and ethambutol among antituberculosis drugs (Martial et al., 2018). Therefore, the application of this technique must be weighed against the errors associated with the sample collection and analysis (Edelbroek et al., 2009).

Saliva

The drug quantification in saliva is becoming more popular due to technical advancements in TDM. This has become a more valuable technique due to noninvasive nature, advantage of self-sampling, and comparability with plasma concentration because most of the drugs present in plasma are also found in saliva. If the pharmacodynamic action of drug is proportional to its plasma/serum concentration and if concentration in saliva is proved comparable to that in serum such as in case of caffeine (Chaabane et al., 2017), then this method is very useful for TDM in order to prevent distress and ensure safety in infants (Hutchinson et al., 2018). Only free drug can diffuse into the saliva; therefore, the salivary drug levels reflect only free drug rather than total plasma drug concentration (Leon Shargel, 2015). The salivary concentrations of drug have been proved suitable for TDM of several drugs, including pregabalin (Idkaidek et al., 2018), nevirapine (Lamorde et al., 2014; van Heeswijk et al., 2001), fluconazole (Koks et al., 2001), and gentamicin (Berkovitch et al., 2000).

Urine

The measurement of drug concentration in urine is the indirect method for estimation of bioavailability of drug, and this has been used for the TDM, enalapril, and its metabolites (Magiera and Kusa, 2015). However, a recent study failed to prove the suitability of urine colorimeter method for therapeutic drug monitoring of pyrazinamide (Zentner et al., 2018).

The advantages and disadvantages of each matrix are described in **Table 1**.

Table 1 Advantages and disadvantages of biological matrices used for therapeutic drug monitoring

Matrix	*Advantages*	*Disadvantages*
Plasma/serum	• Traditional and most commonly used method • Metabolites can also be measured • High drug concentration are measured • Large volume of plasma or serum can be collected • Free and bound drugs can be quantified • Also suitable for estimation of plasma protein binding	• Invasive • Requires services of expert personnel • Plasma proteins can interfere with results • Risk of infection • Painful for patients • Expensive • Storage requires special conditions
Dried blood spot	• Less invasive • Self-sampling • Suitable for neonates and infants • Low risk of infection • Storage and transportation are easy • Small blood volume	• Necessity of expensive and sensitive analytical technique is required, e.g., LC–MS. • Hematocrit can affect the sample volume adsorbed on paper • Not suitable for analysis of metabolites • Not suitable for volatile drugs
Saliva	• Noninvasive • Self-sampling • Repeated sampling is possible • Inexpensive • Low risk of infection • Less interference of lipids and proteins.	• Low volume of sample • Suitable only for free drug quantification • Blood contamination of saliva can affect the results • Highly sensitive analytical method is required • Variation in pH can affect the ionization and then drug levels
Urine	• Noninvasive • Can be tested by dried spots • Useful to quantify drug and its metabolites • Useful for estimation of renal clearance of drugs • May be used for toxicological screening	• Not suitable for all drugs • Catheterization can cause infection • Drug measurement is possible after 2–3 days of administration

Bioanalytical Techniques used for TDM

A bioanalytical method is a series of procedures used for the analysis of chemical compounds or drugs in biological matrix (Bhinge et al., 2014). Different bioanalytical methods are being used for the quantification of drugs in biological fluids and its application to TDM and pharmacokinetic studies.

Immunoassay

Immunoassays are used for quantification of drugs based on antigen–antibody reaction. The drug molecules are labeled and act as antigens to compete with other components of mixture for binding on specific sites of antibodies and form an immune complex, which is separated by physical or chemical methods. The analysis is performed by measuring the activity of labeled drug (enzymes, radiation, fluorescence, or absorbance of light) in either bound or free form (Darwish, 2006).

The most commonly used immunoassays are listed below

- Radio immunoassay (RIA)
- Fluorescence polarization immunoassay (FPIA)
- Enzyme multiplied immunoassay technique (EMIT)
- Particle enhanced turbidimetric inhibition immunoassay (PETINIA)

These immunoassay techniques have advantage of rapid analysis, which is required for decision making in TDM. Moreover, these are inexpensive and suitable for clinical settings. However, the cross-reactivity of analyte with metabolites may cause overestimation of analyte, which can ultimately affect the clinical decision making based on TDM (Gunther et al., 2013).

These immunoassay techniques have been proven comparable with one another, e.g., RIA versus FPIA (Ackerman et al., 1983) and EMIT versus FPIA (Yeo et al., 1989). The overestimation of vancomycin was observed with FPIA when compared with HPLC due to cross-reactivity of degradation products formed from analyte (Morse et al., 1987). However, PETINIA was proved comparable with HPLC (Usman and Hempel, 2016) and EMIT with LC–MS/MS for quantitation of vancomycin (Yuan et al., 2018). **Fig. 1** shows the comparison of PETINIA and HPLC for vancomycin.

HPLC

High-performance liquid chromatography (HPLC) is an analytical technique that is used for separation, identification, and quantification of the components of a mixture. The basic principle of this technique is separation of the components of a mixture based on its interaction with stationary phase and mobile phase when it is passed through a column at high pressure. The separated

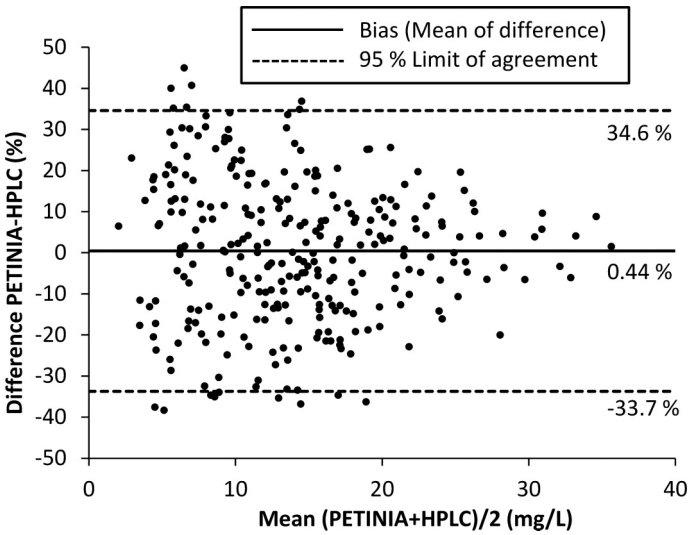

Figure 1 Comparison of HPLC and PETINIA for vancomycin in serum samples. *Adapted after permission from Usman and Hempel, 2016.*

components are then identified and quantified on the basis of signals produced through UV or fluorescent detector. The HPLC method has advantage of high sensitivity and more accuracy as compared to immunoassays. However, this is not as rapid as immunoassay and is not suitable for clinical settings. This techniques has been widely used for the quantification of a number of drugs in biological fluid for TDM and pharmacokinetic analysis such as latamoxef (Dong et al., 2018), vancomycin (Usman and Hempel, 2016), linezolid (Castoldi et al., 2017), and beta lactams (Pinder et al., 2017; Verhoven et al., 2018).

HPLC–MS/MS

This is very sensitive but expensive technique, which utilizes the separating capabilities of liquid chromatography structural identity of separated components by mass spectroscopy (Burkholz, 2014). Despite being expensive, this technique is widely used for the quantification and TDM of narrow therapeutic index drugs such as antituberculosis drugs (Gao et al., 2018), methotrexate (Mulder et al., 2018a), antibiotics (Verhoven et al., 2018), and antidepressant drugs (Weber et al., 2017).

Conditions Requiring TDM

A number of diseased conditions can affect the pharmacokinetics of drugs. Kidney and liver are major routes of drug elimination, and the impairment of these organ functions can affect the drug clearance ultimately needing for dose optimization. In addition to hepatic and renal impairment, age and clinical condition of patient can also affect the clearance of drugs. Some of the conditions requiring TDM are described below:

Renal Impairment

Kidney is the major organ for regulation of body fluids, removal of metabolic waste products, electrolyte balance, and drug elimination (Leon Shargel, 2015). The major reasons for renal impairment are listed in **Table 2**.

The condition of reduced glomerular filtration due to acute kidney disease or damage leads to *uremia* (increased level of urea in blood) and reduced excretion of drugs that are excreted through kidneys ultimately increasing elimination half-life. Uremia can also affect the pharmacokinetics in ways such as change in GIT motility, nausea, vomiting, and diarrhea, leading to reduced absorption of drugs. The change in blood volume due to impaired renal function can affect the protein level in plasma and subsequent alteration in

Table 2 Common reasons of renal failure

Cause	*Description*
Pyelonephritis	Inflammation or destruction of nephrons due to antigens, infection, or other idiopathic reasons.
Diabetes mellitus	The disturbance in metabolism of glucose and acid–base balance can affect renal status.
Hypertension	Excessive fluid and electrolyte load on kidney due to hypertension may cause kidney damage.
Nephrotoxic drugs	Certain drugs are toxic to kidney and can cause irreversible renal damage if taken chronically. Examples are aminoglycosides, vancomycin, heavy metals such as lead and mercury, etc.
Hypovolemia	Reduced blood volume leads to less blood supply to kidney and eventually leads to renal damage due to ischemia.

Table 3 Levels of renal status based on estimated creatinine clearance

Sr. No.	*Description*	*Creatinine Clearance (mL/min)*
1	Normal	>80 mL/min
2	Mild renal failure	50–88 mL/min
3	Moderate renal failure	30–50 mL/min
4	Severe renal failure	<30 mL/min
5	End-stage renal disease	Requiring dialysis

the volume of distribution of drug. The dose adjustment in case of renal impairment is made on the basis of reduced glomerular filtration rate (GFR). The exogenous (Inuline) and endogenous (Serum Creatinine) substances are used as markers for the estimation of GFR. The SeCR is formed as a product of muscle metabolism, and creatinine clearance CL_{CR} is most widely used marker for the estimation of GFR. Different formulae are used for the estimation of CL_{CR} from SeCR among those Cockcroft and Gault equation is most widely used in clinical conditions.

$$CL_{CR} = \frac{[140 - \text{age (years)} \times \text{body wt (kg)}]}{72 \times \text{Serum conc of creatinine}} \times 0.85 \text{ (for female)} \tag{8}$$

Despite the wide application, the Cockcroft and gault formula has some limitations in its applications as this is not suitable for elderly patients due to reduced production of creatinine. Moreover, this can also overestimate GFR in obese patients due to more fat contents than muscle. Therefore, use of ideal body is recommended for estimation of GFR in extremely obese patients.

Another equation is the calculation of GFR from urine collection data which is given below

$$CL_{CR} = \frac{\text{urinari excretion rate of creatinine}}{\text{Serum conc of creatinine}} \times 0.85 \text{ (for female)} \tag{9}$$

FDA describes different levels of renal impairment based on estimated GFR as given in **Table 3** (FDA Guidance for Industry, 2010).

The other less commonly used method for estimation of GFR is modification of diet in renal disease (MDRD), which utilizes serum creatinine (SeCR), age, gender, and ethnicity (Leon Shargel, 2015).

$$\text{eGFR} = 175 \times [\text{SeCR } (\mu\text{mol/L}) \times 0.011312]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$$

Serum cystatin C is another marker for GFR and was proved as an alternate of creatinine clearance for estimation of meropenem clearance and dose optimization based on renal condition of the surgical ICU patients (Kees et al., 2015).

Methods used to maintain the desired plasma concentration after multiple doses are based on renal clearance of drug. As the total renal drug clearance (Cl_T^u) is changed in uremic patients, the new dose of drug can be calculated by Eq. (10).

$$D^u = \frac{D^N Cl_T^{uN} \tau^u}{Cl_T^N \tau^N} \tag{10}$$

where D^u is the dose for uremic patient, Cl_T^u is the drug clearance in uremic patient, τ^u is the dose interval for uremic patient, Cl_T^N is the clearance of normal individual, and τ^N is the dose interval for normal patients.

If dose interval is kept constant for normal and uremic patient, Eq. (10) becomes,

$$D^u = \frac{D^N Cl_T^{uN}}{Cl_T^N} \tag{11}$$

Hepatic Impairment

Liver is also an important organ for drug elimination. Hepatic disease, therefore, can alter the elimination of drugs and necessitates the dose adjustment in order to maintain plasma level within desired concentration levels (Leon Shargel, 2015). The most common liver diseases include liver cirrhosis, chronic infection with hepatitis B and C virus, while less common diseases include biliary cirrhosis, α_1 antitrypsin deficiency, and primary sclerosing cholangitis (FDA Guidance for Industry, 2003). In addition, the drug intoxication is also a major cause for hepatic impairment (Chang et al., 2007). The dose optimization in hepatic impairment is based on the fraction of drug metabolized and cleared by impaired liver. The drug clearance in hepatic patients is calculated by equation given below

$$Cl_h = Cl(1 - fe) \tag{12}$$

wher, *fe* if the fraction of drug eliminated unchanged.

Critically Ill Patients

The varying pharmacokinetic behavior of drugs is commonly observed in critically ill patients due to unpredictable pathophysiological changes, which poses a substantial threat for the attainment of optimum outcomes, especially with antibiotics. This situation potentially challenges the clinicians to ensure appropriate antibiotic dosing. The TDM is a commonly used dosing strategy to reduce toxicity and maximize the efficacy of drugs, especially with a narrow therapeutic index. Dose optimization of vancomycin is performed through TDM in critically ill patients receiving renal replacement therapy (DelDot et al., 2004; Escobar et al., 2014; Petejova et al., 2014; Udy et al., 2013) as well as critically ill children (Giachetto et al., 2011).

Infants and Children

The dosing requirements are different for infants and children as compared to adults and necessitate a meticulous consideration of the variation in the pharmacokinetics and pharmacodynamics of a particular drug. The major source of variation in pharmacokinetics is the body composition as well as maturity levels of kidney and liver in infants and children. Body weight of children is also reported to be a significant covariate for clearance of drugs (Lo et al., 2010; Stockmann et al., 2013). A number of studies on TDM in infants and children have been reported recently due to advancement in analytical techniques (Wu et al., 2018) and requirement of small blood volume such as in dried blood spot analysis (Martial et al., 2018). The very recent TDM studies performed in children and infants have been reported for voriconazole (Allegra et al., 2018; Hu et al., 2018), antituberculosis drugs (Martial et al., 2018), and anti-TNF therapy (van Hoeve et al., 2018). Dose optimization for infants and children has also been performed by population pharmacokinetic modeling of different drugs including valproic acid (Xu et al., 2018), azithromycin (Zheng et al., 2018), piperacillin (Beranger et al., 2018), and cephalosporins (De Cock et al., 2017; Maksoud et al., 2018; Zhi et al., 2018).

Elderly Patients

The elderly population is defined as the people who are older than 65 years of age although many of these live healthy and active life. In addition, the people who are above 85 years of age are termed as older elderly (Leon Shargel, 2015). The dosing in elderly is more complex as compared to young children and infants because the decrease in homeostatic reserve occurs to a different level in each patient depending on factors including life style, eating habits, occupation, environmental factors, exposure to microorganisms, etc. (Yamni Nigam et al., 2012). These changes lead to altered pharmacokinetics of drugs and may necessitate the dose optimization. However, old age alone is not an indication for dose optimization of certain drugs (Crombag et al., 2018; Pan et al., 2018; Usman et al., 2018). In addition to physiological changes, polypharmacy due to certain pathophysiological conditions attributed to elderly patients requires special consideration for dosing due to possibility of drug interactions. Moreover, elderly patients are more prone to be affected by the adverse effects of certain drugs such as nephrotoxicity caused by vancomycin (Pan et al., 2018).

Obese Patients

Obesity is considered as a major factor for dose optimization due to altered pharmacokinetics (Grace, 2012). According to WHO database, by 2030, approximately 60% of population will be classified as overweight or obese worldwide (Kelly et al., 2008). In addition to body mass, obesity is also associated with high level of plasma proteins that are required for binding of certain drugs and ultimately affects the free drug level in plasma. This condition enhances the need for dose adjustment in obese patients (Grace, 2012). A number of studies have been reported for dose optimization of drugs in obese and morbidly obese patients (Adane et al., 2015; Alobaid et al., 2015, 2016; Grace, 2012).

Candidate Drugs Requiring TDM

The requirement for dose optimization becomes more important when the administered drug has narrow therapeutic window. Below are some examples of most commonly used drugs with the requirement of TDM.

Vancomycin

Vancomycin is used against infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible species of *Staphylococcus aureus* (MSSA) (Kullar et al., 2011; Lundstrom and Sobel, 2004; Van Bambeke, 2004). The subtherapeutic levels of vancomycin cause insufficient bacterial killing and overdosing can cause toxicity such as nephrotoxicity. Therefore, TDM of vancomycin is highly recommended for safe and effective administration (Martin et al., 2010). The recommended target trough concentration range for vancomycin is as follows:

- 10–15 mg/L for mild to moderate infection (Helgason et al., 2008),
- 15–20 mg/L for severe infection (Joint Formulary Committee, 2015).

A risk prediction model was constructed and used for the prediction of vancomycin-associated nephrotoxicity at the time of initial TDM. The patients were classified into subgroups as low to high risk of nephrotoxicity based on 5.2%–70% incidents of nephrotoxicity, respectively (Imai et al., 2018). A two point AUC-based TDM approach for vancomycin was implemented on patients with MRSA infections (Mogle et al., 2018).

Antiepileptic Drugs

The requirement of TDM for antiepileptic drugs has provided a pragmatic approach for tailored doses in order to maintain the drug concentrations at optimal levels and to ensure the successful clinical outcome (Patsalos et al., 2018). Much of the data have been accumulated for the first-generation antiepileptic drugs such as phenytoin (Shaikh and Guo, 2017), phenobarbital (Bentue-Ferrer et al., 2012; Messina et al., 2005), carbamazepine (Babaei and Eslamai, 2007; Dalaklioglu, 2013; Shokry et al., 2015; Vucicevic et al., 2007), and valproic acid (Shaikh et al., 2018; Smith et al., 2016). The therapeutic ranges for these drugs are given below (Roger Walker, 2012).

- Phenytoin 10–20 mg/L
- Valproic acid <100 mg/L
- Phenobarbital 15–40 mg/L
- Carbamazepine 4–12 mg/L

Anticancers

Cancer chemotherapy is a big challenge due to the attributed adverse effects of anticancer drugs. Most of the dosing of anticancer drugs are made on the basis of body surface area (BSA) of the patients and this may led to the interindividual variability with high risk of either under or overdosing (Wilhelm et al., 2016). The TDM studies have been conducted to optimize the dosing strategy for the patients receiving 5-fluorouracil (5-FU). The tailored dosing of 5-FU for individual patients based on TDM resulted in significantly improved therapy and minimal incidents of toxicity (Morawska et al., 2018; Wilhelm et al., 2016). Methotrexate is also a target for TDM among the anticancer drugs, and a number of analytical methods have also been reported for its quantification in order to monitor the drug concentration and optimize the dose for individual patients (Fornasaro et al., 2016; Kaneko et al., 2016; Mulder et al., 2018a; Mulder et al., 2018b; Silva et al., 2018).

Ciclosporin

Ciclosporin is a potent immunosuppressant agent and is used to prevent the graft rejection after tissue or organ transplantation. This is a narrow therapeutic index drug with high possibility of interindividual variability, which enhances the need for tailored dosing of ciclosporin (Ni et al., 2013). The whole blood drug concentration within the therapeutic range is used for dose optimization. As this is a lipophilic drug, the pharmacokinetics may be affected due to altered plasma lipid levels. Therefore, the monitoring of ciclosporin concentration in plasma is highly recommended for safe and effective administration (Sugioka et al., 2006). The target therapeutic range for ciclosporin is as (Roger Walker, 2012);

- 100–200 ng/mL for initial 6 months after transplantation
- 80–150 ng/mL from 6 month onward.

Amikacin and Gentamicin

Amikacin and gentamicin belong to aminoglycoside group of antibiotics and are considered among first choices for treatment of infections caused by *Pseudomonas aeruginosa*. These are narrow therapeutic index drugs and produce dose-related nephrotoxicity and ototoxicity (Roger Walker, 2012). Therefore, dose optimization is needed for safe therapy with these aminoglycosides. The therapeutic concentration ranges for gentamicin and amikacin are

- Amikacin 25–48 mg/L (peak) 4–8 mg/L (trough)
- Gentamicin 5–12 mg/L (peak), <2 mg/L (trough)

The TDM of amikacin has been performed in a number of clinical situations in order to keep the serum drug concentration level within the acceptable therapeutic range, which include the population pharmacokinetics of amikacin in critically ill elderly patients (Sadeghi et al., 2018) and patients with cystic fibrosis (Illamola et al., 2018). The dosing recommendation is also made based on TDM of gentamicin in a variety of populations such as neonates and infants (van Donge et al., 2018), obstetrics, and gynecology patients (Singu et al., 2018).

Digoxin

Digoxin is the oldest pharmaceutical agent used for the treatment of heart failure. This is also a narrow therapeutic agent and requires vigilant dosing strategies in order to maintain the plasma concentration within the required limit that is 0.8–2 ng/mL (Roger

Walker, 2012). Dosing strategies have been designed for safe and effective administration through the development of analytical techniques for TDM of digoxin (Dalaklioglu, 2013; Grzesk et al., 2018; Pushkin et al., 2016).

Theophylline

Theophylline has a number of clinical uses including CNS stimulation, diuresis, vasodilation, bronchodilation, and increased cardia output. Bronchodilation is the major therapeutic use of theophylline, and TDM is being performed for safe administration of this drug in chronic respiratory disease (Mennini et al., 2017). The therapeutic range for maintaining the plasma concentration of theophylline is 10–20 mg/L (Roger Walker, 2012).

Recent Advances in Clinical PK and TDM

With the advancement in analytical and sampling techniques, new developments have been introduced for TDM wherein sweat diagnosis is especially taken up by scientists with keen interest due to low volume. A novel noninvasive decentralized monitoring of lithium drug concentration through sweat analysis is proposed using all-solid-state ion-selective electrode (ISE) with a nanostructured solid-contact (SC) to detect lithium ions in sweat even under wide pH variation (pH 4–12) and with fast response (15–30 s) (Criscuolo et al., 2018). Such applications can reduce patients visit to hospitals and provide a measure of close monitoring of narrow therapeutic index medicines under chronic use.

6-Mercaptopurine and azathioprine are common treatment options for inflammatory bowel disease. With the recent discovery of Asian-specific DNA variants in NUDT gene, and their link to thiopurine toxicity, current method of TDM used for purine derivatives has shown limited applicability in this specific population (Lim and Chua, 2018). Hence, the possibility of use of knowledge of ethnicity-specific genetic markers with thiopurine metabolites measurements for predicting therapeutic response is under investigation (Lim and Chua, 2018).

Certain areas also need clarity in the need of TDM. Use of biological TDM, by measuring the serum (anti)-drug level in rheumatoid arthritis is extensively investigated but is found controversial in a recent review as the current evidence do not recommend biological TDM in the treatment of rheumatoid arthritis (den Broeder et al., 2018). However, further study is still needed in selected clinical scenarios (den Broeder et al., 2018).

Interesting findings have come across for Parkinson's disease patients, where theophylline serum levels were found to be lower than the normal human subjects. The information provides applicability of theophylline immunoassay technique used for TDM, as a new diagnostic biomarker for Parkinson's disease. Moreover, this also informs about a varying expected level of theophylline in these patients (Ohmichi et al., 2018).

Metabolomics reveal disease-specific metabolic patterns or metabolic changes produced in response to a therapeutic intervention. Potential of nuclear magnetic resonance (NMR) spectroscopy has been explored in evaluating drug efficacy as well as safety and screening toxicity. Its nondestructive, nonselective, and minimum sample preparation requirement makes it an attractive module for regulators and biopharmaceutical researchers. The technique is high-throughput (i.e., >100 samples a day is attainable) and has high reproducibility of results. Guleria et al. discuss recent developments related to NMR-based metabolomics for use in therapeutic drug monitoring and identification of organ specific toxicity along with other applications (Guleria et al., 2018).

These advances and new approaches in monitoring efficacy and toxicity of medicines will influence the future designs of clinical trials as well as their postmarketing surveillance targeting toward more rational use of drugs.

Conclusion

Therapeutic drug monitoring constitutes essential pharmacy service that is needed to ensure the efficacy and safety of drug use particularly in the pediatric and elderly patients, patients with renal and hepatic impairment, and for the narrow therapeutic index medicines. With advances in the bioanalytical techniques, application of the clinical pharmacokinetics can be made useful by fast and less invasive techniques. Use of techniques like dry blood spot has minimized many reservations previously considered with therapeutic drug monitoring.

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Clinical Pharmacy Practice: Concepts, History, and Development

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Clinical Pharmacy Concepts and Definitions

"Clinical pharmacy services optimize patient health outcomes and care" (SHPA, 2013). This is the title of the Society of Hospital Pharmacists of Australia Position Statement on Clinical Pharmacy Services, published in 2013.

In the international literature, there are many definitions for clinical pharmacy. While these different statements reflect the development and context for health-care services and medication management in different countries over time, there are common elements in these definitions.

The American College of Clinical Pharmacy (ACCP) has defined clinical pharmacy as an area of pharmacy concerned with the science and practice of rational medication use.

> Clinical pharmacy is a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; it blends a caring orientation with specialized therapeutic knowledge, experience, and judgment for the purpose of ensuring optimal patient outcomes. As a discipline, clinical pharmacy also has an obligation to contribute to the generation of new knowledge that advances health and quality of life.
>
> Clinical pharmacists care for patients in all health-care settings. They possess in-depth knowledge of medications that is integrated with a foundational understanding of the biomedical, pharmaceutical, sociobehavioral, and clinical sciences. To achieve desired therapeutic goals, the clinical pharmacist applies evidence-based therapeutic guidelines, evolving sciences, emerging technologies, and relevant legal, ethical, social, cultural, economic, and professional principles. In accordance, clinical pharmacists assume responsibility and accountability for managing medication therapy in direct patient care settings, whether practicing independently or in consultation or collaboration with other health-care professionals. Clinical pharmacist researchers generate, disseminate, and apply new knowledge that contributes to improved health and quality of life.
>
> Within the system of health care, clinical pharmacists are experts in the therapeutic use of medications. They routinely provide medication therapy evaluations and recommendations to patients and health-care professionals. Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications (American College of Clinical Pharmacy, 2008).

It should be noted that this unabridged definition is organized into three sections:

> "the discipline of clinical pharmacy, the clinical pharmacist, and the roles of the clinical pharmacist in the health care system" (American College of Clinical Pharmacy, 2008).

The International Pharmaceutical Federation and the World Health Organization published joint FIP/WHO Guidelines on Good Pharmacy Practice: Standards for Quality of Pharmacy Services (FIP/WHO, 2011).

In these guidelines Good Pharmacy Practice is stated to be

> " . . . the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care."

This comprehensive and international collaborative document provided guidance to national pharmacy professional organizations and followed the earlier publication of the 2006 Handbook on Developing Pharmacy Practice: A Focus on Patient Care (Wiedenmayer et al., 2006). The handbook provided an international approach to educate pharmacists to provide clinically oriented, patient-centered services.

Historical View of Practice of Pharmacy

Pharmacy practice and models of clinical pharmacy have developed in the context of changing health-care services and roles for many health professions. Just as technology in health care and drug development has evolved, so have the skills and knowledge requirements for practitioners. Social and cultural influences in health and society have also changed perspectives on, and expectations of, the roles of health practitioners and patients. Historically, hierarchical models of health care have reflected the social mores of the time. Increasingly, well-informed patients may view themselves as consumers and this has also influenced the approach to clinical practice for pharmacists. Patients are consumers of medicines and health information provided by pharmacists and other health professionals. In parallel, the pharmacy profession has sought to define and distinguish general and specialist practice and service roles in pharmacy. Defining and developing roles and services require approaches for education, standards of practice, and research-led practice and policy change.

While many historical definitions for pharmacy were based on preparation, procurement, supply, and distribution of pharmaceutical products, there has been an increasing understanding of patient-focused, consumer-centered health care in pharmacy practice. Pharmacists, as "experts in medicines," may contribute to the clinical assessment and management of patients with respect to medicines, often in partnership with consumers, doctors and other health professionals. These roles are broader than "supplier of medicines."

In parallel to these societal changes, global health-care costs continue to increase. There is an evidence-based approach sought for the impact and value of clinical pharmacy services with respect to patient outcomes and health-care costs (Dooley et al., 2004). Health-care spending in the United States and other high-income countries vary (e.g., in the United States 17.8% gross domestic product; Australia 9.6%; Switzerland 12.4% (Papanicolas et al., 2018)), and the increasing costs of newer pharmaceuticals contribute to these figures. Newer, high-cost drugs, along with the associated clinical services (pharmacy and other), are evaluated using health technology assessment approaches to inform policy and access. A systematic review by Schumock et al., published in 2003, reported on the evidence of the economic benefit of clinical pharmacy services and provided some methodological guidance for future studies (Schumock et al., 2003). A subsequent systematic review published in 2017, by Gammie et al., noted that economic evaluations of pharmacy services had become increasingly commonplace (Gammie et al., 2017). This review of 14 studies observed that cost-utility methods were the preferred method of economic evaluation of health-care interventions.

Clinical Pharmacy may be considered to be "part of" or "supported by" other pharmacy services and activities. There has been different terminology used, both within the profession and externally, and this may contribute to some confusion about pharmacy practice and clinical pharmacy. The notion of clinical pharmacy as being a specialist or generalist, patient-centered role has been variously interpreted. These interpretations are important, as they are crucial to pathways in professional education, practice standards, and credentialing of practitioners.

Hospital Pharmacy Services

In the Society of Hospital Pharmacists of Australia Standards for Clinical Pharmacy Services, a figure is used to illustrate the overview of hospital pharmacy services (Taylor et al., 2013). These activities are described as "patient-specific" and "nonpatient-specific," but all are required for delivery of patient care (**Fig. 1**).

Stowasser et al. have described steps in medication management as "understanding the medicines management pathway" (Stowasser et al., 2004). In this model, there are nine steps (cognitive and physical) and three background processes as depicted in **Fig. 2**. The consumer is the central to this approach, and this could be applied to all medicines, in all settings, for all health professionals. Clinical pharmacy practice may be considered as "embedded" in this pathway.

Clinical Pharmacy

Clinical pharmacy services are a range of activities, as documented in the SHPA Standards of Practice for Clinical Pharmacy Services (SHPA, 2013), and include:

- Medication reconciliation
- Assessment of current medication management
- Clinical review, therapeutic drug monitoring, and adverse drug reaction management
- Contribution to the medication management plan
- Providing medicines information

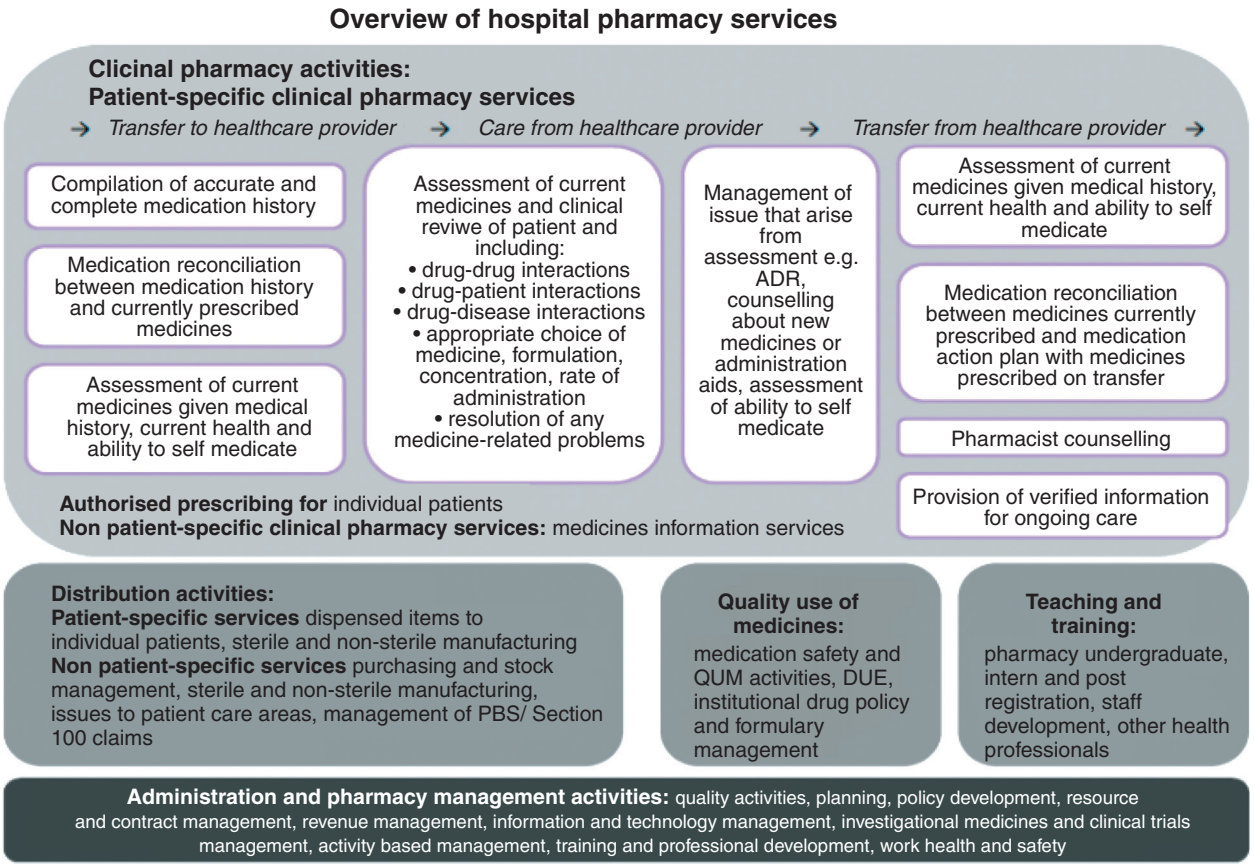

Figure 1 Hospital pharmacy services that support the medicines management pathways. *Source: Taylor, G., Leversha, A., Archer, C., et al., Overview: Standards of Practice for Clinical Pharmacy Services. J. Pharm. Pract. Res. 43 (2 suppl) (2013) S1–S5.*

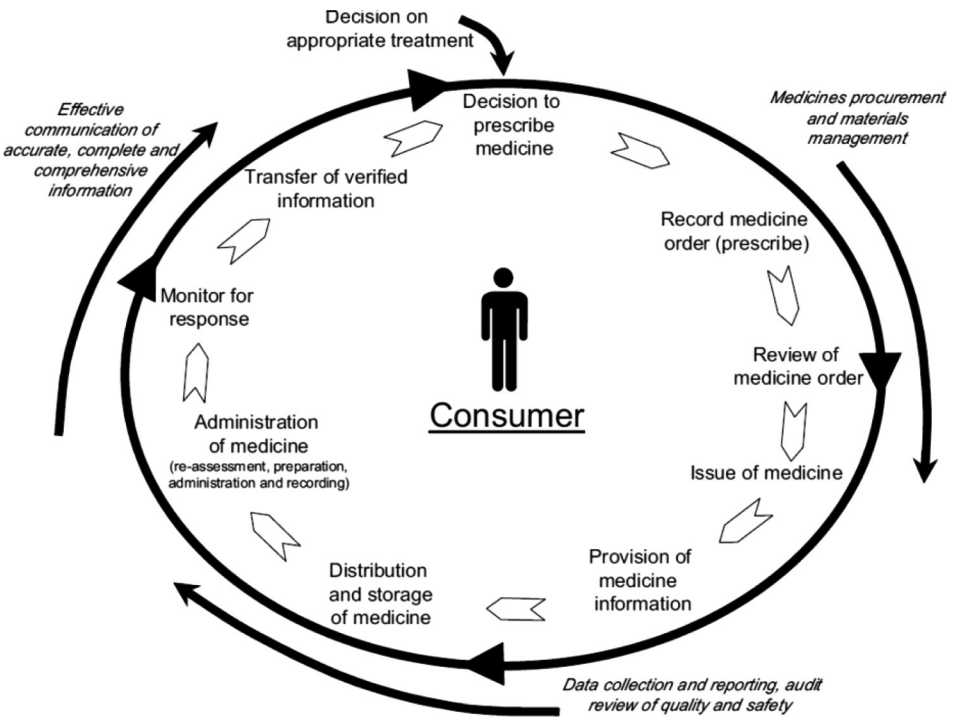

Figure 2 Overview of the medicines management pathway cycle.

- Facilitating the continuity of medication management on discharge or transfer
- Participation in interdisciplinary ward rounds and meetings
- Training and education
- Participating in research
- Quality improvement activities and peer review.

These activities are recognized as key components of medication safety and the quality use of medicines.

The American College of Clinical Pharmacy (ACCP) has sought to distinguish clinical pharmacists from other pharmacists who perform some clinical functions as part of their practice. In 2008, ACCP stated that clinical pharmacists (Burke et al., 2008):

- have a broad scope and depth of pharmacotherapy knowledge and clinical skills;
- spend most of their time providing pharmacotherapy independently or in collaboration with other health-care providers;
- have completed postgraduate residency training; and
- maintain and further develop competence through practice and continued professional development.

In 2016, the ACCP Certification Affairs Committee reviewed and updated these competencies, with the expectation that clinical pharmacists

> "be competent in six essential domains: direct patientcare, pharmacotherapy knowledge, systems-based care and population health, communication, professionalism, and continuing professional development. Although these domains align with the competencies of physician providers, they are specifically designed to better reflect the clinical pharmacy expertise required" (Saseen et al., 2017).

The ACCP has defined clinical pharmacists as

> "practitioners who provide comprehensive medication management and related care for patients in all health care settings" (American College of Clinical Pharmacy, 2014).

ACCP's definitions of clinical pharmacy and required competencies for the clinical pharmacist are composed of statements that encompass the core competencies identified by the Institute of Medicine:

(1) provide patient-centered care to diverse populations,
(2) work effectively as members of interprofessional teams,
(3) employ evidence-based practice to optimize care,
(4) apply quality improvement techniques, and
(5) use informatics in practice (Institute of Medicine, 2003).

These five attributes represent the overarching core competencies for members of all health professions.

Internationally, there have been developments in recognition of, and requirements for, further education and training for advanced (clinical) practice, through residency or certification and credentialing programs. It is generally agreed that clinical pharmacy competence is supported by additional knowledge, skills, and experience during postgraduate clinical training and/or after entering clinical practice (Murphy et al., 2006). It has long been recognized that local national reimbursement models have an impact on clinical pharmacy practice, education, and training (Penna and Knapp, 1986). While education pathways vary across the world, the publication of standards of practice and definitions has assisted the development of clinical pharmacy globally.

An integral component of the definition and development of clinical pharmacy is the incorporation of research-led practice. This is in both the evidence-based approach to therapeutics for individual patients and populations, as well as the research-led models of practice and assessment of impact of clinical pharmacy service provision. A number of research studies have explored the impact of clinical pharmacy services in the hospital setting.

A systematic review of clinical pharmacists and inpatient medical care published in 2006 concluded that:

> "the addition of clinical pharmacy services in the care of inpatients generally resulted in improved care, with no evidence of harm. Interacting with the health care team on patient rounds, interviewing patients, reconciling medications, and providing patient discharge counseling and follow-up all resulted in improved outcomes" (Kaboli et al., 2006).

A seminal series of papers published by Bond, Raehl et al. demonstrated direct relationships and associations between clinical pharmacy services, pharmacist staffing, and drug costs in United States hospitals (Bond et al., 1999a) (as clinical pharmacy staff increased, drug costs decreased) and found associations between health-care professional staffing, hospital characteristics, and mortality rates hospital mortality rates (Bond et al., 1999b) (pharmacists were associated with lower mortality rates). In 2001, Bond, Raehle, and Franke published a comprehensive study evaluating interrelationships among mortality rates, drug costs, total cost of care, and length of stay in United States hospital and provided recommendations for clinical pharmacy services and staffing (Bond et al., 2001). In 2007, a follow-up study on clinical pharmacy services, pharmacy staffing, and hospital mortality rates confirmed previous findings that an increase in clinical pharmacists was associated with reduced mortality rates (Bond and Raehl, 2007). As Angaran had noted in his commentary—"Clinical pharmacy saves money and lives—so what's new?" (Angaran, 1999). Further to these studies, Bond, Raehl, and Patry published recommendations for evidence-based core clinical

services in United States hospitals in 2020 (Bond et al., 2004). The core services identified in their series of studies were "drug information, adverse drug reaction management, drug protocol management, attending medical rounds, and admission drug histories" (Institute of Medicine, 2003).

Clinical Pharmacy in Community Pharmacy Settings

It should be noted, however, that the understanding of clinical pharmacy should not be limited to pharmacists working within a hospital environment. The application of clinical pharmacy skills and knowledge is important in both primary and tertiary health care. In an opinion statement of the of the Ambulatory Care Practice and Research Network of the American College of Clinical Pharmacy (ACCP), it is stated that

> " . . . pharmacists can improve the health of populations by participating in activities that optimize medication management. Multiple published articles support clinical pharmacist involvement in the Patient Centered Medical Home (PCMH) with regard to promotion of team-based care, enhanced access, care coordination, and improved quality and safety of care. A survey of clinical pharmacist members of ACCP who operate in such a model depict a variety of activities, with some members pioneering new and innovative ways to practice clinical pharmacy. Although this is a significant opportunity for pharmacists in the primary care setting, a unified vision of pharmacy services is needed" (Nigro et al., 2014).

There are differences in national and regional health-care regulatory jurisdictions which influence organization of, and reimbursement for, professional pharmacy services. Nonetheless terminology a "unified vision" of pharmacy services may remain difficult when different terminology is applied.

The different definitions and interpretations of pharmacy practice and clinical pharmacy are also important for the promotion of global education for pharmacists. The International Pharmaceutical Federation (FIP) Pharmacy Education Taskforce, whose objective was to develop pharmacy education globally using a local needs-based approach, published a commentary about the difficulties in applying consistent terminology, with regard to pharmaceutical care and pharmacy practice (Whitmarsh et al., 2010).

Pharmaceutical Care

Pharmacists make decisions daily in their practice—managerial, nonclinical, and clinical (Bridie et al., 1980), and in recent decades there has been an established literature basis for recognizing, understanding, and teaching clinical decision making (Einarson et al., 1985). Teaching methods in health disciplines have historically focused on facts and data collection and analysis, rather than decision making. Protocols and algorithms may assist but may not always enlighten clinical judgment. While problem solving and decision making are separate processes, solving a problem that is defined by a number of choices may lead to a decision (Angaran, 1999). Clinical judgment is based on effective decision making.

In 1990, Hepler and Strand provided a taxonomy for pharmacy practice and defined "pharmaceutical care."

> "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Strand, 1990).

Strand et al. developed the framework for pharmaceutical care based on the utility of definitions for drug-related problems (DRPs). In the paper, "Drug-related problems: their structure and function" a means of categorizing DRPs was presented: (Strand et al., 1990)

> "A DRP exists when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy. Eight different categories of DRPs are described and examples of each category are offered. This categorization serves a number of functions, such as: (1) to illustrate how adverse drug reactions form but one category of extant DRPs, (2) to make tangible the pharmacist's role for the future, (3) to serve as a focus for developing a systematic process whereby the pharmacist contributes significantly to the overall positive outcome of patients, (4) to bring to pharmacy practice a vocabulary consistent with that of other healthcare professionals, and (5) to aid in the development of standards of practice for pharmacists."

In adopting the definition for pharmaceutical care in 1998, the International Pharmaceutical Federation (FIP) added one significant amendment:

> "achieving definite outcomes that improve or maintain a patient's quality of life."

The term "pharmaceutical care" has been used broadly as a philosophy of practice, and "comprehensive pharmaceutical care" has been offered to better describe value-added services (Tomechko et al., 1995). However, although the term has spread among different countries, pharmaceutical care is now less used in the United States and is more commonly superseded by medicines management, or medication therapy management services in the UK and elsewhere (Kaboli et al., 2006).

A number of commentators have contributed to these international discussions on terminology and definitions. Simpson wrote "What is medicines management and what is pharmaceutical care?" (Simpson, 2001) McGiveny et al provided comment on the

relationships between medication therapy management, patient counseling, disease management, and pharmaceutical care (McGivney et al., 2007). Barber has asked "Pharmaceutical care and medicines management—is there a difference?" (Barber, 2001)

Twenty-three years after Hepler and Strand published their definition of pharmaceutical care, the Pharmaceutical Care Network Europe (PCNE) has provided an updated definition, intended to be applicable for the present time, representative for various work settings, and valid for countries inside and outside of Europe: (Allemann et al., 2014)

> "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes."

Quality Use of Medicines and Medicines Policy

Irrespective of physical location and setting for pharmacy practice, the desired outcomes for clinical pharmacy services are well described in achieving the Quality Use of Medicines.

"Quality Use of Medicines" means:

- Selecting management options wisely by:
  - considering the place of medicines in treating illness and maintaining health, and
  - recognizing that there may be better ways than medicine to manage many disorders.
- Choosing suitable medicines if a medicine is considered necessary so that the best available option is selected by taking into account:
  - the individual
  - the clinical condition
  - risks and benefits
  - dosage and length of treatment
  - any coexisting conditions
  - other therapies
  - monitoring considerations
  - costs for the individual, the community, and the health system as a whole.
- Using medicines safely and effectively to get the best possible results by:
  - monitoring outcomes,
  - minimizing misuse, over-use, and under-use, and
  - improving people's ability to solve problems related to medication, such as negative effects or managing multiple medications.

This definition of QUM applies equally to decisions about medication use by individuals and decisions that affect the health of the population (The National Strategy, 2002).

The Quality Use of Medicines (QUM) is incorporated in the Australian National Medicines Policy and strategy (Bond et al., 2004). Australia began to develop aspects of the National Medicines Policy in the 1950s, and by the 1990s a comprehensive policy was in place. In 1999, a formal policy document entitled *Australia's National Medicines Policy* was launched (National Medicines Policy, 2000). Around the world, many countries have, or are in the process of developing, national policies on medicines (Hoebert et al., 2013).

The World Health Organization (WHO) has defined rational drug use:

> "Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met" (Holloway and van Dijk, 2011).

Furthermore, the WHO has added the complementary term "responsible use of medicines" that:

> "implies that the activities, capabilities and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them. This incorporates the importance of stakeholder responsibility and recognizes the challenge of finite resources" (World Health Organization, 2012).

Whether at the level of population data or for individual patient management, adherence to "rational and responsible" medications remains elusive. There is evidence that approximately 50% of all patients fail to take their medicine correctly (World Health Organization, 2003) and in many circumstances, the capability of the (health) system is not sufficient to support the optimal use of medicines (The National Strategy, 2002). The fact that prescribed medicines are not taken, as so often is assumed, occurs in highly regulated clinical trials and resource rich environments (Azvolinsky, 2014), as well as in community settings in management of chronic illnesses. Identifying and managing medicines adherence is one core element of pharmaceutical care and clinical pharmacy.

Historical Perspectives

A contemporary view of health care and health professionals is enriched by consideration of some historical perspectives and milestones. While there is focus on current definitions of clinical practice roles and training, it is of note to recognize that this is a continuum.

A description of the hospital of Altopascio (Italy), in 1239, reveals details of clinical staff roles (apothecary, surgeon, physician, and other) and responsibilities with regard to diagnosis, treatments and patient care (Henderson, 2006). Apart from supply of medications, the pharmacy emphasis appears to be on evidence-based formulary management and safety. There were a range of contractual arrangements between hospitals and *speziale* (specialist hospital pharmacists). The staff (and patients) of renaissance hospitals had a wide range of flexibility in roles and different terminology was used, and contracts were used to define responsibilities.

In a contract dated 1507, it is stated that, apart from " . . . making medicines and syrups . . . ," the pharmacist needed to

> " . . . take care not to make mistakes at the times when a patient's fever is increasing . . . ."

A note book was used to record treatments prescribed on daily ward rounds. The pharmacist made up the treatments, and there is guidance on labeling clearly so the right patient received the medication (Azvolinsky, 2014).

In a commentary on the period between the two world wars in the twentieth century, author Isabel Leighton dubbed the era as the "aspirin age," a social commentary on the search for a "cure all" (Leighton, 1949). In 1966, Magnus Pyke captured the sense of excitement about modern science and advances in his book "What scientists are up to," including a chapter on "What medical research is up to" (Pyke, 1966). These are reminders of how clinical practice is embedded in and influenced by in the social, cultural, and scientific milieu of the time. In the twenty-first century, there are expectations that current advances in genomics, big data, robotics will have an impact on all aspects of living, including the practice of pharmacy and delivery of health care. National and international statements of professional roles, knowledge, and skills will continue to be progressed to meet the changing environments.

Future Perspectives

As Carter outlined in his 2016 overview of the evolution of clinical pharmacy and future directions:

> "Clinical pharmacy services and direct patient care have a promising future in many countries. Clinical pharmacists are now more specialized for specific services or complex care. Recent advances in education and clinical pharmacy research enabled development of clinical pharmacy services in many countries all over the world. The large increase in complex older patient populations suggests that the involvement of clinical pharmacists in interdisciplinary care will become more important to improve medication safety, efficacy and effectiveness" (Carter, 2016).

As health care continues to become even more complex and expensive, pharmacists will continue to develop and define clinical roles that are patient-centered, research-led, evidence-based, and cost-effective. Updated knowledge and skills for clinical pharmacy practice will require more integrated, interprofessional, and rigorous education and professional standards. The historical context for the development of clinical pharmacy practice provides a sound basis for future pharmacists. International collaborative approaches to inform and articulate standards for education and practice are key. The published revision of the International Pharmaceutical Federation's "Basel Statements on the future of hospital pharmacy: From Basel to Bangkok" (Vermeulen et al., 2016) provides an example of guidance for the pharmacy profession, health-care funders, and consumers.

Basel Statements on the Future of Hospital Pharmacy: From Basel to Bangkok

Overarching and Governance Statements

1. The overarching goal of hospital pharmacists is to optimize patient outcomes through collaborative, interprofessional, responsible*use of medicines, and medical devices.
2. At a global level, evidence-based hospital pharmacy practice standards should be developed. These should assist national efforts to define standards for the extent and scope of hospital pharmacy services and should include corresponding human resource and training requirements.
3. Hospital pharmacists should engage health authorities and hospital administrators to ensure appropriate resources for, and design of, the hospital medicine-use process.
4. Health authorities should ensure that each hospital is serviced by a pharmacy that is supervised by pharmacists who have completed advanced training in hospital pharmacy.
5. The Chief Pharmacist/Director of Pharmacy should be the accountable professional coordinating the responsible use of medicines* in the hospital.
6. Hospital pharmacists should serve as a resource regarding all aspects of medicines use and be accessible as a point of contact for patients and health-care providers.

7. All prescriptions should be reviewed, interpreted, and validated by a hospital pharmacist prior to the medicine being dispensed and administered.
8. Hospital pharmacists should monitor patients taking medicines to assure patient safety, appropriate medicine use, and optimal outcomes for inpatients and outpatients. When resource limitations do not permit pharmacist monitoring of all patients taking medicines, patient-selection criteria should be established to guide pharmacist monitoring.
9. Hospital pharmacists should be allowed to access and document in the full patient record.
10. Hospital pharmacists should ensure that patients or caregivers are educated and provided written information on the appropriate use of medicines.
11. Hospital pharmacists should provide orientation, drug information and education to nurses, physicians, and other hospital staff regarding best practices for medicines use (a best practice is a method or technique that has consistently shown results superior to those achieved with other means and that is used as a benchmark).
12. Undergraduate pharmacy curricula should include hospital-relevant content, and postgraduate training programs and specializations in hospital pharmacy should be developed.
13. Hospital pharmacists should actively engage in research into new methods and systems to improve the use of medicines and of human resource needs in hospital pharmacy.
14. Hospital pharmacists should take responsibility for the management and disposal of waste related to the medicine-use process and advise on disposal of human waste from patients receiving medicines.
15. Hospital pharmacists should take responsibility for all aspects of selection, implementation, and maintenance of technologies that support the medicine-use process, including distribution devices, administration devices, and other equipment.
16. Hospital pharmacists must ensure proper storage to maintain the integrity of medicines across the supply chain to ensure quality, safety, and security.
17. Hospital pharmacists should ensure appropriate assessment, development, implementation, and maintenance of clinical decision support systems and informatics that guide therapeutic decision making and improve the medicine-use process.
18. Each pharmacy should have contingency plans for medicine shortages and emergencies.
19. The "seven rights" (right patient, medicine, dose, route, information, documentation, and time) should be fulfilled in all medicine-related activities in the hospital.

Theme 1—Procurement

20. Hospital pharmacists should be involved in the complex process of procurement of medicines and health products, promoting equity and access. They should ensure transparent procurement processes are in place in line with best practice and national legislation, are free from conflict of interest, and are based on the principles of safety, quality, and efficacy.
21. Procurement practices must be supported by strong quality assurance principles, regularly reviewed, and adapted to fit different settings and emerging needs in the most appropriate and cost-effective way.
22. Procurement should not occur in isolation but rather be guided by the formulary selection process. This includes the procurement of standard concentrations of high-risk medicines including electrolytes.
23. Procurement must be supported by a reliable information system that provides accurate, timely, and accessible information.

Theme 2—Influences on Prescribing

24. Hospitals should utilize a medicine formulary system (local, regional, and/or national) linked to standard treatment guidelines, protocols, and treatment pathways based on the best available evidence.
25. Hospital pharmacists should be key members of pharmacy and therapeutics committees to oversee all medicines management policies and procedures, including those related to off-label use and investigational medicines.
26. Hospital pharmacists should have a key role in educating prescribers at all levels of training on the access to and evidence for responsible use of medicines, including the required monitoring parameters and subsequent prescribing adjustments.
27. Hospital pharmacists should be an integral part of the multidisciplinary team responsible for therapeutic decision making in all patient care areas.
28. Hospital pharmacists should promote seamless care by contributing to the transfer of information about medicines whenever patients move between and within health-care settings.
29. Appropriately trained and credentialed hospital pharmacists should participate in collaborative prescribing.

Theme 3—Preparation and Delivery

30. Hospital pharmacists should assume responsibility for storage, preparation, dispensing, and distribution of all medicines, including investigational medicines.

31. Hospital pharmacists should assume responsibility for the appropriate labeling and control of medicines stored throughout the facility.
32. Hospital pharmacists should be involved in determining which medicines are included in ward stock and standardizing the storage and handling of ward medicines.
33. Hospital pharmacists should ensure that compounded medicines are consistently prepared to comply with quality standards. This includes taking responsibility for ensuring medicines not commercially available in a suitable formulation are prepared to accepted practice standards and ensuring that injectable admixture services comply with accepted practice standards.
34. The preparation of hazardous medicines including cytotoxics should be under the responsibility of the hospital pharmacist and prepared under environmental conditions that minimize the risk of contaminating the product and environment minimize exposure of hospital personnel to harm using accepted practice standards.
35. Hospital pharmacists should implement evidence-based systems or technologies (e.g., automated prescription filling, unit dose distribution, machine-readable coding systems) to decrease the risk of medication errors.
36. Hospital pharmacists should support the development of policies regarding the use of medicines brought into the hospital by patients, including the evaluation of appropriateness of complementary and alternative medicines.
37. Hospital pharmacists should implement systems for tracing medicines dispensed by the pharmacy (e.g., to facilitate recalls).
38. Concentrated electrolyte products (such as potassium chloride and sodium chloride) and other institutionally identified high-risk medicines should be dispensed in ready-to-administer dilutions and stored in secure, separate areas with distinct labels.
39. Hospital pharmacists should develop simple, rules-based approaches to advancing patient safety; for example, when a large number of dosage units are needed to give a dose (more than two tablets, vials, etc.), the prescription should be verified prior to preparation or dispensing.

Theme 4—Administration

40. Hospital pharmacists should ensure that the information resources needed for safe medicines preparation and administration are accessible at the point of care.
41. Hospital pharmacists should ensure that clinically relevant allergies, drug interactions, contraindications, past adverse events, and other relevant medication history details are accurately recorded in a standard location in patient records and evaluated prior to medicine use.
42. Hospital pharmacists should ensure that medicines are packaged and labeled to ensure identification and to maintain integrity until immediately prior to administration to the individual patient.
43. Medication labels should be clear and have sufficient information to ensure safe administration, including at least two patient identifiers, the name of the medicine, prescribed route, dose in mass and, where appropriate, volume, and rate of administration.
44. Hospital pharmacists should ensure that health-care professionals who administer medicines are appropriately trained in their use, hazards, and necessary precautions.
45. Doses of chemotherapy and other institutionally identified high-risk medicines should be independently checked against the original prescription by at least two health-care professionals, one of whom should be a pharmacist, prior to administration.
46. Hospital pharmacists should develop and implement policies and practices that prevent route errors. Examples include

    a. Labeling of intravenous tubing near insertion site to prevent misconnections,
    b. Use of enteral feeding catheters that cannot be connected with intravenous or other parenteral lines,
    c. Packaging vinca alkaloids to prevent inadvertent intrathecal administration,
    d. Use of oral syringes that are distinctly different from hypodermic syringes to prevent injection of enteral or oral medicines.

47. Hospital pharmacists should ensure the development of quality assurance strategies for medicines administration to detect errors and identify priorities for improvement.
48. The medicines administration process should be designed such that transcription steps between the original prescription and the medicines administration record are eliminated.

Theme 5—Monitoring of Medicines Use

49. An easily accessible reporting system for defective medicines should be established and maintained. Reports of defective or substandard medicines should be reviewed internally and sent in a timely manner to regional or national pharmacovigilance or regulatory reporting programs and the manufacturer.
50. An easily accessible reporting system for adverse drug reactions should be established and maintained. Reports of reactions should be reviewed internally and sent in a timely manner to regional or national pharmacovigilance or regulatory reporting programs. These data should be regularly reviewed to improve the quality and safety of medicine-use practices.
51. An easily accessible, nonpunitive reporting system for medication errors, including near misses, should be established and maintained. Reports of medication errors should be reviewed internally and sent to regional or national medication error

reporting or regulatory programs. These data should be regularly reviewed to improve the quality and safety of medicine-use practices.

52. Medicine-use practices should be self-assessed and compared with benchmarks and best practices to improve safety, clinical effectiveness, and cost-effectiveness.
53. The medicine-use process should be reviewed through an external accreditation or quality-improvement program. Hospitals should act on reports to improve the quality and safety of their practices.
54. Pharmacists' clinically relevant activities should be documented, collected, and analyzed to improve the quality and safety of medicine use and patient outcomes. Activities that significantly impact individual patient care should be documented in the patient record.
55. Systematic approaches (e.g., trigger tools) should be used to provide quantitative data on adverse drug events and optimal medicine use. These data should be regularly reviewed to improve the quality and safety of medicines practices.

Theme 6—Human Resources, Training, and Development

56. At a national level, competency frameworks are defined, established, and regularly assessed.
57. At a national level, hospital pharmacists should engage health authorities to bring together stakeholders to collaboratively develop evidence-based hospital pharmacy human resource plans to support the responsible use of medicines, including those in rural and remote areas.
58. Hospital pharmacists should work with key stakeholders to ensure that work-force education, training, competency, size, and capacity are appropriate to the scope of services, coverage, and responsibilities of all cadres providing pharmacy services.
59. Hospital pharmacy work-force plans should describe strategies for human resource education and training, recruitment and retention, competency development, remuneration and career progression pathways, diversity-sensitive policies, equitable deployment and distribution, management, and roles and responsibilities of stakeholders for implementation.
60. Hospitals should maintain human resource information systems that contain basic data for planning, training, appraising, and supporting the work force. Data should be collated at a national level to improve work-force planning.
61. The training programs of pharmacy support staff should be nationally formalized, harmonized, and credentialed within a defined scope of practice.
62. Hospital human resource policies should be founded in ethical principles, equity, and human rights and be compliant with labor regulations, guidelines, and hospital pharmacy practice standards.
63. Hospitals should use the nationally accepted competency framework to assess individual human resource training needs and performance.
64. To promote interprofessional education and team-based care, the role of hospital pharmacists, including collaborative prescribing, should be included in the curricula of other health-care professionals, and the roles of other health-care professionals should be included in the pharmacy curricula.
65. Postgraduate clinical courses should be developed to prepare hospital pharmacists for collaborative prescribing of medicines, including instruction in legal and professional accountability.

* The responsible use of medicines means

- That a medicine is only used when necessary and that the choice of medicine is appropriate based on what is proven by scientific and/or clinical evidence to be most effective and least likely to cause harm. This choice also considers patient preferences and makes the best use of limited health-care resources.
- There is timely access to and the availability of quality medicine that is properly administered and monitored for effectiveness and safety.
- A multidisciplinary collaborative approach is used that includes patients and those in addition to health professionals assisting in their care.

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Development of Therapeutic Guidelines

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Synonyms

Medical guidelines - Clinical guidelines - Clinical pathways- Clinical practice guidelines - Drug therapy guidelines - Therapeutic guidelines – Standard treatment guidelines

Definition of Terms

Clinical guidelines are recommendations on the appropriate treatment and medical care of specific diseases and conditions. They are based on the best available evidence in order to help health-care professionals with their mission, but they do not replace the professional's knowledge, skills, and clinical judgment. Another but similar definition of clinical guideline is "a systematically developed guidance document prepared to assist health-care staff in the safe diagnosis, prescribing, preparation, control, and administration of medicines for specific clinical conditions" (Gagliardi et al., 2011; Gopalakrishnan et al., 2014; Steinberg et al., 2011).

According to the Institute of Medicine (IOM), clinical practice guidelines are defined as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." In brief, clinical practice guidelines are recommendations for clinicians about the care of patients with specific conditions (Inistitute of Medicine [IOM], 2011).

Some guidelines come in the form of algorithms, which in turn, identify all available and possible decision options and their health outcomes. Clinical guidelines are derived from top quality evidence, most up-to-date data and best practical experience about the prevention, diagnosis, prognosis, and therapy of specific disease(s). They contain some data on the dosage of drugs, risk/benefit, and sometimes cost-effectiveness of therapeutic and/or diagnostic interventions (Woolf et al., 1999).

Terms and Concepts that are Interchangeable with Therapeutic Guidelines

One might think that clinical and therapeutic guidelines are two different terms. Yet, in the literature, the two terms are used interchangeably giving the same meaning. There are many terms that have been used interchangeably with therapeutic guidelines such as clinical practice guidelines, clinical pathways, medical guidelines, drug therapy guidelines, and these will be used throughout this chapter.

The Difference between Evidence-based Guidelines and Consensus/Expert Guidelines

Evidence-based guidelines are the guidelines developed using systematic reviews to report specific clinical situations (Lim et al., 2008). They are developed through a thorough literature review, critical evaluation of the evidence's quality, and interpreting the outcomes according to the patient's preferences and societal values (Guyatt et al., 2004). In order to develop an evidence-based guideline, the clinical question that will be addressed needs to be determined first, followed by setting the eligibility criteria for the included studies in the guidelines' development. Then a systematic literature review is performed, and the evidence is appraised (Guyatt et al., 2008a). The quality of the included studies is graded by a grading system that reflects the guideline's strength and the quality of supporting evidence (Kavanagh, 2009).

Evidence-based guidelines benefit both the patients and health-care providers. From a patient's perspective, guidelines improve the quality of care by backing the useful interventions and discouraging harmful ineffective ones, which eventually decreases the mortality and morbidity and improve the quality of life of patients and benefit the society as a whole (Grimshaw and Russell, 1993). Guidelines can augment consistency of care so that the patients with similar clinical problems receive a consistent and appropriate treatment irrespective of the place or the person offering the treatment (Lim et al., 2008). From a health-care provider's perspective, guidelines improve the quality of clinical decisions; as they act as a reference for clinicians who are uncertain about their interventions (Grimshaw and Russell, 1993).

There are some limitations to evidence-based guidelines. The guideline can be erroneous due to lack of evidence as there are few medical areas that are guided by high number of high-quality studies. Another limitation is that the guideline can be misleading due to limitations in the studies used as evidence leading to biased results. Eventually, guideline's authors can misinterpret the evidence due to conflicts of interest (Grol et al., 1999). These limitations can be overcome by critical valuation and grading of the guidelines (Lim et al., 2008).

The publication by the American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy serves as an example for evidence-based guidelines (Hirsh et al., 2008). This publication provides new important information in the management of thromboembolic disorders.

Consensus guidelines are defined as "systematically developed statements to assist practitioner's and patient's decision about appropriate health care for specific clinical circumstances" (Goodman and Baratz, 1990). The purpose of consensus is to advise health-care providers about the most acceptable way to make a particular decision in diagnosis, management, or treatment. Consensus statements provide new data mainly from recent and ongoing research that may participate in reevaluation of routine medical practices. However, consensus statements do not offer specific algorithms as they are dependent on cost, available expertise, and local circumstances. For production of consensus statement, an independent team of experts are brought to meet together usually by a medical association or governmental authority. The consensus declares the general opinion of the participant experts, but this does not mean that they all agreed on that opinion. Consensus statements must be reevaluated often as they represent the time frame when they are announced (De Boeck et al., 2014). An example for consensus guidelines is the World Heart Federation Expert Consensus Statement on Antiplatelet Therapy in East Asian Patients with Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention (Levine et al., 2014).

What Therapeutic Guidelines are not?

As important as it is to understand the purpose of therapeutic guidelines, understanding what therapeutic guidelines are not intended for is important too. Without this understanding, health-care providers may be concerned about the effect of therapeutic guidelines on their professions and organizations may misuse the guidelines in situations where they were never intended. Guidelines are *not* reimbursement policies, performance measures, legal precedents, measures of certification or licensing, not for provider selection or public reporting, or recipes for "cookbook medicine" (Rosenfeld et al., 2013)

Guidelines are never meant to replace professional decision; yet, they may be viewed as a relative restriction on individual clinician judgment in a certain clinical circumstances (Marcuse and Shiffman, 2004). Guidelines simply express the best decision of a team of experienced clinicians and methodologists responding to a particular situation by scientific evidence. Eventually, therapeutic guidelines are not intended for cost control or health-care rationing (Rosenfeld et al., 2013).

History of Development of Therapeutic Guidelines

Historically, textbooks were used as the main sources of information needed for the management of diseases. They were revised every now and then in order to be updated with the latest changes in clinical practice (Dubois and Dean, 2006). However, there was always a time lag between the time content of a book is compiled and the time of publication, where the information often becomes outdated. Many years later, clinical practice guidelines replaced textbooks as primary resources for disease management in clinical practice.

Although available data about the emergence of guidelines are lacking and imprecise, it is apparent that therapeutic guidelines were first produced in the late 1970s in Australia when there was a need to think about outlines that can regulate the use of antibiotics (Hemming et al., 2003). Concerns surrounding bacterial resistance surfaced after inappropriate antibiotic use in Melbourne Teaching Hospitals (Pavillard et al., 1982). This first known guideline consisted of 31 pages focused on antibiotic usage and included guidelines for the use of 31 antibiotics in 59 different indications. These guidelines document was adopted in Victoria's public hospitals where it was printed in the size of the physician's whitecoat pocket. The guidelines were regarded as a good aid for clinicians in decision making for both clinical and cost-effectiveness outcomes. Also it was used as a source of continuous learning. Subsequently, other guidelines were developed. Some examples of the earliest guidelines include:

- The first version of the Joint National Committee (JNC) guidelines, specialized in the management of high blood pressure, appeared in 1977 (Joint National Committee, 1977)
- Analgesic guidelines by World Health Organization (WHO), entitled "WHO Guidelines for the Use of Analgesics in Cancer Pain," was published in 1985 (Ventafridda et al., 1985).
- The first respiratory guidelines were published by the American Thoracic Society in 1987 entitled "American Thoracic Society Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma" (American Thoracic Society, 1987).
- The first guidelines focusing on dyslipidemia were published in 1988 by the National Cholesterol Education Program (National Cholesterol Education Program, 1988).
- Cardiovascular guidelines such as "American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures" were published in 1991 (American College of Cardiology, 1991).

In the United States of America, guidelines were first defined and published by the institute of medicine in the early 1990s (Lohr and Field, 1990). In England, the Cochrane Collaboration was established in 1993 (Bhaumik, 2017).

Purpose of Developing Therapeutic Guidelines

The guidance of the decision-making process to both clinicians and consumers is considered the main purpose of guidelines development. This results in improvement of the quality of care, risk management, and patient outcomes. It also acts to reduce the diversities in clinical practice toward a more consistent and transparent approach (Martina, 2014).

In the light of the overwhelming medical literature and research nowadays, guidelines serve as systematic and organized sources to represent and implement the best available evidence in clinical practice. Nowadays, and due to limited health-care resources, guidelines are intended to provide evidence about the cost-effectiveness of care as well, which leads the way to judicious allocation of resources in health care (Lohr and Field, 1992; Peetermans and Ramaekers, 2002). This can explain the reason behind the interest of policymakers in the development of therapeutic guidelines.

In addition, guidelines can be employed as a good source for continuing professional development and updating medical information for groups and individuals (Lohr and Field, 1992). In this context, Weisz et al. argued that the main aim for guidelines development, besides the rationalization of medical costs and the maintenance of physicians' professional autonomy, is the "regulation" of the use and quality of medical care (Weisz et al., 2007).

Characteristics of Valid Therapeutic Guidelines

Guidelines should have specific clinically oriented objective(s) and scope that are specified a priori to the guidelines document development. The guidelines presentation should be concise and structured, yet comprehensive enough to fulfil the objectives. A guideline recommendation should be clear and easy to follow. Guidelines development should consider scientific evidence of benefits, harms, and, if feasible, costs. This evidence can be based on randomized controlled clinical trials, cohort or nonrandomized controlled studies. Guidelines should be dynamic and iteratively reviewed and updated in accordance with the emergence of new evidence. Discussion of the benefits shows health gain and discussion of harms such as adverse effects shows the safety of drug therapy. Explicit and practical guidelines should avoid injudicious words (such as "may be, perhaps") and arbitrary numbers (such as months of treatment, intervals between screening tests) (Burgers et al., 2003; Davis and Taylor-Vaisey, 1997; Qaseem et al., 2012).

Benefits of Using Therapeutic Guidelines

Guidelines serve as a great help for clinicians. They serve as a clean and organized presentation of enormous amount of data. Having the level of evidence sorted in guidelines is an important guide for clinicians in taking clinical decisions. In addition, the regular update of guidelines is crucial for providing the most effective management for patients and for continuing education of health-care professionals. Since they contain different options for treatment, guidelines provide flexibility for clinicians in taking therapeutic decisions according to the available resources which vary from one country or setting to another (Shea et al., 2012).

Furthermore, therapeutic guidelines are an important tool for setting priorities that can be considered in conducting future research. Guidelines can also act as a major player in health policy formation (Browman et al., 2003).

Responsible Bodies for Issuing Guidelines

Therapeutic guidelines are issued at local, national or international levels, whereas health professional organizations/associations or governmental bodies issue their own guidelines or adapt other evidence-based ones. Guidelines are either specialized or unspecialized. All guidelines issuing organizations are united in the Guidelines International Network (G-I-N) (www.g-i-n.net), an international network of clinical guidelines developers.

National guidelines issuing bodies, including, for example, the United States Agency for Healthcare Research and Quality (AHRQ), issue national guidelines. Likewise, in England, clinical practice guidelines are primarily developed by the National Institute for Health and Care Excellence (NICE). In the Netherlands, the Institute for Healthcare Improvement (CBO) publishes specialized guidelines, whereas College of General Practitioners (NHG) publishes unspecialized care guidelines. Similarly, the German Agency for Quality in Medicine (ÄZQ) adopts a national program for different disease management guidelines (Shea et al., 2012; Woolf et al., 1999).

The WHO also issues series of guidelines providing recommendations for clinical practice or public health policies. These guidelines are examples of internationally developed and implemented guidelines. Examples of medical associations issuing their own specialized therapeutic guidelines include National Asthma Education and Prevention Program (NAEPP) Guidelines for Diagnosis and Management of Asthma (National Asthma Education Prevention Program, 1998), the Joint National Committee's eighth guidelines (JNC 8) for the management of hypertension (James et al., 2014) and the international clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (Gupta et al., 2011).

To facilitate the implementation of therapeutic guidelines, some specialized computer software packages known as guideline execution engines were developed. Guideline execution engines import guidelines in the form of guideline interchange format (GLIF format) and use an electronic form of medical record system to implement the guidelines. Countries archive their guidelines in medical guideline clearinghouses. The American National Guideline Clearinghouse keeps a catalogue of high-quality guidelines published by numerous health professional associations.

Development of Therapeutic Guidelines

For many decades, the process of development and dissemination of therapeutic guidelines has been well established. However, the process has been much improved from being haphazard and irregular to being well-integrated into the thinking of expert groups and professional clinical organizations (Davis and Taylor-Vaisey, 1997). The improvement of health-care quality, the quality use of medicines (reduction of unnecessary, ineffective, or harmful interventions), and optimum treatment of patients with maximum benefits and minimum risks are the main benefits of developing, writing, and publishing therapeutic guidelines. These guidelines are written mainly for clinicians (including prescribers, particularly general practitioners and trainee physicians, pharmacists, and nurses) to assist them in the management of patient-specific conditions and to ensure receiving the optimum treatment to their patients. This occurs by providing them with clear, practical, and up-to-date therapeutic information that are essential for everyday clinical decision making (Graham and Harrison, 2005).

Key Principles for Developing Therapeutic Guidelines

For developing therapeutic guidelines, nine principles should be applied (Browman et al., 1995; Davis and Taylor-Vaisey, 1997; National Health and Medical Research Council, [NHMRC] 1999; Qaseem et al., 2012):

- The development process has to focus on outcomes, ranging from survival rates to quality of life attributes.
- They have to be based on the best available evidence in addition to including a statement about both the strength and the quality of the recommendations.
- The turning of the evidence into recommendation depends on judgment, experience as well as the good sense of the group who is responsible for developing the guidelines.
- Being multidisciplinary and the inclusion of consumers are necessary in the development process for the guidelines to be relevant.

Figure 1 Therapeutic guidelines development process. *Source*: Adapted from National Health and Medical Research Council (NHMRC), 1999. The Guiding Principles. A guide to the development, evaluation and implementation of clinical practice guidelines. National Health and Medical Research Council, Australia; Shekelle, P.G., Woolf, S.H., Eccles, M., Grimshaw, J., 1999. Developing guidelines. Br. Med. J. 318, 593–596; Davis, D.A., Taylor-Vaisey, A., 1997. Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Can Med Assoc J 157, 408–416; Browman, G.P., Levine, M.N., Mohide, E.A., et al., 1995. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J. Clin. Oncol. 13, 502–512.

- Guidelines have to be flexible and adaptable to the continuously varying conditions and constraints.
- During the development process, resource constraints are among the main factors that should be considered.
- Therapeutic guidelines should be disseminated and implemented taking into account the practitioners and consumers who are considered the main target audience.
- Evaluation of the validity and usefulness of guidelines should be done.
- Regular revision of guidelines should be done in a scheduled manner.

Therapeutic Guidelines Development Process

For a successful development of therapeutic guidelines, a systematic framework with definitive steps has to be developed (Browman et al., 1995). In addition, the methodology of guideline development should ensure that the desired outcomes will be achieved upon treating the patients according to the guidelines (Shekelle et al., 1999). The steps of the therapeutic guidelines development process are summarized in Fig. 1.

Identification of the Scope and the Need for the Guidelines

The first step in developing therapeutic guidelines is to identify the need for the guidelines. Therefore, a clear and specific scope and clinical objectives should be determined. The responsible body for developing the guidelines should specify the clinical practice problem that may be well resolved by the implementation and dissemination of these guidelines which offer the most appropriate practice (NHMRC, 1999). As an example, a checklist for defining the scope and clinical objectives for the guidelines development process is developed by the American College of Cardiology and American Heart Association (ACC/AHA) (see **Checklist 1**). This checklist defines the important guideline topic-related clinical objectives, the subtopics and related topics that must be included in the guideline, whether they are already covered by another organization, and whether the flow diagrams are appropriate to them, the comorbidities which are being covered or should be covered by the topic area/guideline, the potential benefits and risks for individual patients associated with an intervention or procedure, the amount of clinical flexibility appropriate for the topic area, the available clinical options, and the topics already covered in existing ACC/AHA Guidelines. Consequently, literature searching and sorting, and the compilation of guideline recommendations will be based on these predefined clinical objectives.

To the best of our knowledge, the decision to develop new guidelines is based on many factors such as the expressed need by general or specialist practitioners, feedback from clinicians, evidence from drug usage data, and the presence of a clear problem (e.g., magnitude of health burden, cost, variations in practice and care, lack of evidence) that would be assisted by establishing guidelines for appropriate practice. A precise, structured, and well-defined overall guideline outline should be determined during

Checklist 1 Determining the Guideline Scope and Clinical Objectives

Questions related to the guideline overall

- ☐ What is the guideline's targeted health condition(s), diagnostic test(s), or interventional procedure(s)?
- ☐ What is the purpose of the guideline?
- ☐ What is within the scope of the guideline?
- ☐ What is outside the scope of the guideline?
- ☐ What is the literature inclusion date range?
- ☐ What is the epidemiology of the topic?
- ☐ Who are the guideline's intended users?
- ☐ What is the public health impact?
- ☐ What is the target patient population to be addressed in the guideline?
- ☐ How does the guideline relate to other existing ACCF/AHA documents (e.g., expert consensus, scientific statements, performance measures, data standards, appropriate use criteria, quality improvement)?
- ☐ Can flow diagrams and evidence tables help summarize the guideline, or at least key subsections?
- ☐ How does the guideline impact and improve broad health system based public health improvement goals such as the Healthy People 2010 Initiative?

Questions related to the guideline's clinical objectives

- ☐ What are the important clinical objectives related to the guideline topic?
- ☐ What subtopics and related topics must be included in the guideline? Are the subtopics and related topics already covered by another organization? What comorbidities are being covered or should be covered by the topic area/guideline?
- ☐ Are flow diagrams appropriate to these subtopics and related topics?
- ☐ What are the potential benefits and risks for individual patients associated with an intervention or procedure?
- ☐ What amount of clinical flexibility is appropriate for the topic area?
- ☐ What clinical options are available?

Adapted from (Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines, 2010)

the early stages of guidelines development to improve consistency across guidelines and facilitate the effectiveness of online searching of these guidelines.

Forming Guideline Development Expert Groups

Expert groups

For each published guidelines, a committee for practice guidelines or expert groups of representative members take the responsibility of text development in therapeutic guidelines. The group or committee has innovative roles in the involvement of these guidelines in the new health-related policies and in clinical practice, prevention, quality assurance, research programs, and health economics for patient-specific conditions. The composition of these groups will vary depending on the nature of the guidelines, but should be designed to be representative of various interests. In general, the following members should be involved in the expert groups, as appropriate: a chairman, an editor, experts in relevant medical specialties, clinicians with general expertise, and other relevant health professionals (pharmacists, experts in physiotherapy and nutrition, and nurses). In addition, consumer groups, public policy analysts, health economists, industry representatives, bioethicists, and representatives of regulatory agencies may be also included in the group (NHMRC, 1999).

Group members are invited to participate in developing recommendations for practice based on the best available published evidence in addition to their knowledge of clinical practice. Besides expert groups, the presence of the editorial office is crucial in the process of therapeutic guidelines development. Both the chairperson and editor have distinguishable roles in the manuscript development process. The main role of the chairperson is to coordinate and ensure that the group functions effectively, that the project proceeds harmoniously, that the aims are achieved, and that true consensus is attained for all recommendations (Shekelle et al., 1999). The editor assists in the communication between the chairperson and expert group members in order to be sure that the manuscript develops effectively, on the scheduled time and within the set budget. Also, he/she is responsible for preparing the documents for each meeting, including the agenda, minutes, feedback on the previously published version (where applicable), correspondence regarding draft manuscripts, content, and other relevant background information. In addition, the editor prepares a detailed transcript of each meeting to document the basis for all recommendations, especially those that are new or controversial.

Planning meeting

Generally, for each expert group, an initial planning meeting or teleconference is done to provide the members with detailed explanation and guidance on several aspects including intellectual property, conflict of interest, objectives and format of the guidelines, clarification of the scope of the content for the target audience, importance of documentation of evidence to support the recommendations, and desirability of consultation with colleague experts in the area.

Before proceeding, a clarification of the purpose and the target audience for the guidelines should be done by the expert group members. Therefore, within each subject area, the group decides on which medical conditions and clinical problems to be covered and the level of detail to be included, in addition to the likelihood that a condition will be encountered. However, advice on rare but serious diseases will also be included. Moreover, feedback from users of earlier version of the guidelines may also influence the decisions about which conditions need to be covered. This means that the starting point for content is what a clinician needs to know in order to appropriately treat a patient with specific condition (Graham and Harrison, 2005; Shekelle et al., 1999). Also, the type of health-care providers and consumers for whom the guidelines are intended and the interventions that have to be evaluated are among the issues that have to be specified by the group members (NHMRC, 1999).

In addition, topics selected by expert group members for guideline development should be feasible where sufficient high-quality evidence derived from randomized controlled trials is available. Also they should adopt the high-priority criteria, which are as follows (Rosenfeld and Shiffman, 2009):

- Significant health burden with high extent of disability, morbidity, or mortality not only on patients but also on families, communities, and society overall.
- The presence of a clear clinical practice problem that will most likely be resolved by the most appropriate practice offered by the guidelines.
- Topics that are controversy or uncertain.
- The presence of significant economic cost of the clinical condition, procedure, treatment.
- The presence of new published evidence that may have the potential to change conclusions.
- High potential impact on health outcomes and quality of life.
- Topics of high public or provider interest.
- The presence of variations in health care.

Reviewing and Assessing Scientific Evidence

After the planning meeting, unbiased and comprehensive literature review should be done by the expert group members to ensure the validity of the evidence-based guidelines, help them in answering the clinical questions, and highlight the gaps in evidence. The process of identifying evidence involves identification of systematic reviews, previously published guidelines, randomized controlled trials, nonrandomized studies, case studies, and opinion documents. All of the literature search should be documented to ensure transparency and reproducibility (Rosenfeld and Shiffman, 2009).

Translating Evidence into Therapeutic Guidelines

Initial drafts, based on the authors' clinical expertise and the current best available evidence from the latest international literature in the relevant area, are prepared. Also, authors in each group are encouraged to prepare a justified summary of their recommendations. At this stage, the editor and the medical librarian help the authors identify and access the relevant supporting information the authors need. This may include primary scientific papers, systematic reviews, and previously developed guidelines.

The drafts are sent to all the group members to give them the opportunity to consider the material before the topics are discussed. Then, successive and more exhaustive discussions are made for each draft until agreement is reached on the content. Consequently, controversial areas are identified and further literature searches are undertaken if necessary. Once the intent of the expert group is clear with respect to specific content, the editor becomes responsible for the text, reorganizing it according to house style and format, and communication as necessary with authors and the chairman. Therefore, the finished manuscript is the result of detailed scrutiny, collaboration, and revision, involving many authors and several editing stages. As a result, all expert group members become responsible for the entire manuscript without any of the topics being attributable to any of them. At the final meeting, all topics are scrutinized to ensure all members approve the whole text (Shekelle et al., 1999). Once sufficient evidence has been collected, the evidence should be synthesized in a systematic way that lends itself to decision making. For each clinical objective within the guideline, the following components have to be included; statement of the clinical objective/question, one or more clinical recommendations answering the clinical question/objective, explanatory text, references, evidence table to identify and extract the key data from the relevant studies, and diagram, table, or graphic summary.

Grading recommendations

Documenting the relevance and strength of the scientific evidence is very important in the development of the content in therapeutic guidelines. It is common to grade each recommendation in the guideline. This information is very important for the users because it gives them an indication of the guideline development group's confidence that the desired health outcomes will be produced using these guidelines. Moreover, the strength of any recommendation depends mainly on two factors: the trade-off between benefits and risks and the quality of the evidence regarding the treatment effect. Regarding the trade-off between benefits and risks, the strength of recommendation falls in one of two categories according to the GRADE system (Atkins et al., 2004): 1 (strong recommendation), in which there is a clear trade-off where the benefits outweigh the risk or vice versa and therefore most patients would make the same choice; and 2 (weak recommendation), in which the trade-off is less clear and the benefits are closely balanced with the risks and therefore patients would have different choices. In some instances, the recommendations may fall in "Not Graded" category. In this category, the guidance is based on common sense or the topic does not allow adequate application of evidence. This includes the recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists.

As for the quality of evidence, it may be high, moderate, low, or very low-quality evidence according to US Preventive Services Task Forces. High-quality evidence (denoted as "A") is obtained from well-designed and performed randomized controlled trials where the expert group members are confident that the estimate of benefit and risk is not possible to be altered by future research. Moderate quality evidence (denoted as "B") is obtained from randomized trials with significant limitations where the confidence of the expert group members in the estimate of benefit and risk is likely to be affected by future research, which may alter that estimate. Low-quality evidence (denoted as "C") the confidence of the expert group members in the estimate of benefit and risk is very likely to be affected by future research, which is likely to alter that estimate. Very-low quality evidence (denoted as "D") is obtained from observational studies, unsystematic clinical experience, or from randomized trials with serious flaws, so any estimate of effect is uncertain. High likelihood of bias, inconsistency of results, imprecision, and indirectness of the evidence are considered the main factors that reduce the strength of an evidence (Guyatt et al., 2008b; Kavanagh, 2009; Shekelle et al., 1999; Woolf et al., 2012). However, other organizations may have different grading systems. Based on the American Academy of Pediatrics, four categories of recommendations are used ("strong recommendation," "recommendation," "option," and "no recommendation") (American Academy of Pediatrics Steering Committee on Quality Improvement and Management, 2004). In addition, lots of guidelines-developing organizations do not use any grading system for defining recommendations' strength (Lomotan et al., 2010). In England and Wales, the NICE does not assign letter grades to its recommendations and uses three levels of certainty. These three levels of certainty include:

1. Recommendations for interventions that must (or must not) be used. These recommendations apply to all patients, and there is a legal duty to apply them.
2. Recommendations for interventions that should (or should not) be used. These mean that there is confidence that the intervention(s) will do more good than harm and will be cost-effective for the majority of patients.
3. Recommendations for interventions that could be used. These mean that there is confidence that the intervention(s) will do more good than harm and will be cost-effective for most of patients. However, other options may have similar cost-effectiveness, or patients prefer a less effective but cheaper intervention. Therefore, the choice of such intervention(s) varies depending on a person's values and preferences.

The written recommendation is considered the core of any guidelines. All recommendations should be written in an unambiguous language with clearly defined terms. Usually, they are written in complete sentences using the correct verbs and with assigned references. The target population, subpopulation, and exceptions should be specified when writing recommendations. The recommendations that are practical in the real-world settings are those which are usually written in the guidelines.

Dissemination of Guidelines

As previously mentioned, therapeutic guidelines should be disseminated and implemented taking into account the practitioners and consumers who are considered the main target audience. During the process of guideline development, the expert groups have to develop a scheduled plan for the dissemination and implementation of therapeutic guidelines targeting all potential users (NHMRC, 1999). The presence of multiple guideline formats will improve the dissemination of the guidelines. Guidelines can be published as booklets, containing comprehensive information, or in summary form providing information about the main findings. Also, they may be published in other forms including professional journals, professional associations' newsletters and magazines, industry newspapers, institutional newsletters, as posters, as brochures, as audio or video tapes, on computer disks, in summary form or as full guidelines published on the Internet and linked to websites appropriate for the target audience. For example, European Society of Cardiology (ESC) Clinical Practice Guidelines are available in different formats including pocket guidelines, mobile application, guidelines presentations, webcasts, summary cards, and reprints. These different formats provide easy access and quick reference guides for the practicing clinician.

Scheduled Reviewing and Updating Guidelines

After the publication of the therapeutic guidelines, it is expected that they will be reviewed and updated with a scheduled review date. As an example, NICE guidelines should be evaluated at least once every three years. More frequent evaluation will be performed in case of subjects areas prone to rapid change. With the increasing rate of published new studies, several concerns will be raised if guidelines are not up-to-date. First, the guideline users will not trust that the care is based on the best available evidence in these outdated guidelines. Second, no reflection of the clinicians' experience and their knowledge of recently published research is presented in that version of the guidelines, making their clinical choices inappropriate, or spending much time searching for more valid published evidence (Clark et al., 2006). Therefore, the review process should be done to ensure that the content of the guidelines is valid, clear, and applicable (Graham and Harrison, 2005; Shekelle et al., 1999). For example, the National Kidney Foundation—Kidney Disease Outcomes Quality Initiative (NKF KDOQI) performs continues update for its clinical practice guidelines. This occurs upon the availability of high quality new evidence that drives them to change the currently available recommendations (e.g., recommended intervention causes unknown harm, presence of new superior intervention to a previously recommended one, new intervention targeting new population).

Briefly, the review process has six components, which includes assessment of guidelines dissemination, assessment of their relevance to clinical practice, assessment of the change of the health outcomes, assessment of the contribution of the guidelines to any changes of clinical practice or health outcomes, assessment of the impact of guidelines on consumers' knowledge and understanding, and finally the economic evaluation of guideline process. The regular review and update of therapeutic guidelines

may result in many changes. Addition, removal, or change to recommendations or suggestions may occur. Moreover, the strength of a recommendation may be upgraded or downgraded based on the new available evidence.

The decision to update the guidelines is based on many factors; changes in evidence, the resources available for health care, feedback from clinicians, changes in practice, changing patterns of drug usage, and other relevant issues (Shekelle et al., 1999; Shekelle et al., 2001). However, clinical areas covered in guidelines may not be considered for updating in certain circumstances. This occurs when the evidence base is poor, and it is unlikely that any of the recommendations will change (Shekelle et al., 2001).

Withdrawal of guidelines

Upon consultation with stakeholders, the decision to withdraw a guideline will be made when inaccurate, misleading, or erroneous recommendations are detected in the published version, when the recommendations in a guideline are no longer applicable and at the same time the guideline is not of sufficiently high priority for updating, or when concerns regarding the effect of conflicts of interests by the authors of the guideline in the critical appraisal of the evidence was detected (Jorge, 2014). In the EUROPAEM EMF Guidelines 2015 for the prevention and treatment of EMF (electromagnetic fields)-related health problems and illnesses, unintentional errors were detected where many citations were lost and deleted during its preparation. Therefore, the authors have retracted the guidelines for a revised version to be published at a later date (Belyaev et al., 2015).

Cons/Harms/Limitations

Clinical guidelines are sometimes resented by some clinicians as an invasion of personal expertise. Specialized guidelines may sound biased to generalists. Often times, to specialists, guidelines developed without their input are lacking adequate expertise.

1. Wrong recommendation (at least for individual subjects).
   Apart from humanistic errors, guideline development groups may miss what is best for patients for:
   a. Lack of scientific evidence.
   b. Misleading scientific evidence: Inappropriate experimental design leads to bias, which compromises generalizability.
   c. Misinterpreted scientific evidence: Lack of time, resources, and skills to gather complete information and criticize every detail of evidence may lead to misinterpreted evidence. Moreover, subjective judgments may miss the best intervention for individual patients.
   d. Guidelines are influenced by the judgment, clinical expertise, and compilation of their development group.
   e. Patients' needs may not represent the only priority during guideline development. From the patient's perspective, suboptimal practices may be recommended to help control costs for example. The implementation of these flawed guidelines can spread serving ineffective, harmful, or wasteful interventions.
   f. Inflexible guidelines impair the feasibility of patient-oriented pharmaceutical care of nonconventional clinical problems, thus the achievement of more consistent practice may impede individualized care.
   g. Clinical guidelines can affect stakeholders to drop access to beneficial interventions and likely costly interventions may displace less costly yet effective intervention thus loses its cost-effectiveness.
2. Potential harms to health-care professionals
   a. Inaccurate scientific information and clinical advice compromise the quality of care.
   b. Conflicting guidelines from different professional bodies
   c. Outdated recommendations may spread outmoded practices
   d. Guidelines can restrict scientific progress if future research is inappropriately discouraged. For example, lack of investment for refining previously ineffective interventions
   e. Simplistic algorithms that reduce patient care to a (yes/no) decisions hierarchy underestimate the iterative thought processes inherent in clinical judgment.

However, the increasing awareness of clinical guidelines limitations (Cabana et al., 1999; Woolf et al., 1999) has done little to the rapid spread of guidelines around the world.

Conclusion

Guidelines are developed by governments or health associations to control acts and sometimes costs of health-care process. These guidelines are written mainly for all clinicians for optimum treatment of their patients. Therapeutic guidelines provide them with clear, practical, and up-to-date therapeutic information that are essential for everyday clinical decision making. Also, guidelines may influence future public health policies. Successful development of therapeutic guidelines requires a systematic framework with definitive steps. The written recommendations, the core of any guidelines, are based on the best available evidence. Guidelines have many benefits that contribute to the provision of better health care, but they are not meant to replace a clinician's expertise and sound clinical judgment. Guidelines should be regarded, as the name implies as "guidelines."

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Glossary

Clinical Guidelines A systematically developed guidance document prepared to assist health-care personnel in the safe diagnosis, prescribing, preparation, control, and administration of medicines for specific clinical conditions.
Clinical Pathways A document outlining a standardized, evidence-based multidisciplinary management plan, which identifies the appropriate sequence of clinical interventions, time frames, milestones, and expected outcomes for a homogenous patient group.
Clinical Practice Guidelines Clinical practice guidelines are statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (Steinberg et al., 2011). Clinical practice guidelines maybe evidence-based or consensus guidelines.
Consensus Guidelines They are systematically developed statements to assist practitioner's and patient's decision about appropriate health care for specific clinical circumstances (Goodman and Baratz, 1990).
Evidence-based Guidelines They are the guidelines using systematic reviews to report specific clinical situations. They are prepared through a thorough literature review, critical evaluation of the evidence's quality, and interpreting the outcomes according to the patient's preferences and societal values (Guyatt et al., 2004).
Quality Use of Medicines It is the process of selecting patient management options wisely by reducing the use of unnecessary, ineffective, or harmful medicines.

Abbreviations

ACC/AHA American College of Cardiology/American Heart Association
ACCP American College of Chest Physicians
AHRQ Agency for Healthcare Research and Quality
ÄZQ The German Agency for Quality in Medicine
CBO Netherlands-Dutch Institute for Healthcare Improvement
EMF Electromagnetic Field
ESC European Society of Cardiology
EUROPAEM European Academy for Environmental Medicine.
G-I-N Guidelines International Network.
GLIF The Guideline Interchange Format
IOM Institute of Medicine
JNC Joint National Committee
NAEPP National Asthma Education and Prevention Program
NHG The Dutch College of General Practitioners.
NICE National Institute for Health and Care Excellence
NKF-KDOQI National Kidney Foundation—Kidney Disease Outcomes Quality Initiative
WHO World Health Organization

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End-of-Life Care Including Pharmaceuticals in Palliative Care

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Learning Objectives

1. You should be able to identify what is required in providing good palliative care, and determine those health care providers that will allow you to support the patient and their family during the patient's last months, weeks, and days of life.
2. You should be able to evaluate the services able to be provided by other health care providers and determine any service provision needs for a palliative care service in your location of practice.
3. After reading this chapter, readers should be able to undertake the provision of palliative care in a manner that is appropriate to the needs of the patient and their extended family and carers.

Palliative Care

"Sparse breaths,
then none
and it was done"

The unfinished.

Christopher Reid, describing the last few days, hours, minutes of life of his wife; from his book of poetry about grief, A Scattering (Reid, 2009).

Palliative care is health care provided to any person with a progressive life limiting or life-threatening illness. The care provided is dependent on the needs of the patient, not their prognosis, and takes into account the needs of the patient and carer. Thus, the care offered is delivered in the knowledge that although it is intended to ease or ameliorate the illness, it is not curative.

As such, palliative care incorporates a holistic approach aiming to improve the quality of life of patients with incurable diseases (Palliative Care Expert Group, 2016; Twycross et al., 2009). This approach is to support the whānau or family, friends, and carers of the patient (Palliative Care Expert Group, 2016; Twycross et al., 2009). The ethical principles of respect for the autonomy of the patient and their significant others are the foundation that pharmacists work with other health care professionals to provide a seamless care package for patient entrusted to their care (Gillon, 2003).

Ideally, palliative care takes the best that each member of the health care team has to offer to prevent and relieve suffering. Often, this may mean that the health care professionals, and particularly the pharmacists working in palliative care, remain abreast of complementary, traditional, as well as integrative medicine approaches to patients (WHO Traditional Medicine Strategy, in press). The palliative pharmacist must strive to compassionately support patients and their families to meet their goals and to live each day as fully as possible (Palliative Care Expert Group, 2016; Twycross et al., 2009).

Take-Home Messages

1. Acknowledging a multifactorial approach to care of the dying.
2. Awareness that the needs of the total family, as well as the patient, may require negotiation at all steps along the trajectory of dying.
3. Remembering that although we cannot cure palliative patients, nor should we actively hasten death, we may ease its progress.

Introduction

Palliative care is not just the care of those dying of or with cancer or neoplastic diseases, as it covers a range of complex and end stage conditions that patients may be diagnosed with. The point of similarity is that any patient should be considered for palliative care if any clinician involved in their care would not be surprised if the patient died in the next 6–12 months (Palliative Care Expert Group, 2016).

As a result, many times medications are used "off license or off label," that is, as an unapproved use, either in the location/country of practice or internationally (Twycross et al., in press). As a matter of principle, when recommending such off-licence use, the clinician (physician or pharmacist) must do so with the knowledge that such use is in the best interest of the patient, in order to ease symptoms, or simplify administration. For example, many medications are administered via the subcutaneous route, as it is less invasive than intravenous route, but often there is little or no data regarding the subcutaneous route.

Worldwide, populations are aging, and an increasing number can be expected to require palliative care, as greater strides are made with treatment approaches and public health initiatives to reduce chronic conditions (United Nations, in press). However, not all governments fully fund hospices or hospice in the home care, or even appropriate analgesics. For example, in Mexico, opiates are largely unavailable outside state capitals, and palliative care services are largely nonexistent. As a result, fundraising, and lobbying governments and local communities are often required to initiate or develop care and treatment of those who would benefit. Those in relatively poor communities frequently struggle to provide services. The paucity of palliative care specialists may be bridged by admission to hospital of palliative patients where they can access specialist health care services such as physiotherapy, occupational therapy, social workers, speech and language therapists, respiratory, cancer, renal, and diabetic specialist nursing care. This is not an appropriate level of service, including medical expertise, and negatively impacts on both the hospital statistics (high rates of inpatient deaths) and impacts on patients receiving holistic palliative care from a multidisciplinary heath care team, trained in palliative care delivery in the nonacute setting. Early referral to palliative care can improve measurable outcomes for the patient as well as reduce futile medical interventions and hospital admissions (Haines, 2011).

Disease/Condition Information

> "There is no cure for birth and death save but to enjoy the interval"
> "How people die remains in the memory of those who live on"
>
> Dame Cicely Saunders (Dame Cicely Saunders, in press).

Initially, palliative care and the modern hospice movement by Christopher was started in 1967 to manage the care of those dying in hospital wards as there was nowhere else for them to go (Dame Cicely Saunders, in press). As such, palliative care then became a specialty for those doctors and nurses who staffed the hospices, as well as a range of other health care professionals who were involved in the care of these patients. As many of the treatments provided during those last days involved medications, pharmacists became integral members of the hospice team.

Hospice patients were largely those suffering from cancer in the early days of hospices, and then other patients under a similar "death sentence" such as Acquired Immunodeficiency Syndrome. These days, all patients who have a life-limiting illness, and whose life expectancy is potentially 6 months or less can benefit from palliative care. Thus, patients often have complex medical conditions about which decisions need to be made with the patients and their family. For example, secondary stroke prevention is not a major issue for palliative patients, and after consultation with the patients and their family, these treatments may be withdrawn to ease the pharmacological burden. In contrast, the patient with a pulmonary embolism may receive low-molecular-weight heparin depending on prognosis. Pharmacists need to be mindful of the spiritual and emotional needs as well as medical needs of patients when determining agreed treatments for their patients.

Epidemiology

Modern medicine has continued to advance management and delay progression of many conditions; however, chronic diseases will eventually cause disability, suffering, and death. Generally, these illnesses occur at the end of a long life, but they may occur in all age groups. The aim of palliative care is the relief of suffering, and as such needs to be addressed at a population-based level as well as for individuals.

Etiology

The WHO's definition of palliative case is "an approach that improves the quality of life for families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." (World Health Organisation, in press).

Diagnosis

The decision to seek assistance from a palliative care team is nowadays made earlier in the trajectory of dying for patients who may ask "how long have I got?" Illness trajectories are used to describe the progress of a chronic condition or disease (Murray et al., 2005), In western society, these are generally conditions that are the result of organ failure (for example, respiratory, diabetes, cardiovascular), cancer neurological conditions (for example, motor neuron disease), as well as dementia. The trajectory model has a clear progression from diagnosis and a decline but the eventual outcome will be death (Murray et al., 2005).

There are three main trajectories for people approaching death—the relatively short period of decline associated with cancer, the gradual episodic nature of organ failure with exacerbations resulting in never achieving base-line status after an episode, or the dwindling trajectory of the frail elderly, associated with dementia (Lunney et al., 2003). Sudden death, for instance, cardiac arrhythmia and stroke, is another trajectory (Palliative Care Expert Group, 2016).

For each of these conditions, advance care planning is essential to involve the patient while they are able, and their family during the course of their illness in decisions relating to the care offered to the patient.

Clinical Presentation—Symptoms

The common symptoms associated with palliative conditions involve any that may be associated with the underlying condition as well as pain, nausea and vomiting, constipation, delirium, agitation, dyspnea, and respiratory secretions. Care is frequently required for the skin, bowel, bladder, and oral areas as well (Potter et al., 2003).

Pain

> "True compassion means not only feeling another's pain but also being moved to help relieve it"
>
> Daniel Goldman (Daniel Goleman, 2005)

> "Pain is a symphony – a complex response that includes not just a distinct sensation but also motor activity, a change in emotion, a focusing of attention, a brand new memory."
>
> Atul Gawande, Complications: A Surgeons Notes on an Imperfect Science (Gawande, 2003)

Pain may be due to a pre-existing disease (such as arthritis), but fear of uncontrolled pain can be overwhelming in the dying patient, as well as for their family and friends. Thus it is important to understand which pain is new and which is due to other treatable conditions (such as constipation, fear of dying). Thorough history taking and assessment is key to ensuring pain needs are met and managed as effectively as possible. In assessing total pain it is vital to consider physical, psychological, social and spiritual aspects (McLeod, 2007).

A useful tool to assess pain is *PQRST* (Twycross et al., 2009):

P Palliative & provocative factors—What makes it better, what makes it worse?
Q Quality—Describe to me what it is like
R Radiation—Does it spread anywhere
S Severity—How severe is it on a scale of 1–10?
T Temporal—Is it always there or does it come and go, is it worse at night?

It is important to remember in cancer related pain that several mechanisms may be causing the pain, so a combination of treatments may be needed for optimal relief.

After assessment of pain consider what is already being used to manage pain. If the patient can still swallow medicines and is not using and analgesics, then use the WHO three-step analgesic ladder for cancer pain (WHO Cancer Pain Ladder for Adults, in press):

Step 1 nonopioid analgesics (e.g., paracetamol or NSAIDS) with adjuvant analgesics such as corticosteroids or antidepressants
Step 2 weak opioid (e.g. codeine, dihydrocodeine) plus nonopioid plus adjuvant analgesics
Step 3 strong opioid plus nonopioid plus adjuvant analgesics

All analgesics used to manage pain should be given regularly in order to prevent pain. As such you would give a patient the maximum dose of step 1 before going on to step 2 and adding in a weak opioid. As maximum doses of weak opioids are reached, then step 3 requires replacing the weak opioid with a strong opioid until management of pain is achieved.

In the Australian context, codeine is not routinely used in palliative care due to its ceiling effect, its reliance on hepatic metabolism for conversion to active metabolite morphine, and possible severe constipation. Tramadol has the disadvantages of adverse effects and potential drugs interactions in this group of patients (Palliative Care Expert Group, 2016).

Morphine is usually the drug of choice for moderate to severe pain (Palliative Care Expert Group, 2016).

Commencing a different opioid may be appropriate due to factors such as moderate to severe renal impairment, severe liver impairment, unacceptable side-effects, and compliance issues.

In severe renal failure, buprenorphine, fentanyl, and methadone can be used as they are not renally excreted (Palliative Care Expert Group, 2016).

Buprenorphine, fentanyl, morphine, and methadone can be used in severe liver impairment (Twycross et al., in press).

Fentanyl is the safest first line opioid when the eGFR is less than 30 mL/min Fentanyl is subject to significant first-pass metabolism, and is unsuitable for oral use, but is frequently used as a transdermal patch or as a nasal spray (Schug and Ting, 2017). Transmucosal forms of fentanyl are also available for short-term pain relief. The available products are not interchangeable (Palliative Care Expert Group, 2016).

Using a combination of dosage forms such as long acting preparations for background pain and short acting preparations for breakthrough and incident pain enables better pain management. Regular reassessment of pain needs is important, ideally each day if possible (WHO Cancer Pain Ladder for Adults, in press).

Adjuvant Analgesics—Which is Better for What (BPAC Palliative Care, in press)?

Nociceptive pain is associated with tissue injury. It may be felt as an ache or a deep pain. Bone pain is a pain that is worsened by movement or weight-bearing activity. Both nociceptor pain and bone pain may be treated with nonsteroidal anti-inflammatory drugs (NSAIDS). The use of neuropathic agents for bone pain may be warranted as research suggests that there is a neuropathic component (Palliative Care Expert Group, 2016).

Neuropathic pain is helped partially by opioids but often better management is to add in an adjuvant analgesic as this may delay the need to increase the opioid dose. Low-dose tricyclic antidepressants (TCAs), such as amitriptyline or nortriptyline, and antiepileptics (AEDs), such as gabapentin and pregabalin, can be trialed, taking into account such factors such as the need for night time sedation and the adverse drug profile.

Tumor compression pain is often managed with corticosteroids, commonly dexamethasone, as they reduce edema and inflammation.

Pain from muscle spasm, especially if related to anxiety, is relieved by skeletal muscle relaxants such as benzodiazepines.

Pain from blockage or visceral distention is relieved by smooth muscle relaxants such as hyoscine butyl bromide.

Nausea and Vomiting

The causes of nausea and vomiting are complex, but in order to minimize them, it is important to consider prevention strategies when commencing treatment with emetogenic medicines such as opiates. Care must also be taken to exclude regurgitation from gastro-esophageal reflux disease, and treat it accordingly. The opportunity to correct the correctable (for example, prescribe a proton pump inhibitor for indigestion) and prevent the preventable (minimize stress, large meals, or spicy foods) must be taken as a first step. Then it is appropriate to use the most appropriate antiemetic. If nausea is the major problem, then oral doses are generally adequate. if vomiting is more problematic or if the oral route is unavailable, then parenteral treatment may be more useful, often via continuous subcutaneous infusion (CSCI) using a syringe driver (Twycross et al., in press).

Prokinetic vomiting is generally caused by gastric stasis and bowel obstruction. It may be treated by using metoclopramide 10 mg three times daily orally, or up to 100 mg in 24 h, if tolerated. Erythromycin, in low doses, is another useful prokinetic agent (Twycross et al., in press).

Chemoreceptor trigger zone vomiting such as from opiates, hypercalcemia, and renal failure may be treated by using haloperidol. It is helpful when initiating opioid analgesia to use a small dose of haloperidol (0.5–3 mg orally) as a once-daily dose at night or up to 20 mg over 24 h (Twycross et al., in press).

Nausea and vomiting caused by colic or from gastric secretions may be treated with hyoscine butyl bromide 20 mg three times a day or up to 300 mg over 24 h (Twycross et al., in press).

Vomiting arising in the vomiting center is frequently caused by intracranial pressure and is best managed by dexamethasone and cyclizine. Other useful treatments include benzodiazepines, cannabinoids, and aprepitant (Twycross et al., in press).

A useful adjuvant antiemetic is levomepromazine at a dose of 6 mg three times a day orally or up to 25 mg over 24 h. It may be used with other antiemetics in order to manage symptoms (Twycross et al., in press).

Constipation

This distressing symptom is common in palliative patients. Causes are varied, and constipation frequently causes considerable pain and distress. Determining what is the patient's usual bowel habit is helpful, but generally passing less than three bowel motions in a week is considered to be constipation. Reduced oral intake, lessened activity, as well as the use of medications such as opioids, those with anticholinergic side effects, as well as diuretics can all play a part in causing constipation. As with nausea and vomiting, prevention is easier to manage than treating severe constipation. When introducing opioids and other motility affecting medications, laxatives should always be prescribed and used regularly. Passing a bowel motion should be pain free, and the aim of treatment is to ensure that it can happen.

As with other conditions, assessment of constipation in palliative patients should be undertaken daily. Check for signs of dehydration, rectal bleeding, as well as fecal impaction. Patients should have access to a private space to defecate; they should be offered fiber-rich foods such as prunes or kiwifruit if able to tolerate them, before offering osmotic or rectal treatments.

For most patients, regular use of a softener plus stimulant agent such as docusate plus senna, taken regularly twice a day, as well as adequate fluid intake works well on patients who can tolerate a normal diet.

Osmotic agents such as macrogol solution are preferred to lactulose as they are less likely to cause abdominal cramps and nausea. High dose macrogol (1 L taken over 6 h) is also useful for fecal impaction as well as usual laxative treatments maximized.

Laxative suppositories or micro-enemas such as bisacodyl suppositories or microlax enemas are useful when feces are present in the rectum. A stimulant suppository should be inserted blunt end first and aimed at the wall of the rectum. Glycerol suppositories should be inserted pointed end first and directly into the fecal mass to soften and allow evacuation (Addison, 2000).

Methylnaltrexone, an opioid antagonist, is useful for patients who have opioid-induced constipation. It is administered as a once-daily dose, by injection, and generally causes a bowel motion within 30–120 min. As it does not cross the blood–brain barrier, it can be used without reversing analgesic effects of opioids (BPAC Palliative Care, in press). Oral laxatives should be continued when methylnaltrexone is used.

Enemas may be helpful for patients for whom oral laxatives have not worked as a last resort, either osmotic (e.g., phosphate enemas) or other softening agents. However, care must be taken to exclude a tumor in the rectum before using any rectal or parenteral treatments for constipation.

Dyspnea

Breathlessness or dyspnea often occurs in the last days of life in palliative patients, but it may also be present in end-stage COPD patients well before then.

Nonpharmacological management strategies found to be helpful for breathlessness include positioning changes and reassurance; however, often these are not sufficient alone to ease symptoms.

Morphine is used as first-line treatment, generally orally, and in low doses (2–10 mg when required) (Barnes et al., 2016). Patients who are already prescribed oral morphine for pain relief may be converted to a CSCI of morphine for pain relief and a small dose of oral morphine prescribed for breathlessness. Those patients on fentanyl or oxycodone for renal impairment may also use low-dose oral oxycodone or nasal fentanyl for their symptoms. In the anxious patient, addition of a short acting benzodiazepine such as oxazepam or lorazepam may be beneficial (Palliative Care Expert Group, 2016).

If symptoms persist or are unrelieved by oral morphine, then midazolam may be used, either added to the CSCI or as a nasal spray. Oxygen if the patient is hypoxic, and if available, is often a comfort, as is a fan blowing air near the patient's head (McLeod et al., 2016).

Respiratory Secretions

Patients who are in the last days of life are frequently unable to cough or swallow in order to clear their airway. As such, respiratory secretions may cause noisy breathing and rattling sounds in the throat.

First-line treatment is to reposition the patient, to allow the patient to expel the secretions more easily and allow drainage. Keep the oral mucosa and airways clear by using oral swabs if the patient is not able to swallow, and direct a fan to keep air blowing near the patient's head.

If this is not sufficient to manage symptoms, then use of anticholinergic agents such as hyoscine butylbromide, glycopyrronium, or hyoscine hydrobromide may be indicated. These agents can reduce the production of new secretions, but will not affect existing secretions (Palliative Care Expert Group, 2016).

The use of anticholinergic agents is less invasive than using suction to clear the build-up of fluid (NICE Guidance, in press).

Delirium can be described as altered consciousness, generally manifesting as a reduced ability to be aroused or orientated to the environment (DSM V, in press).

In palliative care, terminal agitation or restlessness can be defined as agitated delirium with cognitive impairment (Chand, 2014). These symptoms may be caused by multiple conditions, for example raised intracranial pressure, hypercalcemia, medications, organ failure, or psychological distress. These conditions are common when patients are dying and may be acutely distressing to the family

as well as the health care professionals involved in the care of that patient. Generally, delirium and terminal agitation are treated with benzodiazepines. For patients not on a syringe driver, sublingual lorazepam or nasal midazolam is useful; for patients on a syringe driver, midazolam, haloperidol, and levomepromazine are all used.

Assessment is the key to managing symptoms and quality of life in the dying patient. Using tools such as the *PQRST* tool discussed in relation to assessing pain can be applied to all conditions that the dying patient is aware of, as well as asking if there is anything "new" that they have noticed or that their carers are aware of. Determining if a treatment is working is key to symptom management, and will guide you as to total pharmaceutical and nonpharmaceutical management strategies for the variety of symptoms that the patient may be experiencing. Drowsiness may mean to review or reduce the amount of opioid analgesic, antiemetic, or anxiolytic used. Increasing pain, colic, or nausea may mean to increase doses or change therapies. Do not forget that other members of the health care team caring for that patient may have some solutions that can be helpful to consider.

Role of the Pharmacist

The role of the community pharmacist, when the patient is managed in a "hospice in the home" environment rather than an inpatient unit is key, as the pharmacist often knows "their patient" and family, and will have insight as to changes, past and potential treatments; as well as a relationship where the patient and their family may feel safe discussing complementary, "natural" or alternative therapies. These must be taken into account when compiling the current list of medications taken by the patient, as some may be hindering as much as helping symptom management.

In New Zealand, hospices are not fully funded by the state. The management boards of hospices frequently include general practitioners, community pharmacists, and other health care providers in the locale, particularly in rural areas where in-patient beds are with rest homes or aged care facilities that can offer a hospital level of care. All other palliative patients spend their last days and weeks at home, in the care of their family and friends as well as the team of health care professionals involved in filling the anticipated needs of the patient. In these cases, admission to hospital is seen as a failure of hospice care, as hospitals are not always located in convenient proximity to all patients in need of secondary and tertiary level care. Rural hospitals, unlike hospitals (which are generally located in or near city centers), do not have specialized medical and other health care professionals specifically trained in care of patients in their last days of life, as their focus is, in general, curative, not palliative. (Authors opinion, borne out in fact in the region where I currently work.)

Pharmacists working in the community, hospital, or hospice have unique skills in managing symptoms, particularly in the last days of life for patients. Determining the appropriate medications for continuous subcutaneous infusions (CSCI) in the correct diluent is key to good symptom management. The unique skills of pharmacists, particularly when medications used, are frequently for unapproved indications, doses, or routes of administration, that is, "off license." For example, in New Zealand, midazolam is approved as a premedication or a sedative, but it is not approved for use for hiccough or dyspnea, and its use either bucally or subcutaneously is not approved. There is, however, evidence for its use both in New Zealand and overseas exists, so this becomes "common practice" (Medsafe, in press; Canterbury NZ Health Pathways, in press). Consent is assumed to be given because the use of these medications is in the best interest of the patient, if they are unable to specifically consent to its use.

In New Zealand, in some areas, the District Health Boards in some regions have issued contracts for specifically trained community pharmacists to compound by aseptic transfer injections for use in a syringe driver. These services are not available nationwide; so, in the remainder of New Zealand, medications are dispensed from community pharmacies for those patients requiring CSCI and "when required" subcutaneous injections, and the injections are prepared in the patient's home, usually by a hospice or "district nurse" immediately before use.

A training program for community pharmacists was set up in New Zealand in the early 1990s, by a pharmacist at Auckland Hospital, Julia Kennedy. This allowed for skills and training material to be developed and this service was available to pharmacists who wanted to be involved in continuing care for their patients. The service continued to grow, as did the number of pharmacists interested in palliative care. All hospices in the Auckland region have developed great relationships with the community pharmacists delivering this service and are seen as key members of the palliative care team.

When a new School of Pharmacy was opened at the University of Auckland, specific training on aseptic training was included as a core skill for their graduates. As a result, all graduates from the Auckland School of Pharmacy have been trained and validated in aseptic transfer, and CSCI preparation and principles.

Remuneration for the syringe driver and "when required" subcutaneous medication syringes for community pharmacies that provide this service is based on the agreed dispensing fee under the service agreement for community pharmacy. Pharmacies are paid for each syringe prepared, the cost for complete ampoules of each ingredient, and a four-fold dispensing fee to cover the facilities, training, extra time, and consumables involved in syringe preparation. As such, provision of palliative care dispensing is seen by pharmacists as a service to their patients, in providing more seamless care, rather than a profit center for their pharmacy.

All pharmacies providing this service are suggested to subscribe to www.palliativedrugs.com as well as have access to the current Palliative Care Formulary and Notes on Injectable Drugs, produced by the New Zealand Hospital Pharmacists Association.

These resources provide compatibility charts for commonly used medications in syringe drivers, advice on symptom management and indications. The pharmacists actively involved with their local hospice also provide peer support for other pharmacists,

particularly those with less experience in the area. Regional hospital pharmacies can provide guidance and advice relating to management of patients if the nearest hospice does not have specialized pharmacists as part of their staff.

The role of the pharmacist in palliative care in the Australian setting is similar to that in New Zealand.

Medication reviews can be undertaken in the hospital as an outpatient, as well as in the home and aged care facility through government funded programs. An important part of regular medication review as the patient deteriorates is the rationalization of medications including ceasing those no long appropriate. Discussion with the patient and family is a key step in this process (Palliative Care Expert Group, 2016).

The provision of medicines information for patients and health professionals, and medicines reviews for palliative care patients by a pharmacist in the community palliative care team is an emerging role. Two projects have received government funding, with one role continuing (Hussainy et al., 2011; Kuruvilla, 2018).

The palliative care pharmacist needs to be aware of the complexities when changing an opioid, which may be a different route, or a different opioid. Opioid conversion resources are available but should be used as a guide only as patient factors such as age, frailty, renal, and liver function, and the clinical context need to be considered. The availability of modified release opioids, which are administered twice daily or once daily, influences the timing of the change also. As part of the regular assessment of the patient's pain, the pharmacist can monitor the response to the immediate release opioid for breakthrough pain and recommend dose modifications with a change in the background-modified release opioid.

A point of difference in practice is that the preparation of syringe drivers is undertaken by the nurse rather than the pharmacist. Guidelines for syringe driver management and education are available at https://www.health.qld.gov.au/cpcre/subcutaneous/learn_modules.

However, the role of the pharmacist is important as a resource to staff for advice regarding compatibility of medications used in the syringe driver, with access to appropriate references is required.

For the Australian palliative care pharmacist, an additional text or subscription recommended to www.palliativedrugs.org is the Therapeutic Guidelines: Palliative Care (Palliative Care Expert Group, 2016).

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World Health Organisation. Available from: https://www.who.int/cancer/palliative/definition/en/.

Syringe Drivers Resources

Dickman, A., Schneider, J., 2016. The Syringe Driver. Continuous Subcutaneous Infusions in Palliative Care, 4th ed. Oxford University Press, Oxford.

Syringe Driver Survey Database. Available from: www.palliativedrugs.org.

Australian Resources on Line

- Caresearch palliative care knowledge network—Available from: https://www.caresearch.com.au/Caresearch/Default.aspx
- Tasmania Specialist Palliative Care
  - Tasmanian Palliative Care Formulary—Available from: http://www.dhhs.tas.gov.au/palliativecare/health_professionals/Tasmanian_Adult_Palliative_Care_Formulary
  - Care Management Guidelines—Available from: http://www.dhhs.tas.gov.au/palliativecare/health_professionals/symptom_management_guidelines
- The Palliative Care Bridge—Available from: http://www.palliativecarebridge.com.au/ includes The Palliative Care Handbook

Selected Readings

Living with Dying: Saunders, Dunlop, Baines
The Death of Ivan Ilyich: Tolstoy
A Scattering: Christopher Lloyd
Being Mortal: Gawande
On Death and Dying : Kubler-Ross
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Fundamentals of Pharmaceutical Care Planning

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Pharmaceutical Care—Historical Perspectives

The term pharmaceutical care was first introduced in 1975 by Mikeal et al., who defined pharmaceutical care as "care that a given patient requires and receives which assures safe and rational drug usage" (Mikeal et al., 1975). This was a decade after the new field of clinical pharmacy emerged, in response to the societal need to address poor medicines control systems in hospitals. "Patient-oriented" clinical pharmacists with specialist drug knowledge were contributing to decisions about medicines and gradually becoming therapeutic advisors for hospital clinical teams in large academic centers. The roles of clinical pharmacists slowly evolved, supported by formal residency training programs and Doctor of Pharmacy degree courses. Pharmacists trained through these programs developed both medicines and disease knowledge and the respect of their clinical colleagues, which enabled them to contribute to everything from medicine selection to therapeutic monitoring. Through the 1980s, the number of clinical pharmacists continued to grow and their roles continued to develop, with clinical pharmacists diversifying into a range of highly specialized roles (Kelly, 2018).

The 1985, the American Society of Health-System Pharmacists' Hilton Head Island conference, with Charles Hepler as keynote speaker, attempted to bring this increasingly dispersed field together. This became a defining meeting for the clinical pharmacy profession. For the first time, this meeting defined the roles and responsibilities of clinical pharmacists, including responsibility for the safe and effective use of medicines, leadership of scientifically informed medicine use, and promotion of the best use of medicines. Importantly, while defining the scope of clinical pharmacy, this meeting also identified technical roles that clinical pharmacists would usually supervise, such as drug control, ordering, and distribution (Kelly, 2018).

By 1989 when a second Hilton Head Island conference was held, clinical pharmacy had become a mature branch of the profession. At the conference, Hepler and Strand presented their seminal paper that suggested pharmacists needed to practice patient-centered care rather than drug-centered pharmacy, if they were to achieve their full professional potential (1990). They defined pharmaceutical care as "the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life." In addition, Hepler and Strand suggested that to be effective, pharmacists required a philosophy of pharmaceutical care practice and a consistent organizational framework in which to work. This philosophy required pharmacists to accept a higher level of professional responsibility to ensure medicines use is effective and safe for individual patients. Core components to fully benefit patient care were identifying, resolving, and preventing medicines-related problems and cooperate effectively with other health-care professionals (Hepler and Strand, 1990).

As time progressed, with some debate along the way pharmaceutical care practice has progressively but variably penetrated all sectors of the pharmacy profession. The concepts of pharmaceutical care continued to evolve since 1990 and have become cornerstones of pharmacy education.

The definition of pharmaceutical care has also been redefined numerous times since 1990. A recent redefinition by the Pharmaceutical Care Network Europe group to address the lack of clarity on the current meaning of pharmaceutical care and how it differs from other terminology is "pharmaceutical care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes" (Allemann et al., 2014).

Although the use of the term pharmaceutical care has somewhat fallen out of favor in practicing pharmacists' vernacular, a myriad of concepts, terms and services have evolved which reference Hepler and Strand's vision. Examples of these include medicines optimization (NICE, 2015), medicines management, medication therapy management, quality use of medicines, medication review, medicine use review, and clinical checking (Cipolle et al., 2012; Bluml, 2005; Kanani and Churchill, 2019).

Pharmaceutical Care Practice

Given the rapidly evolving roles of pharmacists, competency in pharmaceutical care practice is needed now more than ever, across the profession. This section will first provide background to pharmaceutical care practice, then will summarize the current barriers and enablers of pharmaceutical care practice, before providing examples of settings in which pharmaceutical care practice can be applied.

Background to Pharmaceutical Care Practice

Medicines are the most common therapeutic intervention in health care. They of course play an essential role both in keeping people well and in treating illness when it occurs. However, when used inappropriately, medicines-related problems and adverse effects cause significant harm. The cost of medicines is continually rising yet the full benefits are not being realized. Up to half of medicines prescribed for long-term conditions are not used by patients as the prescriber intended, or are not taken at all (Nieuwlaat et al., 2014). Appropriate, safe, and cost-effective use of medicines is a priority for policymakers globally (Härkänen et al., in press).

Potential misuse of medicines is being exacerbated by rapid change in health-care systems around the world. Health systems are currently facing a number of significant challenges: an ageing and rapidly growing patient population with significant health inequities, increasing burden from long-term conditions with multimorbidities, rapid implementation of more complex and expensive new therapies, delivered by an ageing health-care workforce not resourced to provide sufficiently patient-centered care (Traulsen and Druedahl, 2018). It is clear that global health needs are not able to be met within current capacities and models of care. The pharmacy profession has been identified by policymakers as providing a relatively untapped resource to address these problems (Kanani and Churchill, 2019; Ministry of Health NZ, 2016a). Assessing the effectiveness of pharmacists applying pharmaceutical care principles to address these problems is challenging, due to the wide range of practice models and services undertaken and inconsistent outcome measures. Nevertheless, across all sectors of health care, pharmaceutical care has been shown to reduce mortality and morbidity and optimize patient outcomes to a range of patient groups, as well as improving quality of life, reducing adverse drug reactions and providing economic benefits (Babar et al., 2018; Jokanovic et al., 2016; Perlroth et al., 2013).

Current Barriers of Pharmaceutical Care Practice

While globally many pharmacists strive to practice using pharmaceutical care ideology and principles, as they take on a growing number of innovative services, pharmaceutical care practice is still not the norm globally. One common reason is that funding models to fully support pharmaceutical care practice are not consistently available. Many pharmacists therefore do not have the opportunity to maintain competence with the required knowledge and skills. In community pharmacy, maintaining financial viability can generate a tension between retail and professional roles (Scahill et al., 2018) with a supply focus remaining prevalent in some community sectors; therefore, technical tasks sometimes need to take precedence over time required for cognitive services (Davies et al., 2014; Traulsen and Druedahl, 2018). In hospital pharmacy practice, patients transition at much higher pace than they did previously, often without a commensurate increase in pharmacy resources, so time to provide adequate pharmaceutical care services has reduced (Dalton and Byrne, 2017).

Current Enablers of Pharmaceutical Care Practice

As described above, more than ever before pharmacists are being recognized as capable of playing a vital role to support peoples' health and well-being. There are a growing number of services being provided across all sectors where pharmaceutical care skills can be utilized (Kanani and Churchill, 2019). The development of extended roles for pharmacy technicians through workforce redesign initiatives has enabled this valuable group to contribute to a greater extent to patient care; for example, with prescription accuracy checking, medication history taking, and providing education to patients. The developing roles of pharmacy technicians and assistants can free up pharmacists to perform more cognitive roles (Keresztes, 2006; Napier et al., 2018).

Examples of Settings in Which Pharmaceutical Care Practice Can Be Applied

In many parts of the developed world, legislative changes and the reclassification of medicines have expanded and extended the scope of pharmacist practice, introducing novel roles. These include the provision of pharmaceutical care within general practice and

aged residential care home settings (Chaplin, 2016; Tan et al., 2013). Pharmacists are increasingly providing pharmaceutical care to vulnerable populations with high health needs such people with intellectual disability (Auckland District Health Board, 2016; Bell et al., 2015), substance misuse, and mental health disorders (McMillan et al., 2017). Pharmacists are now able to utilize their pharmaceutical care skills to a greater extent by prescribing medicines in a number of countries (Shaw et al., 2013).

Pharmaceutical Care—Educational Aspects

To provide quality-assured pharmaceutical care services in any of the settings described above requires pharmacists to be appropriately trained and competent. Pharmaceutical care requires competence in comprehensive patient consultations and medication review, which in turn require skills in person-centered communication and patient assessment, and competent use of frameworks to facilitate consistent pharmaceutical care planning, in addition to the currently recognized pharmacy science, clinical pharmacy practice, and pharmacotherapy subjects. This section will first of all outline the changing expectations of pharmacists, which dictate a change in pharmaceutical care education. The educational benefits of formal pharmaceutical care planning frameworks will then be discussed, followed by the pharmaceutical care learning and assessment needs of both pharmacy students and experienced pharmacists in practice.

Changing Expectations for Pharmaceutical Care Skills

Health-care systems expect consistent quality-assured practice by competent health professionals, which requires both appropriate initial training and assessment and ongoing continuing professional development (Bader and Bates, 2017). Health-care systems also expect that as professionals, pharmacists will continually strive to improve their services, which increasingly includes the pharmaceutical care they provide. In most countries, these qualities are embedded in core competencies defined by the pharmacy profession's regulatory body, linked to the accreditation standards of pharmacy schools and colleges.

As outlined above, roles of pharmacists are changing rapidly. For example, in the United Kingdom, the National Health Service Long Term Plan expects pharmacists to now provide enhanced services that will require person-centered communication skills, additional patient assessment skills, and in some cases prescribing (Kanani and Churchill, 2019). For example, in New Zealand, government policies have refocused on improving access to health services, reducing inequities and increasing sustainability, through new models of practice and a more agile workforce (Ministry of Health NZ, 2016a). The New Zealand Ministry of Health has recognized the value of pharmacists in achieving these goals, and a Pharmacy Action Plan outlines a program of reforms to make better use of pharmacist skills (Ministry of Health NZ, 2016b). As part of this plan, new services are being developed where the pharmacy profession will provide person-centered pharmaceutical care to a much greater extent than it does currently.

However, pharmacists, although highly capable, are recognized as having some learning needs important for person-centered pharmaceutical care roles. Traditionally, pharmacists were not taught person-centered consultation skills, where the focus is on engaging with patients and explore their medicines experiences in order to support them make the best use of their medicines. Learning how to effectively gather information from and provide education to patients has been more usual (Murad et al., 2014). Teaching of patient assessment skills for the purposes of diagnosing and assessing long-term clinical conditions was not commonplace (George et al., 2006). In addition, pharmacists have limited training in precision medicine, where new diagnostic modalities including genomics are used to inform prescribing and prevent medicines-related problems. To meet the new expectations of enhanced skills in pharmaceutical care requires a step change in their learning. For example, the complex skills of clinical reasoning are well researched and systematically taught in medicine and other health professions (Higgs et al., 2018) and are relevant to all aspects of pharmaceutical care planning. However, clinical reasoning remains an emerging and inconsistently taught area for pharmacy (Sinopoulou et al., in press; Wright et al., in press). In addition, team working skills to enable pharmacists to be effective member of health-care teams, while clearly a part of every pharmacists work, may now require reinforced education to support expended pharmaceutical care roles. This education may include formal evidence-based methods to promote safe and effective written and verbal communication, more formal documentation of pharmaceutical care plans, and increasing use of shared patient records with other health professionals.

Above all, to meet these expectations, pharmacy schools and colleges, professional bodies, and governance organizations will in future more than ever need to work together to align the teaching, practice, and assessment/accreditation of pharmaceutical care (Kolar et al., 2017). This will also require a coherent professional identify of pharmacists that incorporates pharmaceutical care as a core skill and activity. At present, the professional identity of pharmacists, and presumably the place of pharmaceutical care practice in their identify, appears to be unclear—this is an area of current research interest.

Pharmaceutical Care Planning Education for Pharmacy Students and Experienced Pharmacists

The pharmacy profession is still transitioning to a position where pharmaceutical care is routine practice in all sectors. This has three consequences for pharmacy education. First, the curricula in some pharmacy schools and colleges are yet to align with the range of roles that may be available to pharmacy students at the time of their graduation. Second, where pharmacy educators are already delivering curricula in which person-centered pharmaceutical care is a key component, they may be preparing students for pharmaceutical care roles that are not yet universally available. Third, pharmacy students may face challenges during their

experiential placements, since not all pharmacists they are placed with will use pharmaceutical care skills. Some students have reported being discouraged from using pharmaceutical care skills by both supervising pharmacists and patients.

In one study, approximately one-quarter of pharmacy student participants reported that their pharmacist supervisors actually discouraged them from even fundamental person-focused practices such as educating patients, which led some of the students having difficulty establishing their pharmacist professional identity (Noble et al., 2014). One approach to these challenges is to openly acknowledge them. Given the transitional nature of pharmacy, it seems sensible to teach pharmaceutical care skills using a range of practice scenarios so that students see how the process can be contextualized to different settings. In pharmacy schools and colleges, ideally pharmaceutical care planning using formal frameworks can be taught intentionally and consistently throughout each program (Kolar et al., 2017). Use of a range of case scenarios can challenge students to apply their nascent pharmaceutical care skills to increasingly more complex medicines-related problems (Farrell et al., in press). This contrasts with curricula that select case scenarios primarily to promote learning about diseases and evidence-based treatment options.

As described above, the current transitional nature of pharmacy means that some experienced pharmacists who have practiced primarily in dispensing roles may need upskilling in pharmaceutical care through continuing professional development. As in pharmacy schools and colleges, the use of a formal pharmaceutical care framework, together with a range of practice scenarios, may be valuable for this continuing education in pharmaceutical care. In addition, case scenarios could be included in regular assessment of pharmaceutical care for practicing pharmacists, as part of the quality assurance programs that are increasingly required by health-care funders. Whether or not ongoing assessment of pharmaceutical care planning skills is formally required, as professionals most pharmacists are likely to seek evaluation of their pharmaceutical care effectiveness, as well as opportunities for ongoing learning. As noted above, formal pharmaceutical care planning frameworks that can be applied to both real patients and case scenarios facilitate both the consistent quality-assured application of pharmaceutical care planning and ongoing evaluation.

Pharmaceutical Care Planning

For the purposes of this chapter, the term pharmaceutical care planning refers to the patient care processes or frameworks through which the pharmacist identifies, resolves, or prevents potential or actual medicines-related problems.

As noted above, there are a large number of pharmacy practice models and services utilized throughout the world that aim to improve patient health outcomes and are informed by the concept of pharmaceutical care. Not surprisingly, there are a corresponding array of approaches to how the activity or service should be conducted, presented as guidance documents, templates, and practice standards. Many contain detailed checklists of points to consider when reviewing patients, rather than overarching frameworks that support clinical reasoning.

A significant initiative in the United States has been the development of the Pharmacists' Patient Care Process (PPCP) by a group of national pharmacy organizations led by the Joint Commission of Pharmacy Practitioners (JCPP) (2014). The JCPP is a national forum of leading pharmacy organizations in the United States. This model is described below as an example of a framework that lends itself to a systematic and consistent approach to pharmaceutical care planning.

The PPCP came about from the recognition of a need for a consistent process for pharmacists and educators that could be applied to any practice setting and service in the delivery of patient care. The Accreditation Council for Pharmacy Education now requires that the PPCP as described by the Joint Commission of Pharmacy Practitioners is included within college of pharmacy curricula.

The model is based on Hepler and Strand's concept of pharmaceutical care and pharmacists using the PPCP are expected to "collaborate, communicate, and document" to optimize patient health outcomes. A person-centered theme is evident throughout, and it is intended that pharmacists support patients to be engaged and involved in their care. While the PPCP is intended to be used in all patient care settings, the time spent on each step and intensity may vary depending on need. The model includes a five-step process, depicted in **Fig. 1**.

The model includes a five-step process:

- Step 1—Collect: Using a person-centered approach, the pharmacist collects necessary subjective and objective information.
- Step 2—Assess: The pharmacist analyzes the information collected in context with the patient's own health goals to identify and prioritize medicine-related problems.
- Step 3—Plan: A person-centered, evidence based, cost-effective care plan is developed in collaboration with the patient or caregiver and other health-care providers.
- Step 4—Implement: The pharmacist implements the care plan in collaboration with the patient or caregiver and other health-care providers.
- Step 5—Follow-up: Monitor and Evaluate: The pharmacist monitors and evaluates the effectiveness of the care plan and makes adjustments as necessary, again in collaboration with the patient or caregiver and other health-care providers.

Further information on the Pharmacists' Patient Care Process can be found in the "Further Reading" section.

The Use of Frameworks and Scaffolds for Effective Pharmaceutical Care Planning

The Pharmacists' Patient Care Process can appear deceptively simple to use; however, pharmaceutical care planning involves a series of complex clinical reasoning steps within the overarching frameworks. Clinical reasoning can be described as "an evidence-based,

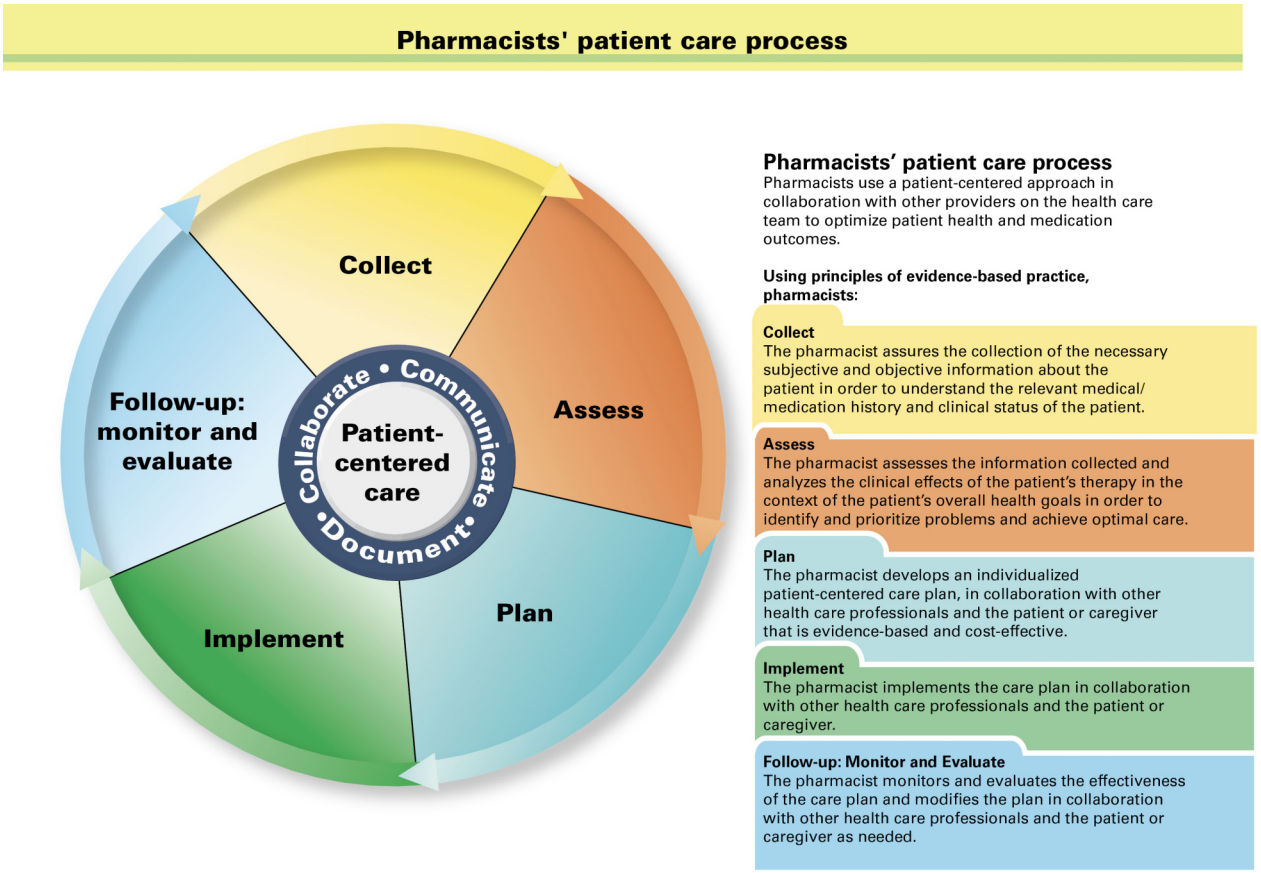

Figure 1 Pharmacists' patient care process (Joint Commission of Pharmacy Practitioners). *Source: Reproduced with permission from: http://www.pharmacist.com/sites/default/files/JCPP_Pharmacists_Patient_Care_Process.pdf.*

dynamic process in which the health professional combines scientific knowledge, clinical experience, and critical thinking, with existing and newly gathered information about the patient" (Sinopoulou et al., in press). Clinical reasoning is required to consider which patients should be targeted for review; the gathering and analyzing of information; generating hypotheses for identifying, prioritizing, and resolving of medicine-related problems; deciding on how the care plan should be enacted; and what follow-up is required, by whom and when.

There is evidence that targeted learning scaffolds are beneficial for novice learners, such as pharmacy students, newly qualified pharmacists, and experienced pharmacists moving into new roles and clinical areas. Scaffolding is "the systematic sequencing of prompted content, materials, tasks, and teacher and peer support to optimize independent learning, it can include instructional elements such as guided questioning; comparing ideas; identifying connections and distinguishing characteristics between concepts; and identifying valid relationships." (Dawn et al., 2011).

The combination of an overarching framework where the big picture can be seen (for example, with the PPCP), combined with targeted learning scaffolds to support clinical reasoning (Higgs et al., 2018), should be considered to promote systematic and consistent learning of pharmaceutical care planning. While formal scaffolds may seem time consuming at first, they promote conceptual learning and reduce the possibility of learning pharmaceutical care planning using flawed clinical reasoning processes once the pharmacist uses a more intuitive approach. As an individual's pharmaceutical care planning skills develop and decision making becomes more intuitive and the scaffolds can be finessed for various clinical contexts.

Students and novice pharmacists can find it challenging to know where to begin when identifying actual or potential medicine-related problems. Examples of frameworks and scaffolds that support a systematic approach to pharmaceutical care planning are provided below.

Medicine-Related Problems Classification Systems

Identifying, resolving, and preventing medicine-related problems (MRPs) is a core component of pharmaceutical care planning. A medicine-related problem has been defined by the Pharmaceutical Care Network Europe as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (van Mil et al., 2017). The use of medicine-related problem or drug therapy problem classification systems is useful to provide a systematic process to identify actual or potential

problems when reviewing a patient's therapy. Some MRPs are more obvious to identify, for example, when a significant medication overdose has unintentionally been prescribed. This may "jump out from the prescription" and prompt the pharmacist to query with the prescriber. Other MRPs can be almost hidden, for example, when venous thromboembolism (VTE) prophylaxis has been inadvertently not considered for a patient at high risk of experiencing a VTE event. It will be missing from the patient's medicine list and may not be thought of.

Unfortunately, many different MRP classification systems have been developed and published, this makes it challenging for pharmacists to learn and use a consistent approach to identifying MRPs and enable comparison of pharmaceutical care services. Nevertheless, MRP classification systems are a useful aid for pharmacists to systematically identify actual or potential MRPs. Basger et al. (2015) have recently developed an aggregated classification system for the causes of MRPs.

The MRP classification system first described by Strand, Morley, and Cipolle et al. is still very relevant (1990). Detailed guidance on the use of this classification system can be found in the Further Reading section below (Cipolle et al., 2012). They identified four unmet medicine-related needs—indication, effectiveness, safety, and adherence. A corresponding list of seven categories of drug therapy problems are associated with these unmet needs:

- Drug therapy problems 1 (unnecessary drug therapy) and 2 (needs additional drug therapy) are associated with the medicine-related need indication;
- Drug therapy problems 3 (ineffective drug) and 4 (dosage too low) are associated with effectiveness;
- Drug therapy problems 5 (adverse drug reaction) and 6 (dosage too high) are associated with safety;
- Drug therapy problem 7 (nonadherence or noncompliance) is associated with adherence.

Categories of Factors to Consider When Identifying Medicine-Related Problems

Table 1 provides a method of systematically identifying problems based on four categories—patient factors, disease factors, medicine factors, and factors related to the environment or system the patient is within.

Table 2 provides some illustrative examples from each of the four categories of factors of actual medicine-related problems that need resolving.

Screening Tools and Guidance Documents to Support Prescribing Appropriateness and Identification of Medicines-Related Problems

A wide range of guidance documents and screening tools have been developed to assess the appropriateness of medicines prescribed for individual patients. Examples include guidance for reducing inappropriate polypharmacy such as the screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START) criteria; the Beers Criteria; the Medication Appropriateness Index; and deprescribing guidelines. These are useful to complement the clinical reasoning processes utilized

Table 1 Categories of factors to consider when identifying potential or real medicines-related problems

Patient factors	Factors related to the patient themselves, for example, their medicines taking experience, health beliefs, understanding of health and medicines, health literacy, demographics, ability/disability, social circumstances, lifestyle
Disease factors	Factor's related to the patient's health status, for example, current and past medical history, known allergies, or adverse drug reactions, comorbidities
Medicine and prescription factors	Factors related to the patient's medicines—medicine interactions, pharmaceutical and/or formulation issues, funding, prescription legality
Environment and system factors	Factors related to the system or environment the patient is situated in, for example, medication reconciliation errors experienced when transitioning care settings

Reference—Print SA, i.e., author's original work.

Table 2 Illustrative examples of medicine-related problems identified using the factor categories

Patient factors	The patient was unable to afford the prescription fee so was unable to collect his prescription for antibiotics from his community pharmacy
Disease factors	Patient is taking a calcium channel blocker (diltiazem) for hypertension; he has now developed heart failure with reduced ejection fraction. Diltiazem may worsen this comorbidity, and the patient therefore requires an alternative blood pressure medication
Medicine and prescription factors	A one-year-old child has been prescribed a cardiac medicine that is only available in capsule form; therefore, a compounded mixture is required to be prepared
Environment and system factors	An older patient was admitted into hospital from her residential care facility with community-acquired pneumonia. One of her usual medicines was prescribed incorrectly (anticonvulsant medicine for her epilepsy inadvertently left off the hospital prescription chart). This was identified by the pharmacy technician during a medicines reconciliation review. The prescribing pharmacist reviews the patient's medicines history and corrects the error

Reference—Print SA, i.e., author's original work.

during pharmaceutical care planning, and there is some evidence of benefit in terms of preventing adverse drug events, improving medicine appropriateness, and reducing medicine costs (O'Mahony et al., 2014; Rankin et al., 2018).

Tools to Promote Safe and Effective Interprofessional Communication

A number of communication tools such as SBAR (situation, background, assessment, and recommendation) and SOAP (subjective, objective, assessment, and plan) have been developed in order to provide structured frameworks for safe and effective communication between health-care team members (Barnett et al., 2017; Reeves et al., 2017; Shahid and Thomas, 2018).

Future Aspects and Threats

As discussed above, around the world pharmacy as a profession is rapidly changing, with expanded expectations for pharmacists to provide pharmaceutical care. This represents both an opportunity and a threat.

The opportunity is for pharmacists to grow the value they provide to individual patients and health-care systems through person-centered pharmaceutical care. This is especially relevant at a time of major health service challenges. Advances such as automation for dispensing, increased ability to share patient information between health-care providers, "telehealth" consultations for rural patients, pharmacogenomics, artificial intelligence to identify obvious medicine-related problems and guide decisions, as well as expanded technician roles can be harnessed by pharmacists to increase the effectiveness of their pharmaceutical care practice (Spinks et al., 2017). By taking opportunities to expand the scope and quality of their pharmaceutical care in an evidence-based manner, pharmacists have a real but time-limited prospect to jointly lead the new age of precision medicine.

The threat is that if the pharmacy profession does not rise to changing expectations and utilize the new opportunities described above, many pharmacist roles could be lost with the pharmacy profession becoming less relevant (Spinks et al., 2017). Pharmaceutical care practice could cease to be the domain of pharmacists, being overtaken by medicines management roles performed by other health-care professionals. Health systems would be poorer without the skills and academic background of the pharmacy profession.

Conclusion

Since it has been only 30 years since the concept of pharmaceutical care became widely introduced, the pharmacy profession is still transitioned from a focus on medicines to a focus on patient care. Due to inconsistencies in implementing pharmaceutical care, unclear perception of pharmacist roles and inconsistent opportunities for education, pharmaceutical care is still only practiced by a subset of pharmacists globally. In addition, the pharmaceutical care concept originally envisaged by Helper and Strand has evolved into a range of disparate models and services. While these models and services have commonality in their intention to optimize medicines and improve patient outcomes, they use varied methodological approaches and outcome measures. This means that pharmaceutical care, when it is performed, is inconsistent in style and depth, making quality assurance and proof of worth difficult. At the same time, health-care systems face increasing challenges and the viability of the traditional pharmacist roles focused on dispensing and technical functions outside of a person-focused framework are coming under increasing threat. On the up side, the pharmacy profession is very well placed to utilize new opportunities and technologies for repositioning itself as the leader of pharmaceutical care practice within health-care teams. A transformative change in both pharmacy practice and education could prepare the pharmacy workforce for the future. Hopefully, through a refocus on the philosophy of pharmaceutical care, pharmacists will achieve Helper and Strand's vision of meeting an urgent societal need by supporting people to get the best out of their medicines. As a side effect, a focus on pharmaceutical care could ensure the profession's long-term value and sustainability.

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Health Outcomes and Quality of Life

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Introduction

Improvements in socioeconomic status coupled with advances in medical interventions and public health services have contributed to a significant increase in life expectancy, especially in high income countries (Christensen et al., 2009; Salomon et al., 2012, Centers for Disease Control and Prevention, 2003). As a result, people in the older age groups have become the fastest growing age groups, making the 21st century a "century of ageing" (Salomon et al., 2012; World Health organization, 2002). Population estimate data indicate that a quarter of the population in western countries will be aged ≥60 years by 2030 and this figure is projected to be 2 billion by 2050 (Payne et al., 2013; World Health organization, 2002).

Although the increase in life expectancy may be considered one of the great achievements of humankind in the 21st century, it may also contribute to social, economic, and health systems challenges. Longevity of life is often at the expense of an individual's quality of life due to the accompanying ageing and age-related problems. Therefore, as a growing proportion of the population is surviving longer, often with multiple chronic diseases (Islam et al., 2014), the impact on HRQoL is a significant consideration. Chronic disease is associated with increased risks such as mortality, frequency of emergency department visits, unplanned hospital admissions and longer hospital stays, and increased utilization of health care resources (Condelius et al., 2008; Hwang et al., 2001; Lee et al., 2007; Payne et al., 2013, Centers for Disease Control and Prevention, 2003). Having multiple concurrent chronic diseases often leads to poor functional status and decreased quality of life, psychological distress, prescribing of multiple medicines (often polypharmacy and hyper polypharmacy), and adverse drug events (Bayliss et al., 2004; Hwang et al., 2001; Payne et al., 2013; Valderas et al., 2009; Wolff et al., 2002).

Over the past few decades, the rise in the prevalence of chronic disease has become the major public health issue, drawing the attention of health care policy makers and practitioners (Centers for Disease Control and Prevention, 2003). Equally, in concert with the demand and focus of chronic disease management, there has been a move toward slowing disease progression and minimizing functional limitations due to the burden of multimorbidity. However, in meeting this demand, health care systems continue to face structural, organizational, and financial challenges (Fortin et al., 2007; Islam et al., 2014; Schoen et al., 2009). To date, tackling the burden of chronic disease remains a key global health agenda, demanding more research, better delivery of health care services, organizational reform, and re-thinking health care policy (Fortin et al., 2007; Norris et al., 2008; O'Brien

et al., 2011; Sipkoff, 2003; Valderas et al., 2009). In recent years, the emphasis on health care policy has turned to "active aging and healthy living" so that individuals can remain active participants in the society as they become older (Clemson and Laver, 2014; World Health organization, 2002). Therefore, besides longevity, ensuring healthy life expectancy is a key consideration for ageing and its related burden at individual, society, and health care systems. However, in complex and dynamic health care systems, a variety of factors may compromise the quality of health care services. Thus, evaluation of key outcomes associated with health care services and interventions has been a growing area of interest to help ensure informed decisions related to health care practice and policy.

Health Outcomes

Health outcomes refer to the impact that health care services may have on people's life. It encompasses all outcomes or end results associated with health care services. The Donabedian framework for evaluating health services is divided into *structural, process, and outcome indicators* (Donabedian, 1988). The evaluation of health care services has traditionally focused on structure and processes measure. But it is outcome measures which provide insight into the impact of health services or interventions on a patient's life from which informed choice of the service and allocation of resources can be made. Types of evidence may include: what impact does a given health care service have on patient's symptoms and functioning, whether a given disease gets better or worse, and ultimately whether patients live or die as a consequence of the service. The overall focus of health outcome is, to question and investigate end results obtained from what is done for patients and how the end results impact on patient's lives.

Types of Outcomes

Outcomes of health care interventions can be described in different ways. The five D's (death, disease, disability, discomfort, and dissatisfaction) is the classical approach, but is used less in contemporary outcome research (Lohr, 1988) for two main reasons. First, this approach captures only limited outcomes in evaluating the quality of health care. Second, it does not reflect any positive outcomes of health care interventions. The Economic, Clinical and Humanistic Outcome (ECHO) model is a more comprehensive and suitable approach, particularly for the evaluation of pharmaceutical care services (Kozma et al., 1993).

Economic outcomes consider the direct, indirect, and intangible costs associated with health care interventions. Models of health economics which apply economic principles to health are used to evaluate economic outcomes of health care interventions. Health economic models of analysis, for example, cost benefit analysis, cost effectiveness analysis, cost minimization analysis methods, have been widely used to evaluate the economic value of the health care services at patient, societal, and health care system levels. Evaluation of economic outcomes in clinical pharmacy interventions is necessary to establish evidence about "value for money" in relation to the allocation of resources and reimbursement of services. For example, the benefit of the service (e.g., number of days free of pain, cases cured, and prevention of medication related complications) worth the cost or extra cost incurred by provision of the service. To date, there is significant body of evidence generated from research into evaluation of various models of clinical pharmacy services indicating the economic benefits of the service to the patient and health care system (Cheng et al., 2013; Graabaek and Kjeldsen, 2013; Marra et al., 2017; McLean et al., 2003; Viswanathan et al., 2015).

Clinical outcomes are events that occur following a disease or treatment. Clinical outcomes are measured as changes in a patient's health and can be used to generate evidence about the clinical benefits of health care services. For example, disease related morbidity and mortality, adverse drug reactions, and medicine related hospitalizations, in addition to surrogate clinical outcomes such as changes in glucose levels, blood pressure, cholesterol levels (Cheng et al., 2013; Fernandez-Llamazares et al., 2012a,b; Jokanovic et al., 2017; Wal et al., 2013). There is a growing body of research evidence indicating the effectiveness of various models of clinical pharmacy services in improving clinical outcomes in various chronic disease conditions such as diabetes (Al Mazroui et al., 2009; Elnour et al., 2008; Johnson et al., 2010; Machado et al., 2007a; Pinto et al., 2014; Turnacilar et al., 2009; Viswanathan et al., 2015), dyslipidemia (Jokanovic et al., 2017; Paulos et al., 2005; Roughead et al., 2005a,b; Santschi et al., 2011; Tsuyuki et al., 2002; Turnacilar et al., 2009), hypertension (Aguwa et al., 2008; Cheema et al., 2014; de Souza et al., 2007; Machado et al., 2007b; Marra et al., 2017; Santschi et al., 2011; Wal et al., 2013), Heart failure (Korajkic et al., 2011; Koshman et al., 2008; Lopez Cabezas et al., 2006; Sadik et al., 2005; Viswanathan et al., 2015), asthma, and Chronic obstructive pulmonary disease (Jarab et al., 2012; Johnson et al., 2010; Ottenbros et al., 2014; Schulz et al., 2001; Wei et al., 2014; Zhong et al., 2014).

Humanistic outcomes focus on consequences of disease and treatment on patient's functional status and quality of life. Unlike economic and clinical outcomes, humanistic outcomes are subjective measures and often considered as patient reported outcomes (PROs). The term PROs encompass a wide range of important outcomes, including patient's experience of disease or treatment related symptoms, satisfaction with treatment, self-rated health status, the impact of disease and treatment on functioning and well-being. PROs are not only the most commonly used but also the best approach to measure the social, physical, and psychological impact of a disease and its associated therapy. Evidence generated from PROs data complement other indicators of health outcomes (i.e., clinical and economic). In some cases, PROs becomes the only practical end points (e.g., pain management) when there are no other observable biological markers of a disease or treatment. In outcome research, health related quality of life (HRQoL) tools are the most common patient reported measures used to evaluate effects of health care interventions, impact of disease and treatment on functioning and wellbeing.

An increase in life expectancy has resulted in a high demand for the evaluation of the quality of life extended due to medical interventions (Pennacchini et al., 2011). Quality of life (QoL) is an important outcome requiring attention, especially in older people with chronic disease conditions (Ernst et al., 2003; Kozma et al., 1993) and in people taking long-term multiple medicines (Bulpitt and Fletcher, 1994). Without evaluation of QoL, the evaluation of a given health care intervention is incomplete. For example, in older people with multiple chronic conditions, evaluation of outcomes of therapy based on biological criteria alone is inadequate. Similarly, measures of death rates or survival alone do not reflect a complete picture of changes in population health. A holistic evaluation of the effects of chronic diseases and its treatment go beyond biological or physiological outcomes and should also include other domains (e.g., humanistic outcomes) in order to gain a more complete picture of the impact of health care interventions (Ernst et al., 2003; Patrick and Bergner, 1990).

QoL and HRQoL: Historical Development

As medical treatments have increasingly extended length of life (Karimi and Brazier, 2016; Pennacchini et al., 2011) sometimes at the expense of the quality of life (Karimi and Brazier, 2016), measurement of QoL has become a key outcome to consider in clinical care. The term QoL began to appear in the medical literature in the 1960s (Elkinton, 1966; Pennacchini et al., 2011; Spitzer, 1987) and started to be utilized in clinical practice to facilitate decision making in the 1970s (Pennacchini et al., 2011). In 1977, the medical subject heading (MeSH) term for QoL was introduced in Medline as "a generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment; the overall condition of a human life" (Pennacchini et al., 2011). Since then, there has been a growing interest in the concept of QoL in outcome research as well as clinical settings. The development of new measures with a focus on their psychometric properties (Guyatt et al., 1993) began to proliferate in the 1990s (Pennacchini et al., 2011). During this period (specifically in 1995), the world health organization (WHO) introduced a broader concept of QoL defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (1995). QoL is a broad concept encompassing health and nonhealth issues impacting on an individual's life. In health care interventions we are rarely interested in nonhealth aspects of QoL (Guyatt et al., 1993; Torrance, 1987) as they may not be affected by the disease and its treatment. Thus, nonhealth aspects of QoL are considered of less importance in decision making for health care providers, health care administrators, and health policy makers. This conceptual issue led to the introduction of a new concept of health focused measures of QoL known as HRQoL measures.

Currently, several definitions of HRQoL exist (Karimi and Brazier, 2016) based on various approaches and viewpoints. For example, HRQoL has been defined as "how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health," "aspects of self-perceived well-being that are related to or affected by presence of disease or treatment," (Ebrahim, 1995) and "values assigned to different health status." Although these definitions have some differences in the interpretation of HRQoL concept, they all encompass the concept that HRQoL is an "aspect of QoL which is related to health, excluding nonhealth factors such as religion, politics and quality of the environment" (Guyatt et al., 1993; Torrance, 1987). Hence, HRQoL is a subset of QoL that is determined primarily by a patient's health status and influenced by health care interventions. Some HRQoL measures focus on a single concept such as emotional functioning while others consider such a concept as one aspect or dimension within a multidomain construct of the measure. There is less agreement about the number or types of dimensions that should be included in HRQoL instruments. However, the general consensus is that HRQoL is a multidimensional construct which includes physical social, psychological, and aspects of patients' health which can be affected by the disease or treatment. In the context of health-related outcomes, it is important to understand and distinguish the conceptual overlap between HRQoL and overall QoL (Karimi and Brazier, 2016). However, the term QoL and HRQoL are often used interchangeably in the literature (Karimi and Brazier, 2016; Spitzer, 1987) without making distinction of their basic differences (Cheema et al., 2014; Leplege and Hunt, 1997; Moons, 2004; Ware, 1995). Readers are advised to infer the implicit definition of a given HRQoL measure from the conceptual characteristics and the level of description of aspects of health the measure is intended to assess, i.e., health states or impairments of health by a disease or treatment.

Relevance of HRQoL Measures: Perspectives of Practice and Research

HRQoL is an outcome through which patients express their feelings and experiences about the impact of a disease and its treatment on their health and wellbeing (Petersson et al., 2013). HRQoL measures are used to obtain information about self-reported health status, that is, improvement or impairment in health status following a health care intervention (Guyatt et al., 1993). HRQoL measures are now commonly called patient-reported outcome measures (PROMs) indicating that patient's self-rated symptoms of the disease and treatment are included in the assessment. In clinical practice, HRQoL measures provide additional information which complement evidence obtained from clinical and biomedical investigations. In evaluating outcomes of therapy, HRQoL measures can be used to assess the impact of acute or curative treatment (e.g., number of days free of symptoms, impact of disease sequelae on productivity) as well as chronic or palliative treatments (e.g., measurement of improvement or deterioration in health status) (Badia and Herdman, 2001). However, in chronic treatment and palliative care where the goal of therapy is ameliorating symptoms rather than a cure, HRQoL becomes a primary outcome to evaluate the long-term impact of an intervention or therapy

(Badia and Herdman, 2001). Information collected from HRQoL measures provides insight into aspects of HRQoL that matters most to patients in relation to their medical condition and or associated therapy. Consequently, this helps to make informed decisions (Carlton and Kaltenthaler, 2011) about therapeutic modalities specific to dimensions of HRQoL requiring attentions of health care providers.

Types of Quality of Life Measures

Since 1990s, numerous HRQoL measures have been developed and used in outcome research including research into evaluation of clinical pharmacy services. These measures have been developed based on various conceptual as well as theoretical approaches and viewpoints. The measures can be broadly classified as generic or disease/condition specific measures (Guyatt et al., 1993).

Generic Measures

A wide range of generic measures are available for evaluation of HRQoL outcomes in medical interventions, e.g., the Medical Outcome Study Short Form Health Survey (SF-36) (Ware, 1995), EQ-5D, WHO-QoL, and Health Utility Index. These measures have been used extensively to evaluate the impact of pharmacotherapy and clinical pharmacy services (Mohammed et al., 2016a; Pickard and Hung, 2006; Pickard et al., 1999) with the SF-36 measure and EQ-5D the most widely used (**Table 1**) (Mohammed et al., 2016a). Conceptually, generic measures are designed to be applicable to all disease conditions (Guyatt et al., 1993), across diverse medical interventions and population groups. Thus, they are preferred measures to assess quality of life outcomes in patients with comorbidities irrespective of the combination of medical conditions (Guyatt et al., 1993). However, generic measures may not be suitable to detect the changes over time in HRQoL of a medical condition, that is, in patients with multimorbidity, the measures lack sensitivity and specificity to differentiate differences between an individual's medical conditions. For instance, despite some similarity between chronic obstructive pulmonary disease and asthma, the two conditions may cause different impairment to an individual's health. Hence, an insight into the burden imposed by an individual condition is obtained by using HRQoL measures specifically designed for that condition. These measures are known as disease/condition specific HRQoL measures (Guyatt et al., 1993).

Table 1 Measures of health-related quality of life (HRQoL) commonly used clinical pharmacy type interventions

Outcome measures	*Domains/dimensions*	*Number of items*
Generic measures		
SF-36	Physical functioning, Role physical, Bodily pain, General health, Vitality, Role emotional, Mental health	36 (12)
EQ-5D	Mobility, Usual activity, Self-care, Pain/discomfort, Anxiety/Depression	15
WHOQOL-BREF	Over all QoL and General health, Physical health, Psychological, Social relationships, Environment	26
PAT-5D	Walk, Hand, Daily, Pain, Feel	100
HUI3	Vision, Hearing, Speech, Ambulation, Dexterity, Cognition, Emotion, Pain & discomfort	45
Q-LES-Q	N/A	16
COOP-WONCA	Physical fitness, Social activities, Feelings, Change in health, Daily activities, Overall health	6
GWBI	General mood/affect, Life satisfaction/vitality, Poor physical health/somatic complaints	22
Health Status		12
Nottingham Health Profile	Emotions, Sleep, Social isolation, Energy, Mobility, Occupation, Social life, Home life, Sex life, Hobbies, Holidays	45
Disease specific		
Heart failure		
MLHF	Physical dimension, Emotional dimension, Overall score	21
CHQ	Dyspnea, Fatigue, Emotional function	16
Hypertension		
HTN/Lipid form 5.1		11
HTN specific Bulpitt Q		46
Diabetes		
DQOL	N/A	15
ADDQOL	Self-care behaviors, Satisfaction with diabetes	13
Gastrointestinal disorders		
GIQLI		36
Asthma		
AQoLQ-J		32
AQLQ-M		20
CAQ		21
PAQLQ		23
LWAQ		68

Table 1 Measures of health-related quality of life (HRQoL) commonly used clinical pharmacy type interventions (*cont.*)

Outcome measures	*Domains/dimensions*	*Number of items*
Chronic obstructive pulmonary disease		
SGRQ	Symptoms, Activity, Impacts	17(58)
CAT		8
Cancer		
QLICP-GM	Physical function, Psychological function, Common symptoms and side effects	32
EORTC QLQ-C30	Physical, Basic physiological function, Sexual function, Independence function, Psychological domain, Emotion, Recognition, Social domain, Social support and safety, Effects on life and economics, Common symptoms and side effect, Side-effect, Common symptom	30
FACT-G	Physical wellbeing, Social/family wellbeing, Emotional wellbeing, Functional wellbeing	27
Arthritis		
LEFS		20
WOMAC	Pain, Stiffness, Physical function	24
QUALEFFO	Pain, Activities of daily living, Jobs around the house, Mobility, Social activities, General health perception, Mental function	41
Renal		
RQLP		43
Epilepsy		
QOLIE-31	Seizure worry, Emotional wellbeing, Energy/Fatigue, Cognitive, Medication effects, Social function, Overall QoL	31
Parkinson's disease		
PDQ-8		8
Psychiatry		
Lehman's QoL	Instrumental, Affiliative	40
Migraine		
HDI	Emotional, Functional	25
Treatment specific		
SCQOL	Social interactions, Self-control, Sleep, Cognitive functioning, Anxiety	21
Ant-coagulant related QoL		32

Abbreviations: ADDQOL: Audit of Diabetes Dependent Quality of Life; AQoLQ-J: Asthma Quality of Life Questionnaire by Juniper; AQLQ-M: Asthma Quality of Life Questionnaire by Marks; CAQ: Childhood Asthma Questionnaire; CAT: COPD Assessment Test; CHQ: Chronic Heart Failure Questionnaire; COOP-WONCA: World Organization of National Colleges, Academies, and Academic Associations; DQOL: Diabetes quality of life; EORTC QLQ-C30: Cancer-specific Quality of Life Questionnaire; EQ-5D: EuroQol5-Dimension Questionnaire; FACT-G: Functional Assessment of Cancer Therapy Scale—General; GIQLI: Gastrointestinal Quality-of-Life Index; GWBI: General Well-Being Index; HDI: Henry Ford Hospital Headache Disability Inventory; HUI3: Health Utilities Index Mark 3; LEFS: Lower Extremities Function Scale; LWAQ: Living with Asthma Questionnaire; MLHFQ: Minnesota Living with Heart Failure Questionnaire; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; PAT-5D: Paper Adaptive Test-5D; PDQ-8: 8-Item Parkinson's Disease Questionnaire; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; QLICP-GM: Quality of Life Instruments for Cancer Patients; QOLIE-31: Quality of Life in Epilepsy Inventory–31; QUALEFFO: Quality of Life European Foundation for Osteoporosis; RQLP: Renal Quality-of-Life Profile; SCQOL: Smoking Cessation Quality of Life Questionnaire; SF-36: Short Form 36 items health status survey; SGRQ: St George's Respiratory Questionnaire; WHOQOL-BREF: World Health Organization Quality of Life–Short Form; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Disease Specific Measures

Disease specific measures are intended for assessment of longitudinal changes in HRQoL pertaining to a specific disease (Guyatt et al., 1993). However, they are not suitable to make a comparison of HRQoL outcomes across different medical conditions or to assess HRQoL outcomes in patients with multiple medical conditions.

Numerous disease-specific HRQoL measures exist, for a variety of conditions such as asthma, diabetes, heart failure, cancer, and arthritis (Guyatt et al., 1993). Many of these measures have been used to evaluate the outcomes of pharmacotherapy and clinical pharmacy services (**Table 1**) (Mohammed et al., 2016a; Pickard and Hung, 2006; Pickard et al., 1999). A recent systematic review with content analysis by researchers from the university of Sydney (Mohammed et al., 2018a) found that between 1990 and 2015, twenty-seven different disease specific HRQoL measures had been used in research to evaluate various models of clinical pharmacy services.

HRQoL and Clinical Pharmacy Services: Measurement Issues

In any intervention that involves pharmacotherapy, three possible outcomes of HRQoL is expected following the intervention: (i) HRQoL is improved compared to the baseline value, (ii) HRQoL is maintained, or (iii) HRQoL declines compared to the baseline value (see **Fig. 1**) (Mohammed et al., 2018b).

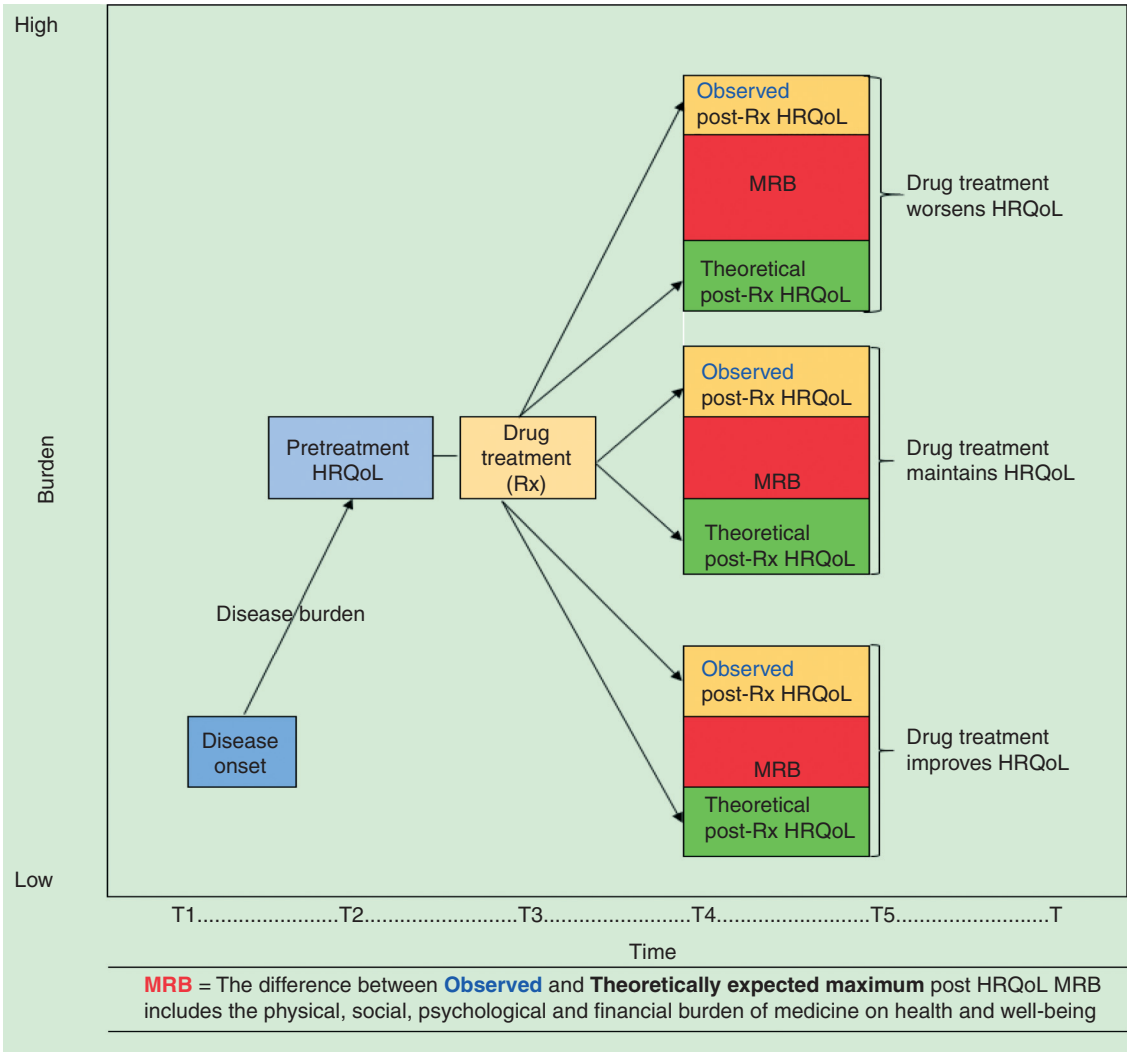

Figure 1 Pre- and posttreatment HRQoL outcomes in relation to disease and medicine burden. *Source: this figure is reproduced from "Figure 3: The gap in literature that this thesis aims to address through the development and validation of a novel measure of medicine burden" a doctoral thesis at the University of Sydney (Mohammed et al., 2018b), with a permission of the owners of copy right.*

The ultimate goal of provision of a patient-centered and outcome oriented clinical pharmacy interventions is to achieve improved therapeutic outcomes and thereby improve the patient's quality of life. This is anticipated to be achieved through identification and resolution of a patient's drug related problems (DRPs) which are an important component of the therapeutic care plan in the provision of pharmaceutical care services. If the causes of DRPs such as suboptimal dose, drug-drug interactions remain unresolved, a patient's pharmacotherapy goals may not be achieved and pharmacotherapy may result in undesirable consequences (Basger et al., 2015). Causes DRPs such as the need for additional therapy or wrong dose can result in poorer quality of life outcomes (Ernst et al., 2003; Wallace et al., 2015). However, there is limited evidence on how resolution of DRPs can pragmatically translate to improvement in HRQoL outcomes (Alldred et al., 2016). This is mainly due to the fact that existing measures of HRQoL used in evaluation of the impact of pharmacotherapy as well as the benefit of pharmaceutical care services do not encompass the concept of DRPs or medicines as a domain. Similarly, measures or classification systems for the causes of DRPs are neither humanistic measures nor patient-centric or self-rated measures.

The lack of a suitable measure that encompasses the concept of medicines and HRQoL has been a challenge to link DRPs and changes in HRQoL outcome. As a result, despite a significant body of research in this area (Mohammed et al., 2016a; Pickard and Hung, 2006; Pickard et al., 1999; Roughead et al., 2005a,b), evidence of clinical pharmacy interventions improving patients' HRQoL remains mixed and inconclusive (Bladh et al., 2011; de Lyra et al., 2007; Gourley et al., 1998; Holland et al., 2008; Isetts et al., 2006; Jarab et al., 2012; Malone et al., 2001; Mohammed et al., 2016a; Petersson et al., 2013; Pickard and Hung, 2006; Pickard et al., 1999; Pinto et al., 2014; Renberg et al., 2006; Schulz et al., 2001; Viswanathan et al., 2015). In general, HRQoL measures used in the evaluation of clinical pharmacy services lack sensitivity and specificity to capture aspects of humanistic outcomes related to the impact of pharmacotherapy (Mohammed et al., 2016a). Conceptually, all generic or disease specific HRQoL measures, are

specifically designed for evaluation of the burden of chronic disease, not specifically the burden associated with long term medicine use and the consequence of unresolved DRPs on patients' health and wellbeing (Malone et al., 2001; Mohammed et al., 2016a, 2018a).

Choosing a Suitable HRQoL Measure for Clinical Pharmacy Services

A comprehensive evaluation of the social, psychological, and physical impact of drug therapy on patients' lives is essential to determine the benefit of medicine-focused interventions (Mohammed et al., 2016a). Currently, with available instruments, there are only three options to evaluate HRQoL in clinical pharmacy type interventions: (1) using generic measures, (2) using disease specific measures, or (3) combination of generic with disease specific measures (Mohammed et al., 2016a; Pickard and Hung, 2006; Pickard et al., 1999). There is a number of theoretical and methodological issues regarding the suitability of existing HRQoL measures for clinical pharmacy interventions. Both generic and disease specific measures of HRQoL may generate some evidence for the value of clinical pharmacy interventions on a patient's HRQoL. However, it should be noted that generic and disease specific HRQoL measures used in clinical pharmacy interventions have been designed to evaluate the burden of disease on patients' health and wellbeing, not specifically the impact of drug therapy (Mohammed et al., 2016a, 2018a). The lack of sensitivity and specificity of HRQoL measures to clinical pharmacy interventions has been reported (Mohammed et al., 2018a). A recent systematic review with content analysis identified 37 different HRQoL measures (n = 1019 items) in 117 research studies into clinical pharmacy published between 1990 and 2015 (Mohammed et al., 2018a). The findings of this review indicated that only 34 of the 1019 items identified (from 37 measures), pertained to medicines (Mohammed et al., 2018a). This review further highlighted that items about medicines were also not focused on the burden of medicines, indicating that the measures may lack specificity to the types of services provided in clinical pharmacy interventions and sensitivity to detect changes in HRQoL attributed to the burden of long term medicines.

Drug Therapy Focused Measures of Quality of Life: Rationale for the Need

The importance of measuring quality of life related to drug therapy is to ensure not only the longevity of life after a particular drug therapy, but also the quality of life extended as a result of drug therapy taking into account the burden attributed to drug therapy on patient's functioning and wellbeing. The general principle is that longevity should be improved following a drug therapy in a biological sense, and that therapeutic options chosen should be those that ensure the patient's health condition is better than a pretreatment stage, if not similar to a predisease health condition.

Along with the expansion of medical services and an increase in longevity of life, there has been a gradual shift in the focus of chronic disease management from disease mortality to limiting disease morbidity and PROs of disease morbidity. Pharmacotherapy is by far the most common health care intervention in chronic disease management. As a result, there has been a surge in interest in collecting information about the impact of drug therapy on patient's lives for evaluation of clinical and nonclinical aspects of medical interventions. Collecting patient experiences about the impact of drug therapy on their functioning and wellbeing is essential to compliment a wide range of clinical outcomes of medical interventions. However, the traditional approach to evaluation of quality of life outcomes in drug therapy interventions has focused on using HRQoL measures, which were designed based on theoretical and conceptual models of HRQoL not related to drug therapy. This provides an explanation for why clinical pharmacy interventions have had a mixed and inconclusive impact of HRQoL. The lack of a drug therapy specific quality of life measure suitable for evaluation of the effectiveness of clinical pharmacy interventions, and the variability in HRQoL measures used in the evaluation of clinical pharmacy services has been reported as a major contributory factor (Mohammed et al., 2016a,b, 2018a,b; Pickard and Hung, 2006; Pickard et al., 1999).

A growing body of literature indicate that long-term drug therapy can lead to poor outcomes particularly in people with complex disease conditions and therapy (Gallacher et al., 2011, 2013; Mohammed et al., 2016b; Sav et al., 2013a,b, 2015b; Tran et al., 2015b). Investigation of medication related burden (MRB) on a health and well-being is relatively a new concept that has been gaining more emphasis in recent literature (Gallacher et al., 2011; Mohammed et al., 2016b; Sav et al., 2013a,b, 2015b; Tran et al., 2015b). The burden of long-term medicine use on patient's beliefs and behaviors and the impact on psychological, social, physical, and financial wellbeing has now been well documented (Gallacher et al., 2011, 2013; Mohammed et al., 2016b; Sav et al., 2013a,b, 2015b; Tran et al., 2015b). MRB can induce nonadherence to care plans, predisposes patients to DRPs, decreases quality of life, and increases utilization of health care resources (Mohammed et al., 2016b, 2018a). Findings from research studies into this area emphasized that sound medication therapy decisions cannot be made without good insights and attentions to the lived experiences of patients with medicines (Mohammed et al., 2016b). Some researchers argue that the impact that medicine attributed burden imposes on a patient's health and wellbeing would be underappreciated if measurements of humanistic outcomes are restricted to existing generic and or disease specific measures of HRQoL (Mohammed et al., 2016a,b, 2018a,b). Moreover, in clinical practice, health care providers face ongoing challenges in differentiating the decline in patient's quality of life due to the burden of drug therapy that a patient is taking, from the burden imposed by underlying disease conditions for which drug therapy has been prescribed. Similarly, it is difficult to distinguish between improvements in a patient's quality of life outcome due to drug therapy focused interventions or other nonpharmacologic treatment modalities prescribed along with drug therapy. Furthermore, unless

Table 2 Drug therapy focused measures of quality of life and their psychometric properties

Measure	Measurement properties							
	Reliability		Validity					
	Internal consistency (Cronbach's α)	Test-retest reliability	Convergence or discriminant validity, reference measure(s)	Known-groups validity	Other validity	Final domains and items	Conceptual Framework	Psychometric analyses, country/ population
MRB-QoL	✓	NR	C, D DBI, MRCI	✓	NR	5, 31	MRB-QoL	EFA, Australia
MRQoL	✓	✓	C, D MBRS, PDC	✓	NR	3, 14	NR	PCA, Taiwan
PROMPT-QoL	✓	NR	✓	NR	Content validity	10, 43	PROMPT-QoL	Rash analysis, Thailand
PTRQoL	NR	NR	NR	NR	NR	9, 33	PTRQoL	EFA, USA

Abbreviations: C: Convergent validity; D: Discriminant validity; DBI: Drug Burden Index; EFA: Exploratory Factor Analysis; MRCI: Medication Regimen Complexity Index; MBRS: Medication Behavior Rating Scale; MRB-QoL: Medication Related Burden Quality of Life; MRQoL: Medication Related Quality of Life; NR: Not Reported; PDC: Psychological Distress Checklist; PROMPT-QoL: Patient Reported Outcome Measure of Pharmaceutical Therapy for Quality of Life.

evaluated with a suitable measure, it would be impossible to generate strong evidence that reflects the real benefits of some widely practiced clinical pharmacy services such as pharmacist-led medication management reviews. Consequently, this may have an impact on policy decisions and influence professional remuneration for professional services.

To date, the sensitivity and specificity of existing HRQoL measures for evaluation of clinical pharmacy interventions is questionable. There is also no consensus regarding which HRQoL measure to use in clinical pharmacy interventions. These issues imply that an alternative drug therapy-focused measures of quality of life are needed for evaluation of clinical pharmacy interventions (Kheir et al., 2004; Krska and Rowe, 2010; Krska et al., 2013; Mohammed et al., 2016a,b). The ideal drug therapy-specific measures of quality of life should include dimensions of HRQoL relevant to clinical pharmacy services (Kheir et al., 2004; Mohammed et al., 2016a), incorporate key aspects of the burden of drug therapy on functioning and wellbeing (Krska et al., 2013; Mohammed et al., 2016b; Sav et al., 2015a; Tran et al., 2015a) and have greater sensitivity to pharmacist interventions (Mohammed et al., 2016a, b, 2018a). However, development and validation of such a measure is labor intensive requiring long-term efforts and various stages of evaluation before the measure is applicable in research and practice. In the past few years there have been attempts to design a more sensitive measure of quality of life, suitable for evaluation of humanistic outcomes in clinical pharmacy interventions. Measures such as medication related burden quality of life (MRB-QoL) (Mohammed et al., 2018b), patient-reported outcomes measure of pharmaceutical therapy for quality of life (PROMPT-QoL) (Sakthong et al., 2015), and medication related quality of life (MRQoL) (Tseng et al., 2016) are some of the novel measures that are receiving attention.

Although these measures aim to target drug therapy, they were designed based on different approaches and conceptual models. A conceptual model is a comprehensive description for the underlying concepts of the measurement and the interrelationships between concepts that a given measure is intended to measure. It provides the rationale for the measurement and reflects procedures followed to develop scales and subscales of the measure. An example of a conceptual model in drug therapy related quality of life measure is the medication related burden quality of life (MRB-QoL) model (Mohammed et al., 2018a,b). This model was developed by integrating three concepts: pharmacist-led pharmaceutical care, HRQoL, and the burden attributed to drug therapy, i.e., medication related burden. In this conceptual model Mohammed et al. stated that MRB is the difference between the observed and theoretically expected posttreatment HRQoL (**Fig. 1**). Major dimensions of medication related burden commonly encountered by patients on long term medicines; the interrelationships between dimensions of medicine burden; how MRB predisposes patients to DRPs, nonadherence to therapeutic care plans and poor quality of life outcomes has been reported in qualitative research used in the development of this measure (Mohammed et al., 2016b, 2018a). The development of other measures such as PROMPT-QoL and PTRQoL were based on conceptual models of quality of life and patient-centered pharmaceutical care (Sakthong et al., 2015). In addition to variability in the conceptual model on which these measures were based, there are also variations in the methods employed to developing the measures such as item generation and statistical analysis approach in psychometric testing, and concurrent measures used in their validation process (**Table 2**).

Approaches to Developing a New Patient Reported Measure of Quality of Life

The development of a new measure of QoL should follow a process that involves rigorous stages of development and validation. This includes definitions and conceptual framework specific to the quality of life measure intended, generation of an initial item bank; refining the items and pretesting; and then testing for validity. It is recommend that the research questions should be formulated a priori and be informed by a comprehensive review of literature. Furthermore, it is suggested that there be a clear justification for the

importance of a new measure in the area, specification of the objectives in measuring QoL, development of a comprehensive framework reflecting major issues that a new measure encompasses, proposal of dimensions that are to be assessed, and identification of intended end users and groups of respondents to be involved in the process. The development and validation process can be labor intensive and often requires multimethod approach. Qualitative methods (focus group and interviews with end users of the measure) are a critical component in the development process and a well-recognized traditional approach for generation of items. However, methods other than focus group discussion and interviews have now also been used (Mohammed et al., 2018b; Terwee et al., 2007).

Following a literature review, qualitative methods of concept elicitation, item development and refinement; the next stage is testing the psychometric properties of the measure. Commonly tested measurement properties include: (a) validity such as content validity, construct, criterion, and known-groups validity; (b) reliability such as internal consistency and test-re-test reliability; and (c) sensitivity and responsiveness (ability to detect clinically important change) of the measure.

Validity

Assessment of the validity of a new PROM generally focuses on whether the instrument measures what it intends to measure (De Civita et al., 2005; Gable and Wolf, 1993; Walters, 2009). Although other measurement properties are important, evaluation of the validity is the ultimate question to be addressed when developing a new measure (Gable and Wolf, 1993; Nunnally, 1978). In contrast to evaluation of reliability of a measure, there is no "gold standard" and clear cut measurement for validity (Gable and Wolf, 1993). Hence, validity is not directly measured but it is inferred from empirical evidence. Commonly evaluated types of validity include content validity, construct validity, criterion, and known-groups validity.

Content Validity

Content validity refers to the extent to which a given measure comprehensively covers relevant issues both in terms of its scope and content of the items that it contains. This validation process may involve assessing the conceptual constructs and how it has been defined, the importance and applicability of the measure for the intended purpose (Gable and Wolf, 1993). Expert panel from diverse background in the area of interest including end users of the measure (e.g., patients) are invited to critique the coverage, relevance, and importance of each item within a measure. Relevance and coverage are the two central elements in evaluating the content validity. Evaluation of relevance is focused on whether all items are relevant to the concept being assessed while coverage is mainly related to whether the entire range of relevant issues are considered in the measure. Following expertise feedback, the developers of the measure may need to critically revise the items to enhance the clarity by remove ambiguity on the wording of some items. There are also quantitative approaches (e.g., content validity index) to help decision making about the number of items in the measure, that is, whether to retain or remove a given item from the measure.

Construct Validity

Construct validity refers to the extent to which a given instrument measures the construct that it intends to measure (Bowling, 2014), and it is considered the most important approach to testing validity of a measure (Kline, 2000). Construct validity encompasses a number of known types of validity such as convergent validity and discriminant validity. Some people also consider known-groups validity as construct validity. Evaluation of construct validity involves defining and framing a priori hypothesis, domains of the measure being assessed and whether they are related or unrelated to each other (Kline, 2000). A priori hypothesis and the relationships between domains of the measure are then statistically tested. For example, if the domain/s of a given measure strongly correlates with other domain/s that a priori hypothesis or theory suggests, then that relationship indicates convergent validity. Whereas a weak correlation confirms a discriminant validity of the measure indicating that there are domains which are relatively unrelated. Convergent and discriminant validity are assessed together and may sometimes be assessed across domains of different measures rather than comparing domains within an instrument.

Known-Groups Validity

Known-groups validity refers to testing the sensitivity of a new measure in distinguishing differences between groups hypothesized to differ. For example, a priori hypothesis could be people with multimorbidity and polypharmacy may have poorer scores in a new quality of life measure contrary to those without those issues. Based on this assumption, instrument's ability to detect the difference between the specified groups can be tested. If a measure is not sensitive to distinguish groups with known differences, it is an indication that something may be wrong in development process and thus, usefulness of the measure may be questionable.

Criterion Validity

Criterion validity refers to whether the domains or overall score of a measure correlates with other measure/s often regarded as "gold standard" criteria (Gable and Wolf, 1993). Criterion validity is of two types: predictive validity and concurrent validity. Predictive

validity relates to the ability of the measure to predict future health events, for example, providing prognostic information that complement objective measures. In concurrent validity, a new measure and a standard criterion are concurrently measured/administered and then the magnitude of the relationship is tested. It should be noted that there is no "gold standard" criteria for PROs mainly for two reasons. First, all the instruments measure hypothesized constructs. Second, PROs are subjective in nature and thus, slight variations between measures are inevitable even if they are meant to measure same constructs. Therefore, commonly used approach in testing concurrent validity is by comparing the new measure with other measures which are considered as relatively well established measures. The comparison may be useful to support the rationale for developing a new measure, for example, if it was intended for designing a shorter/simplified version or addressing new concepts/constructs which have not been considered in the other measures.

Reliability

Reliability is about testing if the measure is reproducible and internally consistent (Walters, 2009). Evaluation of reliability of a measure focuses on two areas: (a) whether items within a domain of the measure should all measure same thing, (b) whether the scores of a measure is stabile over time period. The former type of reliability testing is called internal consistency reliability and the latter one is known as test-rest reliability.

Internal Consistency Reliability

Internal consistency of the measure is relates to the coherence between items within a domain, i.e., the degree to which the items are related to each other and the domain they represent. Internal consistency of a measure can be used to check homogeneity of the items in measuring same construct (Nunnally, 1978). Cronbach's alpha, correlation between items, item-domain correlation, and reliability coefficients can be used to check homogeneity of the items (Bowling, 2014; Briggs and Cheek, 1986) however, the most commonly used method to report internal consistency is Cronbach's alpha index (Nunnally, 1978). The ranges for Cronbach's alpha may depend on the nature and purpose of the measure. Commonly reported values are between 0.6 and 0.9. It may also be important to inspect correlations between items within the domain/scale. A very low inter-item correlation (value <0.1) may indicate the items do not hang together (i.e., they do not belong to the same domain) while a very high correlation (value >0.5) may indicate that there is redundancy of the items (Briggs and Cheek, 1986) and thus, removing some items may be needed.

Test-Retest Reliability

Test-retest reliability refers to the stability of the score of the measure. In other words, measure's ability to yield consistent score over time. Scores are compared after administering the measure repeatedly to the same person over a period of time. Intra-class correlation coefficient or Kappa coefficient are commonly used approaches in evaluating test-retest reliability.

Responsiveness

Responsiveness of a measure reflects the extent to which the measure detects clinically important and practically meaningful changes over time (Walters, 2009). Measure's scores are compared after administering to same person before and after an intervention. It is often difficult and challenging to prove measure's responsiveness and the process usually requires longitudinal data. In any measures claiming responsiveness, minimal clinically important difference (MCID) should be reported. MCID reflects the minimum changes in the scores of the measure that is considered clinically important and practically meaningful to inform decision making.

Conclusions

Incorporation of patient-centric measures has become critical component of measuring the value of health care interventions. In outcomes research, including clinical trials of drug therapy, PROs have now become the standard assessment to evaluate the benefits and negative consequences of therapy. PROs have the potential to generate evidence about the benefits gained in treating some chronic diseases in comparison to associated adverse events and functional impairment of the therapy. PROs data are often used to complement biological markers of safety and efficacy of medical interventions. Sometimes they are the only viable approach when other measurable biological markers of a disease and therapy is lacking.

HRQoL instruments are the most commonly used approach to evaluate PROs in relation to the impact of a disease and treatment on functioning and wellbeing. Traditionally, evaluation of HRQoL outcomes in clinical pharmacy interventions has used measures which were conceptualized based on models of disease burden, not specifically for drug therapy. There are different views about suitability of existing HRQoL measures for the evaluation of clinical pharmacy interventions. The use of generic and or disease specific measures of HRQoL in research into evaluation of clinical pharmacy services has been reported as a potential factor for the mixed and inconclusive evidence regarding the benefit of clinical pharmacy services for improving HRQoL. A growing body of

literature indicates that existing HRQoL measures lack sensitivity and specificity for the evaluation of clinical pharmacy interventions. Some researchers argue that until the burden attributed to drug therapy is directly measured with a more suitable measure, it is unlikely that it will be possible to distinguish between the changes in a patients' quality of life attributed to drug therapy, from the burden imposed by a disease condition. Moreover, in the absence of standardized drug therapy specific measures of quality of life, the challenges of distinguishing the improvement in patients' quality of life due to drug therapy focused interventions from that of other treatment modalities will likely remain.

In recent years, there has been increasing efforts to develop alternative medication therapy related quality of life measures specifically designed for evaluation of clinical pharmacy interventions. However, all of the proposed medicine related quality of life measures (**Table 2**) require further evaluation, before they can be applicable to inform decision making. Pending further investigations into measurement properties of medicine related quality of life measures, evaluation of quality of life outcomes in clinical pharmacy services may continue using available of HRQoL measures. Researchers should be aware and careful about the overarching principles in the measurement of HRQoL in clinical pharmacy interventions. The choice of a given HRQoL measure should be based on the type and intensity of the service provided and the sensitivity of a chosen measure to capture aspects of quality of life affected by the burden of medication therapy.

This chapter provides a brief overview of the concepts of HRQoL in relation to medical interventions in general, and clinical pharmacy services in particular. The chapter highlights the importance of HRQoL as a critical component of evaluation of patient outcomes. The chapter also provides new perspectives and insights into how medicine specific quality of life components should be incorporated into the evaluation of overall HRQoL outcomes in medical interventions.

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Military Pharmacy Practice Around the World and the Role of the Pharmacy Officer

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Introduction

For most people, the term "military pharmacist" is not clear. When one thinks of military, images of tanks, ships, and parades come to mind (Duffy, 2015). When we think of soldiers and officers, we either have an image of a parade uniform or camouflage, someone carrying a rifle and executing combat tactics (Duffy, 2015). A pharmacist on the other hand is someone in a white lab coat, perhaps providing patient care at a community pharmacy, working at a research facility or providing advice to physicians and nurses in a hospital. Most people can imagine what a combat medic does or even a surgeon at a field hospital.

While these images form the public perception of both military officers and of pharmacists, they do not reflect the reality of how a modern military functions. For the purpose of this chapter, we will define military pharmacists as a uniformed military officer with formal education in pharmacy who is subject to the rules, regulations, and discipline of the military force they belong to—a Pharmacy Officer. It is important to note the distinction between a civilian pharmacist who works in a military facility and a Pharmacy Officer. For example, the Canadian, United States, Australian, and British forces directly employ civilian pharmacists to provide pharmacy services to its members, but this is in augmentation of their Pharmacy Officers. This chapter then will focus on the practice and roles of Pharmacy Officers around the world.

Historical Accounts of Military Pharmacists

Historical accounts of military pharmacists have been published across the globe. From French and Turkish military campaigns, the American Civil War to the Imperial Army of the Meiji period of 19th century Japan—military pharmacists have been an important part of force sustainment presence (Bonnemain, 2008; Hasegawa, 2000; Horiguchi, 2008; Kleider and Pabst, 2005; Miroshnichenko et al., 2014; Trépardoux, 2014; Yildirim, 1998). Military pharmacists have managed formularies for centuries, as seen in the specific establishment of the Danish Military Pharmacopoeia in 1812 (Kruse, 2000).

Pharmacy Officers are deployed on missions around the world to support the military forces they are part of. There are peer-reviewed publications documenting US Pharmacy Officers deployed to Haiti (Frank, 1996), Operation Desert Storm (Spain et al., 1993; Spain, 1994), and to Honduras (Dasher, 1985). In operations, pharmacists take on many roles.

Pharmacists take part in preparing and planning for operations (Gallup and Masterson, 2007) and provide medication therapy management (Ridderhoff et al., 2015). As the Chief Pharmacists of the Kenyan and Chinese Militaries have put it "pharmacist[s] are part and parcel of the troops in the operational areas both during peace time and war" and when providing "deployed pharmacy services, the military pharmacists usually work as an important part of a medical team, mainly responsible for the medicine [procurement] and supply."

Current Military Pharmacy Practice

While there are many accounts in published journals and mentions of military pharmacists are made in many books, there does not exist a single account describing current military practice at the international level (Anderson, 2002; Worthen, 2001). Military pharmacy practice is a specialty in that it both covers a unique patient population and a unique practice environment. We would like to endeavor to describe what military pharmacy practice is and how it is practiced in different countries throughout the world.

To understand the practice of military pharmacy, we need to begin with defining the domains and populations that this practice covers. Broadly speaking a military force requires health service support both when stationed in garrison and when deployed on operations. When in garrison, military members will require the services of health care providers predominantly for their primary care and mental health. When deployed on operations, a military force can be engaged in several kinds of missions. The two most common ones are the combat operations and the humanitarian missions (NATO, 2018). During combat operations, the health care providers of the military forces will provide care mainly to their own members, as well as members of allied and enemy forces. However, they will not deny care to civilian casualties. In humanitarian missions, mainly following disaster situations, where the military force is providing aid to the civilian population, the role of the health care provider will be to treat patients affected by these disasters. Therefore, military health care providers, including Pharmacy Officers, are required to provide care to both military members (typically healthy adults, between 16 and 60 years of age, predominantly male) as well as civilians (entire spectrum of human population, from all age groups, various geographic locations, different cultural and ethnic groups, and all socioeconomic circumstances).

The domains that military Health Service Support covers are: Education and Training; Patient Care; Health care Logistics; and Policy and Research. All four of these domains take place both in garrison and when deployed on operations.

Health care Logistics is an extensive area of Health Services Support. For the purpose of this chapter, health logistics will be broken down into pharmacy logistics and health materiel logistics and defined as the part of military pharmacy practice dealing with the procurement and supply, of health equipment and blood and blood products. Procurement can be defined as contract negotiation and selection with vendors, payment terms and financial arrangements and purchasing. Health materiel can be defined as any physical good that comprise the health service support framework: pharmaceuticals, blood products, health consumables such as injection devices and dressing materials, and health equipment.

Patient care includes primary care, mental health, urgent care, inpatient care, critical care, and surgical care. The shift in areas of patient care is quite dramatic: from chronic disease management in garrison to surgery in combat operations. Preventive care involves such aspects as prophylaxis of preventable diseases, immunizations, protection of military force from environmental health threats and monitoring of the quality of food, water, and sanitation within military organizations.

Policy management involves defining such things as the scope of health services support, scope of clinicians' practice, spectrum of care, pharmaceutical policy, and formulary management.

Regulatory management includes quality assurance and quality control, patient safety, medical device regulations, manufacturing and licensing of pharmaceuticals.

Education and training involves entry-to-practice training requirements as well as education and training provided at military training facilities to health service support personnel. Education and training also includes providing training to other nations on deployments and international exercises.

Research and development include studying the health of the military population, tracking health data from missions, and conducting health factors research involving military equipment.

Synthesis of Literature on Current Military Pharmacy Practice

This chapter presents a synthesis of literature on current military pharmacy practice. The literature search was conducted by searching PubMed, Google Scholar, Google, and reviewing the references in the obtained articles and books. Senior pharmacy officers from 21 nations were contacted to obtain descriptions of the roles and involvement of pharmacists within their respective organizations. A follow up was done to request original respondents to fill in any missing data using the format seen in the tables in this chapter. Data and graphs were analyzed and prepared in Microsoft Excel.

It is also important to note some limitations to these methods. The authors of this chapter are both Canadian Pharmacy Officers. As with any practice, the details and nuances of the practice are best described by the practitioner. While every effort was made to elicit details from the Pharmacy Officers of countries other than Canada, the details may still be lost to interpretation. Given that this is the first time such a publication is produced, to create order and flow in the chapter, a Canadian bias is introduced into the theoretical framework of this chapter. It is certainly our hope that this is only the first edition and with future editions, more fidelity can be introduced into the data.

Figure 1 Countries which are known to employ Pharmacy Officers are shown in *green*. Countries that do not employ Pharmacy Officers are shown in *red*. Countries not highlighted may or may not employ Pharmacy Officers; however, no information about such employment could be located either through personal communication or through literature searches. It is likely that there are many more countries which employ Pharmacy Officers given that there is such practice on every continent.

Synthesis of Results and Discussion

As we began planning and collecting data for this chapter, we anticipated encountering a wide variety of military pharmacy practice settings and having to analyze very heterogeneous data. As with most things in life however, we are much more alike than we are different. Between the two authors, one of whom is the President of the FIP military pharmacy section, there are more than 30 years of military pharmacy practice—and yet we were surprised to see the homogeneity of the responses we received. We will attempt to highlight some of the unique aspects of the various national pharmacy practices, but it is not the differences but rather the similarities that tell the fascinating story of military pharmacy practice in this chapter.

Responses were received from all the senior pharmacy officers contacted as well as their colleagues. The responses which were received were then grouped into five tables. The follow up solicitations were also received and added to the final tables. A world map was designed to provide a visual demonstration of the geographical distribution of military forces employing Pharmacy Officers (Fig. 1 and Table 1).

Education and Training of Pharmacy Officers

In order to become a Pharmacy Officer, one must not only complete all the requisite education and training to become a pharmacist but must also complete additional military training and specific occupational training. This results in many years of education and training for Pharmacy Officers (Table 2).

Pharmacy Officers begin their careers by obtaining their entry-to-practice degrees at civilian universities. The only exceptions identified were Russia and Greece. Russia trains military pharmacists at military medical academies. In Greece, aspiring military pharmacists must concurrently attend a civilian university and a military academy. In all cases, to become a Pharmacy Officer in the military, pharmacists must undergo military training.

Military training for Pharmacy Officers usually includes basic military training and occupation-specific military training. Basic military training is common to all military officers (such as learning military laws and regulations, how to wear a uniform, use a weapon, and perform parade drill). Occupation-specific training is unique to Pharmacy Officers. Considering, however, the specialized nature of Pharmacy Officers, in some cases the duration of overall military training is shorter than other military officers, as is the case in United Kingdom.

While nonhealth service officers will often receive most of their formative training within the military, Pharmacy Officers will often undertake training outside of the military. For example, Canadian Pharmacy Officers will complete a six-month hospital residency program that is also considered a military qualification. Additionally, Pharmacy Officers do undergo some specialized

Table 1 General overview of the functions of Pharmacy Officers around the world

Country	*Undergo military training*	*Pharmacy policy and regulation*	*Pharmacy administration and logistics*	*Health materiel administration and logistics*	*Provide support on missions (deployments)*	*Work in hospitals (inpatient)*	*Work in field hospitals*	*Work pre-hospital (field care)*	*Work in clinics (outpatient)*
Australia	●	●	●	●	●		●	●	●
Austria	●	●	●	●	●	●	●	●	●
Belgium	●	●	●	●	●	●	●	●	
Cameroon	●	●	●	●				●	●
Canada	●	●	●	●	●	●	●	●	●
China	●	●	●	●	●	●			●
France	●		●	●	●		●		
Germany	●	●	●	●	●	●	●	●	●
Greece	●	●	●	●	●	●			●
Ireland	●		●	●	●	●			●
Kenya	●	●	●	●	●	●	●	●	●
Netherlands									
NZ	●	●	●	●	●	●			
Russia	●	●	●	●	●			●[a]	
Sweden	●	●	●	●	●	X	●	X	X
Switzerland	●	●	●	●	●	●	●	X	X
Tunisia	●	●	●	●	●	●	●	●	●
Turkey	●	●	●	●	●	●	●	●	●
UK	●	●	●	●	●	●	●	●	●
Uruguay	●	●	●	●	●	●			
USA	●	●	●	X	●	●	●	●	●

The "●" indicates the country utilizes a pharmacist for that area of function. A blank indicates that it was not clear to the authors from the obtained documentation whether pharmacists are utilized in this function or information was simply not available. An "X" indicates that evidence exists that Pharmacy Officers of that force are not employed in the specific area.
[a]Russian military have exercised a pharmacy service for light casualties (Khveshchuk and Umarov, 1994).

Table 2 Pharmacy Officer in education and training

Country	*Civilian entry-to-practice education required (military may subsidize)*	*Military training required (military skills, officer training)*	*Postgraduate training (Masters, PharmD, PhD, MBA)*	*Residency training*	*Advanced certifications*	*Subspecialization (not all Pharmacy Officers can work in all positions)*	*Pharmacy Officers teach (at academic institutions, on military courses or teach other health professionals)*
Australia	●	●	●				
Austria	●	●	X	X	X	X	●
Belgium	●	●	●		●	●	●
Cameroon	●	●				●	●
Canada	●	●	●	●	●	X	●
China	●	●					●
France	●	●					
Germany	●	●	●	X	●	●	●
Greece	●	●	●		●		●
Ireland	●	●				X	
Kenya	●	●					
Netherlands	●	●					
NZ	●	●				X	●
Russia	X[a]	●	●[a]				●
Sweden	●	●	X	X	X	●	●
Switzerland	●	●	●	●	●	●	●
Tunisia	●	●	●	●		●	●
Turkey	●	●	●	●	●	●	●
UK	●	●	●	X	●	X	●
Uruguay	●	●	●			●	●
USA	●	●	●	●	●		●

The "●" indicates the country utilizes pharmacist for that area of function. A blank indicates that it was not clear to the authors from the obtained documentation whether pharmacists are utilized in this function or information was simply not available. An "X" indicates that evidence exists that Pharmacy Officers of that force are not employed in the specific area.
[a]Russian military is working on new training for military pharmacists and new definitions for their postgraduate training (Gushchenko et al., 2007). The Russian Military Medical Academy teaches various programs in Pharmacy, Medical Supply Management and even pharmacy economics programs for physicians (Miroshnichenko et al., 2013a,b).

military training beyond a basic course. For example, in Australia, Pharmacy Officers take part in Intermediate and Advance Military Logistics courses. In many cases, Pharmacy Officers are also encouraged to obtain postgraduate degrees. In Canada, most Pharmacy Officers continue to maintain their clinical pharmacy practice skills throughout their careers, regardless of their military duties.

US Pharmacy Officers work in a unique environment because the US military is one of the largest in the world and the military provides care to families and veterans. This unique combination creates a need for a large military health system and creates opportunities for a variety of clinical postgraduate education for Pharmacy Officers. For example, US Army Pharmacy Officers participate in specialty patient safety residency programs and can complete clinical fellowship programs (Watkins, 2003). Tunisian Pharmacy Officers, on the other hand, have a unique training path spending their first six postgraduate months at a military academy followed by a year spent obtaining experience in multiple practical settings. They compete in a specialization examination which separates Pharmacy Officers into the "Hospital-University (HU)" stream and the "Hospital-Sanitary (HS)" stream. The Tunisian training system effectively creates three classes of pharmacy professionals with the HU Pharmacy Officers considered the most specialized and the HU Pharmacy Officers performing in assisting roles with pharmacy technicians looking after technical pharmacy activities.

Belgian Pharmacy Officers also specialize in "CBRN (Chemical, Biological, Radiological and Nuclear) [operations], hospital [pharmacy practice], industrial [pharmacy] or [. . .] in clinical biology." These specializations do not hold any superiority over one another.

German Pharmacy Officers specialize in food science, which is what (from an education point of view) differentiates them from their civilian counterparts. Moreover, German Pharmacy Officers employed in Reserve (or part-time) positions do not require food science specialization.

British Pharmacy Officers may undertake training to become independent prescribers, although this does not alter their employment or career path within the military and therefore is specialization only in a medico-legal sense.

In addition to having opportunities to undertake postgraduate training such as Masters and Doctoral studies, most Pharmacy Officers undertake advanced certification programs. For example Canadian Pharmacy Officers may obtain advanced training in Travel Medicine, Pharmacoepidemiology, Dive Medicine, and Aviation Medicine (Gendron et al., 2017). Many Pharmacy Officers go on to teach other health professionals, teach new Pharmacy Officers and teach at academic institutions. Pharmacy officers also mentor pharmacists from other nations such as the mentoring missions in Afghanistan (Wright, 2003).

Location and Employment of Pharmacy Officers

Pharmacy Officers are present throughout the entire Health Services spectrum of operations. Pharmacy Officers can find themselves on land, at sea, deployed abroad, and sharing their time between civilian and military practice. In some countries, Pharmacy Officers belong to a unified health services group or command and support any branch of the military. This is the case in Canada, Germany, and Belgium for example, whereas some countries specifically assign Pharmacy Officers to support separate branches of the military.

The US Navy, Army, and Air Force each have their own cadre of military pharmacists. In addition, a fourth group of uniformed pharmacists, the US Public Health Services, support the US Coast Guard, and other health functions under the Federal jurisdiction (e.g., the Food and Drug Administration, Correctional Services, Indian Services, and more) (Flowers et al., 2009).

In the UK and Australia there are no Navy Pharmacy Officers, but Army Pharmacy Officers still support the Navy personnel.

Some countries use different uniforms or unique medical insignia to identify Pharmacy Officers. This is the case in the French, Greek, German, and Belgian forces. Most Pharmacy Officers are full-time military officers. Nonetheless, Reserve (or part time) Pharmacy Officers can be found in Austrian, Canadian, German, Swedish, UK, and US forces. Reservists are part-time Pharmacy Officers who spend most of their time in civilian practice and serve their military force on a part time basis. Each military relies on its Reserve Pharmacy Officers to a different extent, with minimal requirement in Canada, to a major contributing component of the Pharmacy Officer workforce in Sweden and Austria.

Patient Care in Garrison

Pharmacy Officers provide patient care and support when military forces are not deployed. The only exception to this is the Swedish military which utilizes the civilian pharmacy provider network. In the Canadian system, provision of care in garrison is a major responsibility of Pharmacy Officers since military members' health care is the responsibility of the Canadian Armed Forces. This is also the case in the US military. Generally, in garrison care provided by Pharmacy Officers is not significantly different from their civilian counterparts other than possibly utilizing a different scope of practice and focusing on different population group. In large health systems, such as in the USA, Pharmacy Officers work in large military hospital centers. In small systems such as in Canada, the military relies on civilian hospital infrastructure to provide inpatient care, when not deployed on missions. This is often referred to as Role 4 care, where patients of any severity can receive definitive care.

Providing Care on Operations

Pharmacy Officers provide support and patient care when forces are deployed in a field environment such as exercises and domestic operations (this usually means work at a Role 1 medical facility, looking after primary care requirements and urgent care which does not require surgery or long-term hospitalization). Pharmacy Officers also work at Role 1 facilities on humanitarian deployments where they provide population level support and care. Pharmacy Officers work at Role 2 and Role 3 Field Hospitals which provide surgical and in-patient care to deployed military members as well as local nationals. US Navy pharmacists also deploy to provide clinical services on large ships (such as aircraft carriers) and Australian pharmacists who deploy on Landing Helicopter Docks (LHDs) (Brouker et al., 2000).

Role of Pharmacy Technicians in the Military

While it is beyond the scope of this chapter to discuss Pharmacy Technician roles in detail, we would be remiss if their role was missed. For the purpose of this chapter, we will use the term pharmacy technician to include trained personnel to assist pharmacists with the technical aspect of pharmacy practice. In some countries, the United Kingdom, for example, the drug distribution function is largely the domain of pharmacy technicians. Austria, Greece, Switzerland, Tunisia, United Kingdom, and the USA employ military pharmacy technicians (in most cases pharmacy technicians are noncommissioned members or noncommissioned officers). The US has an especially large corps of pharmacy technicians and conduct formal military training courses for pharmacy technicians (Erikson, 2015; Holt, 1992; Meadows, 1999; Whisenant, 1984). Military pharmacists in the US work collaboratively with pharmacy technicians to improve patient care (Evans et al., 2016). Internationally, pharmacy technicians are important contributors to military operations.

Providing Patient Care

Most Pharmacy Officers carry out clinical pharmacy functions at almost all levels of care (in primary care clinics, hospitals, Role 1, 2, 3, and 4 facilities). From the Canadian perspective, across the spectrum of military pharmacy practice, logistics will always play an important role, while patient care and clinical practice, although present across the spectrum, will require more specialized clinical skills as you move from the Role 1 health care facilities to the Role 4 hospitals.

For the purpose of this chapter military pharmacy practice patient care is subdivided into four main areas: basic pharmacy, clinical pharmacy, advanced pharmacy practice, and preventive care. The intent of this categorization is to attempt to place pharmacy practice on a continuum from where it historically started (i.e., basic pharmacy) to where it is evolving (i.e., advanced pharmacy practice). Preventive care is a separate category, but it ultimately means that the pharmacist must evolve from basic functions to addressing population health.

This categorization was done to provide a qualitative visualization of the continuum of practice of military pharmacists. It is beyond the scope of this chapter to provide a nuanced description of every type of practice and specialty area. It is also worth noting that military pharmacy practice is a specialty in its own kind and military pharmacists comprise a small group of professionals (both in their own countries and internationally). This categorization is therefore intended to describe this small group of practitioners and not meant to be applied to general pharmacy practice (**Table 3**).

Basic Pharmacy Function

Within the basic pharmacy function, all Pharmacy Officers dispense medications, counsel patients and most will undertake patient-specific drug compounding. In Canada, Pharmacy Officers are not involved in sterile products preparation (intravenous admixtures, ophthalmic preparations, and total-parenteral nutrition preparation). The scope of practice of pharmacy officers may also differ from that of their civilian counterparts. Therefore, "basic" pharmacy does not mean simple pharmacy as some of these skills can be extremely complex.

Clinical Pharmacy

Clinical pharmacy is the next step on the practice evolution continuum. As of 2016, the clinical role of Canadian Pharmacy Officers expanded (The Maple Leaf, 2016). The expanded role includes five clinical activities related to prescribing medications for patients (The Maple Leaf, 2016). Canadian military pharmacists can adapt prescriptions (which mean changing the dose, route of administration, or dosage form of the drug). They can perform "therapeutic substitution" which means substituting a drug from the same pharmacologic class instead of the drug that was prescribed. This is especially useful in times when there are drug shortages. They can also refill medications which were previously prescribed for the patient or refill medications in an emergency (such as providing a patient with inhaled salbutamol in a case of an asthma exacerbation). Finally, they can prescribe independently for a list of preapproved indications. For example, Canadian Military Pharmacists can initiate antimalaria prophylaxis medications for deploying military members or prescribe smoking cessation medications for those wishing to quit smoking (The Maple Leaf, 2016). This new expanded role allows for more efficient utilization of health-resources and better access to care for patients (The Maple

Table 3 Pharmacy Officers in patient care

	Patient care									
	Basic pharmacy						*Preventive medicine*			
Country	*Dispensing*	*Compounding*	*Sterile drug preparation*	*Counseling patient*	*Clinical pharmacy (therapeutic drug monitoring, laboratory monitoring, drug information, antibiotic stewardship, medication therapy management, chronic disease management, modifying drug therapy)*	*Advanced practice (independent prescribing, independent treatment, physical assessment)*	*Initiating prophylactic treatment*	*Immunization*	*Food and water monitoring*	*Hygiene, sterilization, sanitation*
Australia	●			●	●					
Austria	●	●	X	●	●	X	X	X	X	X
Belgium	●	●		●	●					●
Cameroon	●	●		●						●
Canada[a]	●	●	X	●	●	●	●	X	X	X
China	●			●	●					●
France[b]	●			●						●[b]
Germany	●	●	●	●	●	X	X	X	●	X
Greece	●			●	●					
Ireland	●			●						
Kenya	●			●	●					
Netherlands	●			●						
NZ	X			X						
Russia	●	●	●	●						
Sweden	●	X	X	●	●	X	X	X	X	X
Switzerland	●	●	●	●		X	X	X	●[c]	●
Tunisia	●	●		●	●	X	X	X	X	X
Turkey	●	●	●	●	●					●
UK	●	X	X	●	●	●	●	X	X	X
Uruguay	●			●	●				●	●
USA	●	●	●	●	●	●	●		X	X

The "●" indicates the country utilizes pharmacist for that area of function. A blank indicates that it was not clear to the authors from the obtained documentation whether pharmacists are utilized in this function or information was simply not available. An "X" indicates that evidence exists that Pharmacy Officers of that force are not employed in the specific area. Initiating Prophylactic Treatment was categorized under "preventive medicine" as it is usually highly linked to travel and selection of drugs such as antimalarials and vaccines for specific endemic areas. As such, this category is inextricably linked to preventive medicine physicians and scientists and usually linked to Force Health Protection functions in a military organization.

[a]Dagenais and Grenier (2013) and Gendron et al. (2017).

[b]French Military pharmacists are involved in sterilization services depending on the size of operation (Role 2 vs. Role 3 or larger hospital) (Rouault et al., 2017). The French military focuses its reserve pharmacy officer training on the following subjects: drug supply, use of chemical, biological and nuclear weapons in warfare and terrorism, clinical chemistry, toxicology, and hygiene (Labrude, 2004).

[c]Only water monitoring in the Swiss Armed Forces (no food monitoring).

Leaf, 2016). From a US perspective, the US Navy has piloted pharmacy refill authorization services since the 1990s (Riege, 2005). The US Navy has also implemented telepharmacy systems (Traynor, 2010). US Navy pharmacists are involved in running clinics such as pharmacist-led lipid clinics (Cording et al., 2002). Coast guard pharmacists are also involved in clinical services, such as smoking cessation programs (Huntzinger, 2002).

Advanced Pharmacy Practice

One of the newly developing areas is the concept of the pharmacists as advanced practice pharmacists providing independent prescribing, taking on more expanded clinical responsibilities and becoming a more integral part of the patient-care team. The British model has allowed for Pharmacy Officers to become independent prescribers after undertaking a formal qualification. As previously mentioned, in the Canadian model, Pharmacy Officers have gained the authority to independently treat a defined list of conditions (The Maple Leaf, 2016). Of all the countries surveyed, it appears that Canada, UK, and the USA are the only ones which are employing Pharmacy Officers in such a role.

Preventive Care

Preventive health care is another unique role filled by Pharmacy Officers. This area is uniquely important in the military setting due to the exposure of military members to adverse field conditions and environmental stressors on deployments (both domestic and international). For example, Pharmacy Officers in Canada, UK, and the USA can initiate prophylactic treatment of malaria for deploying military members (notice that these activities also fall into either clinical or advanced practice depending on how they are practiced). In Germany and Uruguay, Pharmacy Officers are involved in food and water safety. In Belgium and France, Pharmacy Officers are involved in sterilization of medical and surgical instruments. Finally, Pharmacy Officers from Belgium, China, France, Germany, Switzerland, and Uruguay are involved in hygiene and sanitation.

Health Care Logistics

In almost all cases Pharmacy Officers are not only responsible for patient care, clinical pharmacy, and pharmacy administration, but they are also responsible for Health Materiel Logistics as well. The only exception to that is with the United States military where Health Materiel Logistics is managed by Health Services Materiel Officers (Table 4).

When we think about the logistical support that a Pharmacy Officer provides, it is helpful to think about two groups of products: pharmaceuticals and all other health materiel. Procurement and supply of pharmaceuticals is typically a pharmacists or pharmacy technician responsibility, both in the civilian sector and in the military. On the other hand, procurement and supply of health material is a common function of Pharmacy Officers that is not normally performed by their civilian counterparts.

Procurement and supply are two separate functions given that the two are functionally independent (for example, medicines can be purchased by nonpharmacists, but the storage and distribution of medicines should ultimately fall to those with pharmacy expertise and education). It is not surprising then that every nation surveyed provides some level of pharmaceutical procurement and supply function.

When it comes to health materiel logistics, however, the picture is somewhat more diverse but not drastically so (except, as mentioned, in the case of the US military). Pharmacy Officers within every nation provide some degree of health materiel support and management. The health equipment management function is somewhat more questionable than other areas. This is likely because Pharmacy Officers are rarely involved in technical work on medical equipment (although the Belgian military does train its Pharmacy Officers to conduct technical functions on health equipment). Normally, however, medical equipment is managed by biomedical equipment personnel and (as is the case with the Canadian military). Pharmacy Officers oversee the procurement and management functions.

A special mention must be made of temperature and time sensitive products (TTSP) and their logistics. In a static civilian environment TTSP, also colloquially known as “cold-chain” products, pose a challenge. Storing vaccines, laboratory reagents or drugs requiring refrigeration introduces complexity to the health care system. The complexity is multiplied many fold in the military setting. For example, a field hospital operating in the Middle East would experience winter temperatures dropping below freezing and summer temperatures easily exceeding 50°C. In this environment, maintaining controlled storage conditions for medicines, vaccines, lab reagents, and blood products can be uniquely challenging. The successful transport and storage of such products could indeed be a matter of life and death for the patients waiting to receive treatment.

Another special mention must be made of blood and blood products. Blood and blood clotting factor replacement is critical in saving lives in trauma cases and is especially critical for combat casualties. Blood is also a very clinically complex intervention requiring the expertise of laboratory technologists, specially trained medics and nurses, physicians, and surgeons. Many countries delegate full management of blood products to laboratory scientists as is the case with USA, UK, Australia, and China. In other systems, such as Canada, for example, the military leverages Pharmacy Officers expertise in TTSP management, quality assurance, and health materiel management to oversee and manage the supply of blood and blood products into theatres of operation. In the Netherlands, Pharmacy Officers specialize in blood product management.

Table 4 Pharmacy Officer involvement in health logistics

	Logistics						
	Pharmacy logistics		*Health materiel logistics*				
Country	*Procurement (contracting, finance, purchasing)*	*Supply (TTSP, transport, warehousing, distribution)*	*Procurement*	*Supply (including TTSP)*	*Medical supplies*	*Medical equipment*	*Blood and blood products*
Australia	●	●	●	●	●	●	X
Austria	●	●	●	●	●	●	XX
Belgium	●	●	●	●	●	●	●[a]
Cameroon		●			●	●	●
Canada	●	●	●	●	●	●	●
China	●	●	●	●	●		X
France	●	●	●	●	●		
Germany	●	●	●	●	●	●	●
Greece	●	●	●	●	●		
Ireland	●	●	●	●	●		
Kenya	●	●	●	●	●		
Netherlands							●
NZ	●	●	●	●	●		
Russia	●	●	●	●	●		
Sweden	●	●	●	●	●	X	●
Switzerland	●	●	●	●	●	●	
Tunisia	●	●	●	●	●	●	●
Turkey	●	●	●	●	●	●	●
UK	●	●	●	●	●	X	X
Uruguay	●	●	●	●	●		
USA	●	●	X	X	X	X	X

The "●" indicates the country utilizes pharmacist for that area of function. A blank indicates that it was not clear to the authors from the obtained documentation whether pharmacists are utilized in this function or information was simply not available. An "X" indicates that evidence exists that Pharmacy Officers of that force are not employed in the specific area.

Pharmacy Logistics refers to any logistical (as opposed to patient care or clinical) functions that are required to carry out pharmacy operations related to pharmaceuticals only. Pharmacy Logistics functions can also be thought of as pharmacy management functions that involve stocking the pharmacy and procurement of medications. If any of the criteria listed were met, the country was counted as performing that overall function, not all criteria had to be met. In the "Blood and Blood Products" category, Pharmacy Officer involvement in planning the movement of blood products and managing the TTSP conditions are sufficient criteria to include that as a function of pharmacy practice (normally administration of blood and selection of blood products is managed by physicians and laboratory scientists respectively). In the "Health Equipment" category, Pharmacy Officer oversight and management of biomedical repair or engineering functions was sufficient to count as part of military pharmacy practice as normally the actual technical details and repair of health equipment is carried out by biomedical technicians.

[a]With respect to blood products, Belgian Pharmacy Officer deal with the transport of these products only.

Policy and Research

From a policy and regulatory perspective, it is not surprising that in a specialized and unique environment of military pharmacy practice, a unique set of pharmacy policies and regulations is required. It is also not surprising that to produce effective guidance and policy, Pharmacy Officers involved in this field of practice require extensive and diverse prior experience (Table 5).

For example, The New Zealand Defence Force is very small, but pharmacists are considered a resource of technical expertise and policy advice. Not only have we found that all countries are involved in regulating pharmacy policy, but respondents from Belgium, Canada, Greece, UK have specifically stated that policy and regulation are the domains of the most senior Pharmacy Officers. It is not surprising that Pharmacy Officers of many countries are not involved in manufacturing drugs and medical devices as these functions require processes to meet strict standards, requiring extensive resources, which often, only drug manufacturers can meet. Some countries, such as Belgium, are phasing out this function for Pharmacy Officers.

Nonetheless, Germany, Greece, Russia, Switzerland, and Turkey are still involved in manufacturing. One surprising finding was the low involvement of Pharmacy Officers in research and development activities. For example, Australian and UK Pharmacy Officers are not explicitly involved in research activities. While the many functions that Pharmacy Officers carry out in the military are critical to supporting health services, providing effective patient care and ensuring high standard of care on missions, the majority of research done appears to be in the areas of practice rather than formal research positions. Nonetheless, Belgium, Cameroon, Canada, China, Germany, Russia, Tunisia, and USA have reported Pharmacy Officers employed in research positions, with Canada, China, and USA having formal research positions for Pharmacy Officers. In comparison to pharmacy and health care logistics, however, it appears that there is less information on Pharmacy Officer involvement in research.

Table 5 Pharmacy Officer involvement in policy and research

	Policy and research						
		Research and development					
Country	*Pharmaceutical policy (drug schedules, narcotics and controlled substances regulation, scope of practice regulation, drug safety, quality assurance, formulary management, pharmacy and therapeutics committee)*	*Drug use evaluation*	*Practice research*	*Clinical trials*	*Pharmaceutical and basic sciences research*	*Product evaluation*	*Manufacturing (drugs and/or medical materiel)*
Australia	●			X	X	X	X
Austria	●	X	X	X	X	X	X
Belgium	●	●	●	●	●[a]	●[a]	●[a]
Cameroon	●				●	●	●
Canada	●	●	●	●	X	●	X
China	●				●		
France	●						
Germany	●	●	●	●	●	●	●
Greece	●					●	●
Ireland	●						
Kenya	●						
Netherlands	●						
NZ	●						●
Russia	●				●	●	●
Sweden	●	●	X	X	X	●	X
Switzerland	●		●	X	X	●	●
Tunisia	●	●		●	●	●	X
Turkey	●	●	●	●	●	●	●
UK	●	●	X	X	X	X	X
Uruguay	●	●	●	●	●	●	●
USA	●	●	●	●	X	X	X

The "●" indicates the country utilizes pharmacist for that area of function. A blank indicates that it was not clear to the authors from the obtained documentation whether pharmacists are utilized in this function or information was simply not available. An "X" indicates that evidence exists that Pharmacy Officers of that force are not employed in the specific area. For Pharmaceutical Policy, a country meeting any of the criteria listed was counted as performing this overall function (i.e., not every country met every function listed in that criteria).
[a]As of 2018, the Belgian Military will be discontinuing its drug manufacturing activities and their associated research activities.

Impact of Pharmacy Officers

Despite the wide range of important health services support and clinical functions that Pharmacy Officers undertake, the amount of detailed study of their activities is quite limited. To our knowledge, there is only one published study that reviewed the roles of Pharmacy Officers and assessed their impact on patient care (Gendron et al., 2017). The review conducted by these authors identified only fourteen published accounts which assessed the impact of the role of Pharmacy Officers (Gendron et al., 2017). Thirteen of the fourteen studies described military pharmacy practice in the US, not a surprising finding as military pharmacy services in the US military are likely the most widely described in literature (Bartholomew et al., 1995; Bayles et al., 1997; Cammarata et al., 1987; Lambert, 2014; Snook et al., 1987; Strate and Brier, 1987; Troy, 2006; Williams et al., 1997; Young, 1997). Of the fourteen studies, five described the outcome of clinical interventions: successful dyslipidemia, diabetes, hypertension, anticoagulation, and asthma management by Pharmacy Officers (Gendron et al., 2017; Wallgren et al., 2012). One study described the monitoring of *A. baumannii* infected patients on Imipenem-Cilastatin and managing them to prevent drug shortages (Gendron et al., 2017). One study delved into the impact of Pharmacy Officers on occupational medicine where their interventions prevented soldiers from being deployed (Gendron et al., 2017). Two studies reviewed Pharmacy Officer impact on improved fiscal management and resource oversight (Gendron et al., 2017).

The remainder of the studies was mostly descriptive in nature (Gendron et al., 2017). While it is not surprising that most studies originate in the USA, it is nonetheless unfortunate given that US Pharmacy Officers are the only group not involved in broader range of health materiel management functions. For example, does an all-in-one integrated approach to health materiel management results in faster delivery of care and potentially reduced morbidity and mortality on deployed missions? Perhaps the ability of Pharmacy Officers to manage such critical components as surgical sterilization capabilities and blood delivery to the battlefield could result in increased availability of higher-level care in austere and humanitarian aid environments. Such questions remain unanswered.

The systematic review conducted concluded that further research into the impact of military pharmacy is required. The information collected in this chapter further supports and reinforces this conclusion.

The Future of Military Pharmacy Practice

As the profession of pharmacy evolves outside of the military, so will the practice of pharmacy in the military. The need to provide equivalent standard of care to military members coupled with increasing workload and health care costs undoubtedly means expanded roles for pharmacy officers in patient care, taking greater responsibility for not just pharmacotherapy, but also for more advanced pharmacy practice and greater health care-team involvement. What makes the military environment unique is that pharmacy practice is also affected by the changing nature of international conflict and new demands on leadership abilities of officers.

A survey of US military pharmacists at the rank of Lieutenant-Colonel and above has identified the need for senior pharmacists to have expanded clinical abilities, but also to improve their collaboration and communication skills with other professionals (Meadows et al., 2003a,b). Another US study described the criteria of importance in the domains of managerial and administrative pharmacy (Meadows et al., 2003a,b). These domains included: human resources, pharmacy operations and business practices, drug therapy management, and leadership (Meadows et al., 2003a,b).

The changing nature of conflict and new evidence in managing combat casualties by evacuating them to surgical care faster means surgeons, physicians, and other health care providers increasingly find themselves outside of the robust support frameworks of hospitals and clinics. In a special feature in the *American Journal of Health-Systems Pharmacy* titled "Redefining the practice of military pharmacy," some of the future directions would be to provide "pharmacy technicians to forward surgical teams" and "provide drug therapy advice during high-volume casualty management" (Normark et al., 1999).

Another area suggested in the special feature is for pharmacists to "be prepared to assist in triage, trauma management, and preventive field medicine" and act as advanced practice pharmacists on deployments (Normark et al., 1999). Therefore, the increasing demands on military health systems both domestically and on operations will mean both expanded clinical roles for Pharmacy Officers and expanded executive participation of senior Pharmacy Officers at the levels of medical planning, operational planning, and logistical support planning.

Conclusion

The practice of pharmacy in a Military environment offers unique challenges and opportunities to pharmacists. Some may consider this a specialty of pharmacy, while others may debate that the military pharmacy practice uses skills and knowledge from a wide range of pharmacy specialties (community, hospital, administrative, etc.) in a different and unique environment: the military environment. Pharmacy Officers represent a small proportion of all practicing pharmacists and may explain the paucity of publications describing their work. This chapter now presents a broad description of what is a Pharmacy Officer globally. Looking at the large number of military forces that employ them, it is evident that they play a vital role to the function of a military force. Pharmacy Officers must be able to provide the same pharmaceutical services as their civilian counterparts: work in hospitals and clinics, be adept at pharmacy administration, conduct research and write pharmaceutical policy. Additionally, several organizations require their Pharmacy Officers to undertake military training and to work as health care logisticians, to provide deployed forces with all the required health materiel. They will work in unique settings such as Field Hospitals, Field Health care facilities and even in Prehospital settings (such as in support of Field Ambulances)—both domestically and on international deployments. These environments do not systematically exist outside of the military or disaster-relief settings. Pharmacy Officers are required to gain expertise to work in these setting through life-long military training and additional certifications to enable such skill sets to exist. Considering the impact this relatively small group of professionals has on supporting global military operations, further in-depth research is decidedly required.

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Glossary

Air force Military force comprises of airborne assets such as helicopters, airplanes, and their supporting elements such as the airports and bases on which they are stationed.
Blood and blood products Any products intended to replace lost blood due to trauma and bleeding. Examples range from whole blood, packed red blood cells, blood plasma as well as individual clotting factors such as fibrinogen concentrate preparations.
Dispensing pharmaceuticals A patient care function whereby a health care provider (usually a pharmacist) provides pharmaceutical to a patient and ensures the pharmaceutical is safe and therapeutically appropriate for that specific patient.
Health equipment Any equipment used for monitoring and medical/surgical interventions, which requires the oversight and maintenance by qualified biomedical technicians and/or engineers. Such equipment normally requires complex validation, calibration and typically receives a regulatory authority license. Examples of such equipment would be defibrillators, telemetry monitors, infusion pumps, ultrasounds, radiographic equipment (such as computed tomography scanners), and oxygen delivery devices.
Health supplies Any consumable health care supplies which are not specifically categorized as pharmaceuticals. These would include dressings, injection devices, surgical instruments, laboratory reagents and supplies, medical/surgical sets, and first aid kits.
In Garrison A term used to describe the disposition of a military force when it is not engaged on a mission and is stationed in its home country.
Land Force A military force consisting of elements employed on land such as infantry, vehicles, armored vehicles, artillery, and any supporting elements such as the bases on which they are stationed.
Maritime Force or Navy A water-based military force consisting of ships and submarines as well as their supporting elements such as the ports at which they are normally stationed.
Mission An overall operational goal given to a defined military force, typically by a government or an international body (such as the United Nations).
Role 1 Medical Treatment Facility Terminology used by the North American Treaty Organization (NATO) to describe a health care facility providing primary care and prehospital care in a field setting.
Role 2 Hospital Terminology used by the North American Treaty Organization (NATO) to describe a field hospital with surgical and medical facilities with the ability to provide emergency care and initial wound surgery to stabilize an injured patient for transporting the patient to definitive care.
Role 3 Hospital Terminology used by the North American Treaty Organization (NATO) to describe a field hospital providing specialized care such as neurosurgery, orthopedic surgery, radiology, and full pathology laboratory services and the ability to care for a patient for a longer period in an intensive-care or postsurgical care setting.
Role 4 Hospital Terminology used by the North American Treaty Organization (NATO) describe a military hospital providing definitive care outside of the theatre of operations serving as a definitive evacuation point for casualties from Role 1, 2, and 3 facilities.
Supplying pharmaceuticals A logistic function of appropriately storing and transporting pharmaceuticals and distributing them to health care facilities and health care providers as well as issuing medication to a patient without a clinical assessment of the medication.
Theatre of operations In military terms, an area within which a military force conducts its mission. This includes the specific area of where the humanitarian activities, peacekeeping activities, or war fighting activities take place as well as any adjoining areas where supporting military units (such as a Role 3 hospital) are located.
Time & temperature sensitive health care products (TTSP) Health care materiel which requires defined temperature range and humidity conditions during storage and transport. TTSP includes all pharmaceuticals, fluids for injection, vaccines, blood and blood products, laboratory reagents as well as any medical supplies which may lose their effectiveness, physical properties or whose sterility may be compromised if exposed to conditions outside of the recommended range.

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Role of Pharmacist in Provision of Clinical Services in Prisons

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Introduction

WHO provides the definition for prison as the institutions that held the law offenders, sentenced by courts of law for a period of time in imprisonment (Møller et al., 2007). Prison or jail can be any place including all lands, buildings, where the prisoners are kept in custody on temporary or permanent basis or by the special orders of the government (Bureau of Justice Statistics, 2018). It does not include the place which is used by the police or a subsidiary jail for the detention of criminals (Bureau of Justice Statistics, 2018). Thus, a prisoner is any person whose liberty is restrained as a result of the interaction with the criminal justice system (Enggist et al., 2014).

Prison population represents the most underserved and most marginalized section of a society, mostly from lower socio-economic background with poor education status. Prisoners usually have poor health conditions and present themselves with chronic and untreated disease conditions, thus carrying more burden of disease than other members of society (Møller et al., 2007).

In general, the prison population is characterized by three key features: the population is mostly young, male and the turn-over of the prisoners is quite high among inmate population (Ministry of Justice, 2010). Every year new prisoners make the number up to four times the prison population. Moreover, local prisons receiving prisoners on short sentence or remand prisoners from courts represent the highest turnover. Contrary to this, high security and training prisons have the lowest turnover (Enggist et al., 2014). A total of 60% of the prison population is male and under 30 years of age (Ginn, 2012). Female prisoners are few in number globally, such as, in every 20 prisoners, there is one female prisoner. In England, there are 13 prisons for females, and females make just only 5% of the total prison population (Ginn, 2012). Contrary to this, in Wales, there are no specific prisons for females. However, Northern Ireland and Scotland have one prison, specified for females, and there are two Scottish male prisons with one female unit inside (Prison Reform Trust, 2011).

The prison environment is restricted and the inmates themselves are a challenging population to treat effectively. The social and health needs of patients inside jails are diverse, and the inmates may experience poor health conditions, including both mental and physical health (Ginn, 2012). Also, high turnover and short sentences make effective healthcare delivery difficult.

Moreover, the exposure to illicit drugs and physical abuse is quite common in prisons. Prisoners are dependent on prison staff for almost every aspect of their existence, including right to choose the food, accommodation as well as the ability to exercise (Ginn, 2012).

Population in Prisons

Globally, it is estimated that more than 10.2 million people are held in legal custody as remanded or sentenced prisoners (Walmsley, 2013). Between different regions of the world, the rate of prison population varies considerably; however, the prison population is on a great rise in all five continents of the globe (Walmsley, 2013). The world population has increased by over 20% and however the world prison population has increased to 30% (Walmsley, 2013).

Country-wise Distribution

There are more than 2.2 million prisoners in the United States of America, more than 1.65 million in China, 640,000 in Russian Federation 607,000 in Brazil, with 418,000 in India, 311,000 in Thailand, 255,000 in Mexico and 225,000 in Iran. However, the countries with the highest prison population rate (the number of prisoners per 100,000 of the national population) of Seychelles ranks first with 799 per 100,000, followed by the United States having 698 per 100,000, St. Kitts & Nevis having 607, followed by Turkmenistan with 583, U.S. Virgin Islands having 542, Cuba with 510, El Salvador comes next with 492, followed by Thailand with 461, Russian Federation with 445, then Rwanda with 434 and British Virgin Islands having 425 per 100,000 (Walmsley, 2015).

Based on the data from the United Nations, the world prison population rate, is 144 per 100,000 adult population. Female prison population has raised from 5.4% in about 2000 to 6.8% in 2015 (Walmsley, 2015). Netherlands has the highest number of female prisoners, while Belgium has the most unsentenced prisoners (BBC News, 2018). In Australia the rate of national imprisonment increased from 208 to 216 per 100,000 adult population showing an increase of 4% (Australian Bureau of Statistics, 2017).

Common Health Problems in Prisons

Prisoners have a higher chance to get any clinical problem, compared to the normal population in community, although the problems are common in both settings, but the likelihood of prevalence of the clinical conditions increase in prisons (Marshall et al., 2000). The conditions include air-borne infections, mental health, depression, anxiety, and other mental health affecting problems (Fraser, 2014). However, the following four are considered as priority areas:

- Primary care including epilepsy, respiratory and cardiac diseases, and reproductive system problems in female inmates.
- Infections diseases such as tuberculosis, HIV, and other skin conditions.
- Mental health.
- Dependence to drugs and alcohol (Fraser, 2014).

There are also problems of drug abuse, alcoholism, trauma, homicide, suicide, violence, neuropsychiatric diseases, epilepsy, stress manifestations, HIV infection and AIDS, sexually transmitted diseases, tuberculosis, and skin infections (Marshall et al., 2000).

Globally, noncommunicable diseases are considered as a matter of serious consideration as these diseases are responsible for 36 million deaths each year and constituting a total 63% of the deaths worldwide (World Health Assembly 66, 2013). These diseases mainly comprise of the most common four diseases such as cardiovascular disease 48%, diabetes 3.5%, cancers 21%, respiratory diseases which constitute 12% of the people in incarceration (Enggist et al., 2014). Although these diseases affect people from all nationalities and all socioeconomic background, but it is seen that socioeconomic status and noncommunicable diseases have a direct link, given that most of the 10 million imprisoned belong to the most marginalized part of society with a poor socioeconomic background and are at a greater risk to develop noncommunicable diseases (World Health Organization, 2013). The prison environment offers various risk factors towards the development of noncommunicable diseases such as unavailability of healthy diet, lack of physical exercise, smoking, and use of alcohol. Hence the problems associated with diseases and associated risk factors present a major challenge in providing appropriate prevention and treatment strategies for the treatment of prisoners (World Health Organization, 2013). The risk of blood-borne infections is also very high, especially the infections responsible for HIV, TB, viral hepatitis B and C and other sexually transmitted disease (Hammett et al., 2002). This is coupled with the factors such as over-crowding, delay in diagnosis, less or no hygienic condition of prisons (Hammett et al., 2002).

It is estimated that, female prisoners constitute about 2%–9% of the prison in each country (Walmsley, 2006). Most women in prisons are usually mothers and are sole caregivers for their children. In Brazil, the percentage of mother prisoners is as much as 87% (Atabay, 2014), followed by Thailand with 82% (Atabay and Owen, 2013), United States and Russian Federation have 80% and United Kingdom has 60% of the inmate population as mothers (Atabay, 2014). They require special health care needs, as women in prison have higher mental illness rate compared to the male prison population (Bastick and Townhead, 2008). A high percentage of female prisoners experience physical or sexual abuse, even before their imprisonment (Quaker Council for European Affairs, 2007). Thus, female inmates are at a greater risk to develop Hepatitis C, HIV, and reproductive system related infections such as syphilis, chlamydia infection, and gonorrhea (Stöver, 2008). The health needs of the female prisoners demand personalized care including

treatment for substance abuse, mental health issues, violence, abuse, reproductive health, infectious diseases, and dental health (Enggist et al., 2014).

Healthcare Facilities for the Prisoners

Prisoners like everyone in the community have the right to enjoy good physical and mental health and retain to be entitled for healthcare facilities that are at least equivalent to those outside the confinement (Enggist et al., 2014; United Nations, 2016). The health care delivery starts right at the arrival of the prisoner, when he or she appears for a medical examination and continues throughout the detention period (Enggist et al., 2014).

In this regard, various international standards define the health care quality that should be provided to the prisoners. These standards are discussed below:

United Nations Guidelines

In providing the basic health care to the inmates, the United Nation has established standards as guideline for the provision of healthcare services in prisons (United Nations Organizations, 1990). Article 12 of the International Covenant on Economic, Social and Cultural Rights (United Nations, 1966) described the basic right as "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health". This applies to the prisoners as it applies to every human being. Similarly, the United Nations (1990) mentioned in the principle 9 of their Basic Principle for the Treatment of prisoners that "Prisoners shall have access to the health services available in the country without discrimination on the grounds of their legal situation". This is to strengthen the concept that people in prison should be treated with high standard of health care facilities as this reflects on the part of the state's responsibility (United Nations Office on Drug and Crime, 2008; 2013).

Prison administration not only have a responsibility to fulfill the basic health needs of the prisoners but also to promote the well-being of the prisoners by establishing health care standards in the territory (Gatherer et al., 2014). Around the world prisoners are facilitated with varying levels of health care (Miller, 2013). They have different level of access to health care ranging from places in developing countries, where there is no facility of medical treatment to where there is very little access to the health care facility. However, in developed countries like United States, Canada, New Zealand, Australia, and Europe, the scenario is different as prisons over there are quite advanced in providing health care to the prisons with high standards of care and services (Miller, 2013).

European Prison Rules by the Council of Europe

In Europe, the council of Europe formulated European Prison Rules with the intention to provide the inmates with necessary healthcare needs in the region (Council of Europe, 2006). These rules were formulated with the assistance from the World Medical Association, European Committee for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment (CPT), the International Council of Nurses, the Swiss Academy of Medical Sciences and the World Health Organization. Those rules are based on seven basic principles: "access to a doctor, equivalence of care, patient's consent and confidentiality, preventive health care, humanitarian assistance, professional independence, and professional competence" (Council of Europe, 2018).

Committee of Ministers of the Council of Europe

The Committee of Ministers of the Council of Europe (1998) has stressed that "health policy in custody should be integrated into, and compatible with, national health policy" (World Health Organization Regional Office for Europe, 2013). The Committee further explained that this initiative is not only in the interest of prisoners, but this integration also favors the health of the community at large. It is especially significant for policies related to infectious diseases that may have a chance to spread from prisons to the wider community. Similarly, majority of prisoners in prisons are usually for shorter period of time and eventually they will be released from prisons. They will return to society from which they belong, once their sentence is over. When they rejoin the community, it is important that, they joined back with the good health conditions (World Health Organization Regional Office for Europe, 2018).

World Health Organization Health in Prisons Programme

In order to support and improve the health care in prison and to establish a link between national and prison health system of member states, both at national and international system, World Health Organization has established health in Prisons Programme (HIPP) in 1995 (Bott, 2016). This program is meant to provide the technical assistance to member countries on issues related to mental health, illicit drug use and communicable diseases including hepatitis, tuberculosis and HIV/AIDS (World Health Organization Regional Office for Council of Europe, 2018). As part of HIPP, WHO/Europe established a network of national counterparts and international partner organizations to liaise between WHO/Europe and Member States. The network currently includes 44 national counterparts and meets once a year to discuss specific topics (World Health Organization Regional Office for Council of Europe, 2018).

All countries that are participating members of the WHO Health in Prisons Project (HiPP) are also members of the Council of Europe (Gatherer et al., 2005). It is recommended that in every prison there must be qualified medical practitioner and other medical personnel trained to provide healthcare delivery (World Health Organization Regional Office for Council of Europe, 2018). The European prison rules also made recommendations regarding patients who having mental health problems to be considered for special treatment (Enggist et al., 2014). All these reforms are designed to safeguard the community as a whole. If these inmates are not looked after properly in prisons, they will further increase the burden on the existing facilities, once they return to their communities after their release (Enggist et al., 2014).

The Organization of Prison Health Care

Across the globe, medical care to the prisoners is managed by various agencies by employing different approaches and mechanisms, usually it is the responsibility of Ministry of Health or their equivalents, Ministry of Interior and the Ministry of Justice (United Nations Office on Drug and Crime, 2008). However, to ensure that prisoners can receive better healthcare, it is very much based upon the close contact between public health and prison health administration. To do so, many countries around the world have started to strengthen such collaborations and links (Møller et al., 2007). Many prisons argue that prison health services should come under the public health services system rather being operated as a separate system run by the ministry of prisons. For instance, in Wales and England the responsibility and the prison budget both were transferred to National health Service in 2002 (Hayton and Boyington, 2006). Likewise, in Norway, the responsibility of health care was handed over to local health care authorities for the provision of prison health care services (Coyle, 2014). France introduced the legislation reforms in 1994, by putting prison health care under the Ministry of Health, supervised by General Health Directorate for public health issues (Dubois et al., 2017). The provision of health care in prisons in most of the European countries comes under the Ministry of Justice and further medical services are managed by the hospital administration, such as, in Italy the Ministry of Justice bears the costs of the health care in prisons (Council of Europe, 2014). While other member countries of WHO European Region including Finland, Kazakhstan, Republic of Moldova, Kosovo are planning to involve Health ministry (United Nations Office on Drug and Crime, 2008; 2013; Council of Europe, 2014).

Prisoners are admitted to hospital for treatment inside and also outside of the prisons, for example, in Cyprus, Norway, Sweden, Lithuania, and Turkey, the hospital treatment is only available outside the prison (Council of Europe, 2014). Besides, in many European countries, large prison systems have their own health and medical care staff, while others have appointed part time staff including dentists, psychiatrists, psychologists and gynecologists. However, in prisons, where physicians are part-time employed, a full time trained health care staff with trained nursing staff fulfils the requirements (Marshall et al., 2000). In France, the medical team is composed of general practitioners, dental surgeons, medical specialists, and pharmacists, along with a paramedical team of nurses, radiology technicians, and administrative personnel (Dubois et al., 2017). Contrary to this, in countries like Scotland, nurses are responsible for the delivery of primary health care to the prisoners, being the first point of contact between the prisoner and the health care system (Dubois et al., 2017; Møller et al., 2007). These responsibilities may include prisoner's preliminary health assessments upon arrival, issuance of medicines to patients, or application of prescribed treatments recommended by physician (Møller et al., 2007).

Pharmacy Services in Prisons

Pharmacy practice, for instance, in American prisons remains unique in terms of its distinct features, though it encompasses various aspects of hospital, community, and consultant pharmacy practice. It is also recommended in these guidelines, that such places should hire at least a pharmacist for the delivery of healthcare (American Society of Health System Pharmacists, 2013). Pharmacy services in prisons fall into the following these categories: (Norris, 2005).

1. An in-house service based on the supervision of a pharmacist inside prison.
2. A satellite service provided by a nearby prison to another prison-based patient with a type (a) service.
3. A service provided by outside contractors, such as independent companies, or by a community or hospital pharmacist.

The practicing pharmacist in such territories not only have to be familiar with the community standards of care, but they need to be aware of the rules and regulations implemented by federal or local jurisdictions. As in case of pharmacist practicing in American prisons, familiarity with the community level care as well as standards set by National Commission on Correctional Health Care and ASHP is a necessary requirement (American Correctional Association, 2002; American Correctional Association Commission on Accreditation for Corrections, 2003).

Role of Pharmacist

Since the emergence of pharmacy profession, pharmacist has been considered as the individual who has the knowledge about medicines and their optimum use (World Health Organization, 1997). The role further got the recognition when the subject

of pharmacy received the recognition worldwide (World Health Organization, 1997). Clinical pharmacy services offers the same activities, tailored to optimize the patients' health outcomes, ensure safety throughout the medicine management process and lower the risks associated with the use of medicines (Society of Hospital Pharmacists of Australia, 2014). Clinical pharmacy services also include therapeutic drug monitoring, adverse drug reaction management, medication reconciliation, medicines management plan, and participation in the interdisciplinary health care team (Society of Hospital Pharmacists of Australia, 2014). Hence many pharmacists work in the prison based pharmacy and are majorly concerned with the planning, coordination and delivery of pharmaceutical care to the patients in detention. They are usually assisted by pharmacy technician, employed by the prisons. The health care delivery in prison involves a mutual effort of the prison pharmacy staff and other health care members from multidisciplinary team including dentists, physiotherapists, psychiatrists, and radiologists (Norris, 2005).

It is suggested that the prisoners should get the same level of care and treatment what is available to the outside community. The next section of the chapter specifies the role of a prison pharmacist in the delivery of clinical services to prison-based patients:

As the Director of Pharmacy

In United States, a licensed pharmacist recognized by the National Association of Boards of Pharmacy should be appointed the pharmacy director of the facility. He or she should be hired, at least, on a consulting basis. Health care needs of the facility should be considered before staffing pharmacists for the facility (American Society of Health System Pharmacists, 2016). By the approval of relevant health authority and prison administration, the pharmacy director takes up the responsibility of the operations and policy implementation for pharmacy (Bott, 2016).

Provision of Drug Usage and Other Services

The review and monitoring of prescription by pharmacist focuses on the initiation and discontinuation of the treatment, adjustment of dose for the patient, monitoring of test result in relation to dose and side-effects (Allgeier, 2012). A pharmacist employed in prison is in a better position to provide a number of services and information, pertinent to drug and its interaction, nutrition, drug–food interactions, drug abuse and withdrawal treatment, medicines use in emergency, antidotes for poisoning, mental health, medical devices and supplies, and provision of health care for pregnant women (Bott, 2016).

Medication review by pharmacists is an effective tool to make prisoners understand their medicines and problems associated with the medicine use. It is especially useful for those patients who are on multiple medications, having chronic problems and most importantly for the prisoners going through detoxification treatment (Allgeier, 2012). Hence, pharmacist working in a prison is able to offer his expanding role as a service provider and can contribute through his expertise to be an active team player of the medical team (Bott, 2016).

Provision of Nonprescription Drug Selling and Storing

In some prisons, facility, such as a general store, typically called as commissary sells drug products to inmates without the prescription of the physician (Prison Fellowship, 2018). In some prisons nonprescription medicines are available for purchase by the inmates, pharmacist need to be stringent in checking that medicines are not being abused (Bott, 2016). The purchased quantity of the medicines should be minimized to prevent possible overdosing. Pharmacy director may take the lead in this regard and can inspect the premises to check that which type of nonprescription medication are being sold. He can also inspect the storage conditions to ensure that the quality and safety of the products remain intact. This task can be further improved by providing the leadership through regular meetings with the facility's medical, para medical, and mental health staff (Bott, 2016). Particular attention must be paid to psychotropic medications, medication used for the treatment of communicable diseases, or other medical conditions specific to inmates (American Society of Health System Pharmacists, 2010b).

Dispensing

The dispensing job of a pharmacist is quite different from what he does in community. Because in prison, there are many inmates who are undergoing the treatment for substance misuse. There are also some patients who are getting medication for psychological or depression problems, and the number of patients is higher than the community. There are some medicines, which are labeled as that can be kept by the patient or cannot be and hence labeled as in-possession or not-in-possession based on the type of drug and risk assessment of the prison-patient. So, a pharmacist has to be more careful while dispensing these medications. However, not in possession items are administered by nurses in specialized "medical hatches" to avoid the risk of drug misuse. As some medicines have a great value to the prisoners, and if they are selling those medications to other inmates, they will try to divert or conceal it from medical staff. Therefore, the role of pharmacist in dispensing in prisons is quite challenging. As its more strategic in prisons to provide health care services to the inmates. One example is tramadol which is not allowed to keep in possession by the inmates, but which is otherwise allowed in community to take four times a day. To overcome the challenge, some prison pharmacist has developed a way to dispense the drug as a modified slow release type, which cannot be abused by the prison-patients (Cox, 2018).

Medication Administration

It is not possible to have a huge number of healthcare professionals working in prisons, so sometimes the trained but nonhealth care staff are also involved in the process of drug administration, if nurses are unavailable (National Commission on Correctional Health Care, 2018). In such scenarios, the pharmacy director is considered liable to develop the medicine information forms and should ensure the particulars entry in the forms. The information includes particulars about type of administered drug, dose and its frequency, start and end date of drug administration, and history of allergies to the medicines. The pharmacy director is also responsible to design policies about the administration of the drug to the prisoners, or during court hearing, transfer to or release from the prison. For example, inmates upon their release from prison, may be issued with a discharge prescription having details of the medicines (Bott, 2016).

Substance Abuse and Rehabilitation Service

Various studies estimate that the percentage of individuals reporting problematic substance misuse is comparatively higher in prison than in the community. Different studies have indicated that the percentage of people in prison who have a drug problem, ranges from 40% to 80% particularly for women with drug problems. Substance abuse is a major societal problem bearing significant public health concern (Allgeier, 2012). Data from Centre for Disease Control and Prevention has found that substance abuse in prisons was linked with 7.6% of new HIV cases between years 2008 and 2011, involving transmission through the sharing of syringes for drug use and other equipment, hence proved to be the most common transmission route for Hepatitis C. As a result, substance abuse may be associated with the aggravation of mental illness, which ultimately led toward the use of such substances to deal with the physical or mental complication. Many studies have indicated that the individuals experiencing substance abuse problems are more in prisons than in the general population and they might range from 40% to 80% (Dolan et al., 2007), presenting a high ratio of females with substance abuse problem in incarceration. According to a study by The National Center on Addiction and Substance Abuse at Columbia University has estimated that only 11% of such individuals manage to receive substance abuse treatment in prisons (Centre on Addiction, 2010).

Hence, prison pharmacists are responsible to ensure safe and effective medication-use system. Pharmacist in such territories also need to tackle the legal and organizational responsibilities for medication distribution and control across the continuum of practice settings within prisons (Allgeier, 2012). Pharmacist's responsibilities for the treatment and rehabilitation of inmate patients with chemical dependency include provision of services to meet the medical needs of patients during detoxification; planning and development of detoxification protocols, withdrawal management; treatment options for patients, medication and addiction counseling by pharmacy; education of patients and their families and other clinical staff members (Haynes, 1988). To successfully fulfill this complex role, the pharmacist must have specialized skills to tackle addiction, including skills on nonpharmacological approaches. A pharmacist working in a chemical-dependency rehabilitation program has a unique opportunity to positively influence the physical and mental health of the prisoners (Haynes, 1988).

Special Need Services to the Patients

Pharmacist can assist patients with disabilities to follow their medication regimen by providing special clinical services. Such facilitative adjustments by the pharmacist to the inmate patients include use of large print labels and reminder charts, monitoring dosages, and compliance aids (Allgeier, 2012). Another pharmacist-led service is provided to the patient is the supervised self-administration of medication. This encourages the patients to administer the medicines by themselves. This is focused toward the administration of controlled substance for the treatment of substance abuse, but the administration of other medications is also considered (Allgeier, 2012).

Pharmacist in prisons can promote the healthy life style among inmate patients through verbal advice and provision of written material for the patients such as leaflets. Pharmacist may help to motivate the patients about their lifestyle and can provide behavior modification assistance, as, in case of smoking cessation (Allgeier, 2012). Various prison-based studies have showed that a pharmacist led clinic is useful, as prisoners received better information about their condition and the treatment plan (Mathis and O'Reilly, 2010; Tucker, 2004a, 2004b). A pharmacist led-clinic helped the patients to improve their understanding for the skin problem and to adhere with the treatment, which ultimately resulted in the improvement of their physical condition and quality of life (Tucker, 2004a, 2004b). Similarly, a pharmacist led warfarin management point of care service has resulted in the low incidence of adverse effects (Mathis and O'Reilly, 2010).

Education

Inmate patients have poor knowledge about health-related issues so there is a need to improve their health literacy level (Bott, 2016). The educational programs should encompass information on drug indications, administration, appropriate use for medications stocked for emergency use; monitoring for adverse events and allergic reactions; documentation; accountability; confidentiality; and the importance of adherence to medication regimens (Bott, 2016). This could also include provision of language- and age-based educational materials to the prisoners (American Society of Health System Pharmacists, 2010a). For instance, in Slovenia, a health education based program is provided to both staff and prisoners. These leaflets contain information for prisoners about personal

hygiene and maintenance of the cells, where they are living. Likewise, the staff is educated about control of infection. In addition to such programmed, prisoners are provided awareness about TB and HCV. While in Austria, the system is much developed since 1998, as the new inmates, upon their arrival to prisons are provided with Information & Care pack, that contains information about services and risk behaviors including drug and alcohol education, awareness about HIV and its prevention (United Nations Office on Drug and Crime, 2008).

In addition to this, the prisoners should have freedom to consult a pharmacist or request information about a particular drug, or to make choices regarding their own health care (Bott, 2016). Hence, qualified pharmacists must be authorized to provide such services to the inmate population provided, legal requirements are fulfilled, and necessary collaboration are agreed by the prison authorities (Bott, 2016).

Research

Research is a major trigger which can help in the improvement of quality of health services, because these findings will help the health services provider to have a better idea that whether health programs are appropriately executed. It also guides to find out the prevalence of disease and the associated risk behaviors in prison population. Research in prison health care facility not only aids to monitor the feedback on health interventions, but it also helps to modify the existing policies and procedures (Stevens, 2010).

All research that involves medications use in prisons, should be conducted in consultation with a prison pharmacist. The retrospective and prospective research is the need of the hour to advance the practice of prison-based pharmacy as it provides evidence-based clinical decisions. Research in prisons should be done with the potential to influence the patient care and it must include the informed consent and should be approved by relevant authorities (Bott, 2016).

Conclusion

Providing health care in prisons is a big challenge. However, it has major societal benefits and failure to provide health care to prison population may lead to adverse health outcomes. The services in prisons should be based on individual patient needs and should promote self-care. The role of pharmacist in the delivery of such services is both challenging and crucial. Hence, pharmacist led healthcare delivery can help the people in incarceration, to adopt a healthy and disease-free life style. The extended role of pharmacist in the delivery of clinical pharmacy services may help in the minimization of healthcare disparities among prison population.

Glossary

Incarceration The state of being confined in prison or in imprisonment.
Inmate A person who is forced by law to stay in a prison or hospital or in a correctional facility.
Turnover Turnover refers to the number or percentage of individuals who leave an organization and are replaced by new individuals.

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Long-Term Care

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Learning Objectives

- Describe the pharmaceutical issues associated with long-term care.
- Describe interventions that pharmacists can make to support patients with long-term conditions.
- Summarize the evidence for pharmacist interventions on outcomes for patients with long-term conditions.

Introduction and Need

Modern medicine is reducing mortality but sometimes at the expense of morbidity (BMJ, 2014). Long-term conditions (LTCs) or chronic diseases are conditions for which there is currently no cure, and which are managed with drugs and other treatment, for example: diabetes, chronic obstructive pulmonary disease (COPD), arthritis, and hypertension (The Kings Fund, 2018). LTCs also include defined mental health conditions such as schizophrenia, ongoing conditions such as learning disabilities, symptom complexes such as frailty or chronic pain, sensory impairment such as sight or hearing loss, and alcohol and substance misuse (National Institute for Health and Care Excellence, 2016).

Multimorbidity is the presence of two or more LTCs (National Institute for Health and Care Excellence, 2016) and is now commonplace (BMJ, 2014). Multimorbidity has been shown to be associated with increased patient mortality, increased hospital admission and readmission, increased length of hospital stay, increased demand on health resources and complexity of care, increased dependency, and reduced patient quality of life (Harrison et al., 2016; Kingston et al., 2018).

Multimorbidity is not confined to older people, but the number of LTCs a person has increases with age and is also increased in less affluent areas. (BMJ, 2014; National Institute for Health and Care Excellence, 2016). In addition to multimorbidity, many of the oldest old also have sensory impairment and incontinence (Kingston et al., 2018).

Frailty is a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves (British Geriatrics Society, 2014). Minor stressor events including acute illnesses such as urinary tract infections are associated with adverse health outcomes in patients with frailty such as dependency, institutionalization, and premature death

(Harrison et al., 2015). Around 10% of people aged over 65 years have frailty, rising to between a quarter and a half of those aged over 85 years (British Geriatrics Society, 2014).

As the number of LTCs conditions increases, often the number of medicines prescribed to treat these conditions or prevent complications from these LTCs also increases leading to polypharmacy. Polypharmacy is where an individual takes multiple medicines and is driven by an ageing population and the prevalence of multimorbidity (Duerden et al., 2013) but can also be caused by clinical guidelines, care pathways, and even processes for clinical remuneration (BMJ, 2014). Evidence for recommendations in national guidelines on single health conditions is regularly drawn from people without multimorbidity and polypharmacy (Duerden et al., 2013; National Institute for Health and Care Excellence, 2016) as often these people are excluded either directly or indirectly from clinical trials (Duerden et al., 2013; Hardy and Hilmer, 2011). Therefore, the evidence base for treating multiple LTCs with multiple medicines is poor, and pragmatic clinical trials need to be conducted that include patients with multimorbidity and polypharmacy (Duerden et al., 2013).

The Kings Fund has proposed the use of the terms appropriate and problematic polypharmacy. Appropriate polypharmacy has been defined as the prescribing for an individual for complex conditions or multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best practice. Appropriate polypharmacy can extend life and improve quality of life for people. Problematic polypharmacy has been defined as the prescribing of multiple medications inappropriately or where the intended benefit of the medication is not realized. Problematic polypharmacy increases the risk of adverse drug reactions (ADRs) (Duerden et al., 2013; McGrath et al., 2017), drug–drug, and drug–disease interactions (Duerden et al., 2013; McGrath et al., 2017), falls (BMJ, 2014; Marvin et al., 2016; Ziere et al., 2006); increases health-care costs (McGrath et al., 2017), hospital admissions (Describing deprescribing 2014), (Morandi et al., 2013), and mortality (National Institute for Health and Care Excellence, 2016; Thompson and Farrell, 2013); and reduces functional capacity (McGrath et al., 2017), adherence to medicines (Duerden et al., 2013; McGrath et al., 2017), and quality of life (Duerden et al., 2013). Evidence shows that many medicines are not taken as intended by the prescriber and are unused, underused, or wasted (Duerden et al., 2013). Patients with multimorbidity with a limited life expectancy or frailty may obtain limited benefit from medicines treating single conditions (National Institute for Health and Care Excellence, 2016), especially secondary prevention medicines.

Deprescribing is defined as the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes. Deprescribing reduces the number of medicines prescribed and medicine costs, but there is little evidence of impact on outcomes with the exception of falls so more research in this area is required, focusing on outcomes and the specifics of how to deprescribe safely and effectively (Hardy and Hilmer, 2011; Thompson and Farrell, 2013).

People living in long-term care facilities or care homes are at increased risk of multimorbity and polypharmacy. People often need residential care due to diseases related to ageing and/or frailty. Therefore, people in long-term care facilities tend to be older than those living in domiciliary settings, are more likely to have multiple long-term conditions, and, as a result, polypharmacy is common (Payne and Duerden, 2015). In the United Kingdom, care homes residents were taking an average of 8 medicines each (Barber et al., 2009). In a European study (Onder et al., 2012), half of all residents were taking 5–9 medicines and a further quarter were taking 10 or more. In Canada, 15% of long-term care residents were taking 9 or more medicines (Bronskill et al., 2012). Medication error rates in long-term care facilities result in preventable patient harm. Error rates of two adverse events per 100 resident months have been found in the United States (Payne and Duerden, 2015). In a UK study, 40% of care home residents were affected by a prescribing error and 10% experienced monitoring errors (Barber et al., 2009).

Therefore, pharmacists in various settings are well placed to ensure that people with multimorbidity are cared for appropriately. This should include reviewing how the person's health conditions and their treatments interact and how this affects quality of life; the person's individual needs, preferences for treatments, health priorities, lifestyle and goals; the benefits and risks of following recommendations from guidance on single health conditions; improving quality of life by reducing treatment burden, adverse events, and unplanned care and improving coordination of care across services (National Institute for Health and Care Excellence, 2016). This may include pharmacist involvement in consultations with people to review medicines and/or deprescribing and various tools are available to help pharmacists review long-term medicines.

Management

Care Models for Long-Term Conditions

Individual management of specific long-term conditions is beyond the scope of this chapter. Please see individual chapters for detailed management advice.

Models of care that aim to ensure that people treated for LTCs receive high-quality holistic care have been trialed and adopted into practice in different countries. These include the Chronic Care Model, the Innovative Care of Chronic Conditions, and the Kaiser Triangle Model.

The Chronic Care Model (CCM)

The Chronic Care Model was developed in the United States in 1998. It has 6 main principles: mobilizing community resources to meet the needs of people with LTCs; creating a culture, organization, and mechanisms that promote safe, high-quality care;

empowering and preparing people to manage their health; delivering effective, efficient care, and support for self-management; promoting care consistent with evidence and patient preferences; and organizing patient and population data to facilitate efficient and effective care (Singh and Ham, 2006).

The Innovative Care for Chronic Conditions Model

The World Health Organization developed the Innovative Care for Chronic Conditions model that focuses on improving care at three different levels: micro level (individual and family), meso level (health-care organization and community), and macro level (policy). This model suggests that positive outcomes for people with LTCs can only occur when people and their families, community providers, and health-care professionals are informed, motivated, and work together (Singh and Ham, 2006).

The Kaiser Triangle Model

The "Kaiser triangle," developed in the United States, is a proactive approach to managing care for people with LTCs. This is a hierarchical system where people are stratified according to need with intensive management targeted at those who are at highest risk. The Kaiser triangle includes supported self-care for the majority of people with LTCs (70%–80%) as a first step (Singh and Ham, 2006). Supported self-care aims to encourage individuals to cope and live well with their condition by equipping them, and their carers or supporter peers, with the necessary knowledge, skills, and confidence (NHS Greater Glasgow and Clyde, 2009). The next step is disease management of high-risk people (Singh and Ham, 2006), supporting people with information, monitoring, and proactive management. The aim is to slow down deterioration of their condition(s) and prevent complications including admission to secondary care (NHS Greater Glasgow and Clyde, 2009). The final step is case management of highly complex people (NHS Greater Glasgow and Clyde, 2009; Singh and Ham, 2006), which aims to identify and anticipate the care requirement and coordinate a multidisciplinary and/or multiagency care package to prevent emergency situations leading to admission to hospital (NHS Greater Glasgow and Clyde, 2009).

Assessment and Management of Frailty

Frailty is now recognized as a long-term condition in its own right. Frailty shares many similarities with other LTCs: it can't be cured, is progressive, reduces quality of life, can result in crises intermittently, and is costly to the person and the health-care system as a whole (Harrison et al., 2015). Various tools are available to identify frailty such as the Rockwood Clinical Frailty and Edmonton Frailty scales (British Geriatrics Society, 2014) and proactive identification of frailty can then be used to instigate person-centered, proactive care and treatment (Harrison et al., 2015). Older people with frailty should have comprehensive geriatric assessment (CGA), which is a comprehensive review of their medical, functional, psychological, and social needs and results in an individualized care and support plan outlining their treatment goals, management plan, and plans for urgent care. Reversible medical conditions should be considered and addressed if present, for example, acute infection. End of life plans may also need to be included for some people. The care and support plan should be shared between different health-care professionals and sectors caring for the frail person (British Geriatrics Society, 2014). Older people with frailty are at increased risk of inappropriate prescribing and harm from medicines (BMJ, 2016; Cullinan et al., 2015). Therefore, regular reassessment of medicines is required (BMJ, 2016), and evidence-based medication review should be part of their care (British Geriatrics Society, 2014). Health-care professionals also need to consider the risk of discontinuation reactions in any deprescribing activities as these may be more serious in frail people (BMJ, 2016).

Polypharmacy and Deprescribing

Appropriate polypharmacy that extends life and improves quality of life requires individualized, patient-centered care using medicines optimization (MO) (BMJ, 2014). MO is a process that allows patients to gain the most net benefit from taking medication where medicines are prescribed taking the patient's preferences and characteristics into account (Royal Pharmaceutical Society, 2013) and acknowledging that what is most valued by the person might be different to the health-care professional (BMJ, 2016). This patient-centered care also needs to be shared across the whole health-care system, but this can be difficult to achieve in practice, especially in countries with fragmented health systems, as organizational boundaries and professional silos cause challenges to the effective sharing of care. While it is unclear what the ideal process for delivering MO is, identifying medicines not likely to be benefiting the person and deprescribing should be included (BMJ, 2014). There is a lack of evidence regarding deprescribing and little to guide the person and the prescriber in how to reach a decision on what to stop, when, and how (Barnett and Garfinkel, 2018; BMJ, 2014; Johannon et al., 2016). Effective deprescribing is a complex process (BMJ, 2016) with a number of components. These include participation by patients and/or relatives, carers and supporting peers (Jansen et al., 2016; Reeve et al., 2014), prescriber/patient relationships and communication (Linsky et al., 2015; Straand and Sandvik, 2001; Turner et al., 2016), and shared decision-making (Jansen et al., 2016).

A Patient Attitudes Toward Deprescribing (PATD) questionnaire has been developed and tested in older out-patients and caregivers in Australia and inpatients in Italy (Barnett and Garfinkel, 2018; Galazzi et al., 2016). This showed that many older people were less aware of the reasons for taking their medicines and that many wanted to reduce the number of medicines taken. Key factors identified included perceived burden of medication taking, belief in appropriateness of medication use (benefits and harms),

concerns about stopping medicines, and level of involvement/knowledge of medicines. Another study identified four factors that are important to people in relation to stopping medicines: medication knowledge, concerns, importance, and interest in stopping medication (Barnett and Garfinkel, 2018). Poly-de-prescribing is the cessation of at least three medicines at the same time and one study in older people has shown that this is well tolerated and is associated with better patient outcomes compared to older people who take all the medicines recommended by clinical guidelines (Garfinkel, 2017).

End-of-life care is beyond the scope of this chapter, but clinicians need to apply "end-of-life" medication review where this is appropriate. This is applicable in patients with advanced LTCs and some patients with severe frailty as well as those with advanced terminal cancer (BMJ, 2014). Prescribers often do not receive training on deprescribing; therefore, focus is needed on educating prescribers and other health-care professionals about the benefits of deprescribing. Health-care professionals may be concerned about deprescribing amid perceptions of denying people medicines or cost-cutting and may be wary of stopping medicines started by specialists with more expertise in a particular field (BMJ, 2016). Absolute benefits of treatments can be assessed using the number-needed-to-treat (NNT) and absolute risks using the number-needed-to-harm (NNH). However, estimates of NNTs and NNHs are usually taken from, individual clinical trials (BMJ, 2016) and as mentioned earlier, those who are older, frail or with multiple comorbidities are not well represented (BMJ, 2016; Duerden et al., 2013), so NNTs may overestimate benefit and NNHs may underestimate harm in these groups. However, NNTs and NNHs may be helpful to explain to an individual the likely time for benefit or harm to occur. This is especially important for preventative medicines where benefits may not be seen for years (BMJ, 2016).

Clinical Medication Review

Clinical medication review has been defined as a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems, and reducing waste. Medication review can be used to describe any activity that involves reviewing medicines in any care setting. Different levels of medication review have been described from unstructured, opportunistic reviews to a face-to-face review of medicines and conditions with the patient using the full patient record (Clyne et al., 2008).

As described earlier, medicines optimization using clinical medication review should be conducted in conjunction with the person themselves. A patient-centered approach to managing polypharmacy in practice has been proposed by Barnett et al. (2018). This is a structured approach but still allows flexibility for individualized care and is represented in **Fig. 1** (Barnett et al., 2018).

Other methods to structure the medication review process include the 7 steps. These include Step 1 where aims and objectives of drug therapy are identified; Step 2 where essential drug therapy is identified; Step 3 where unnecessary drug therapy is identified; Step

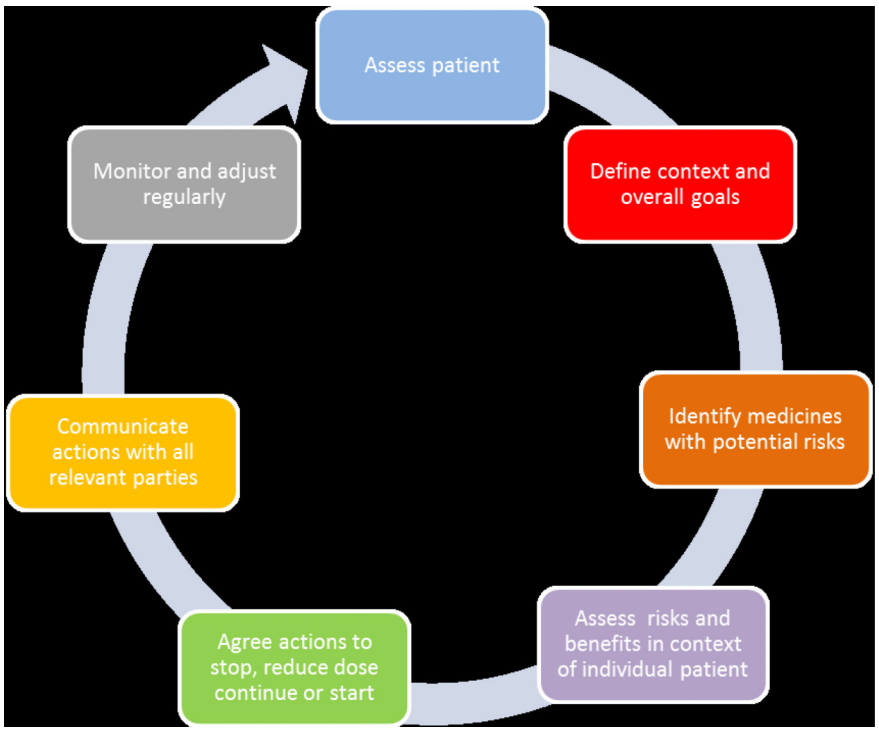

Figure 1 A patient centered approach to managing polypharmacy in practice.

Table 1 Web based tools and resources for review of polypharmacy and deprescribing

Tool	*Description*	*Web-site*
Medstopper	Developed by Canadian experts in evidence-based medicine and prescribing in the elderly and gives information on risks and benefits and how to withdraw treatment for different medicines. Frail elderly cab be selected which adjusts harm rating when using this tool	www.medstopper.com
Medichec	Developed by South London and Mawdsley NHS Foundation Trust to identify and assess the risk of medicines with anticholinergic effects (which increase the risk of cognitive impairment, dementia and early death in older people)	www.medichec.com
Anticholinergic Cognitive Burden Scale	Developed by the Indiana University Center for Ageing Research to identify and assess risk of anticholinergic medicines	www.agingbraincare.org/tools/abc-anticholinergic-cognitive-burden-scale
Canadian Deprescribing network algorithms	Algorithms to aid the deprescribing of certain classes of medicines such as proton-pump inhibitors, antihyperglycaemics and benzodiazepines	deprescribing.org
NHS Scotland resources	Resources for reviewing patients with polypharmacy including 7 steps approach, general guidance, NNT and NNH	www.polypharmacy.scot.nhs.uk

4 reviews effectiveness and whether therapeutic objectives are being achieved; Step 5 reviews safety including presence or risk of ADRs; Step 6 reviews cost-effectiveness of therapy; and Step 7 reviews adherence and patient centeredness (Anon, n.d.). Another option is the Australian 10 step discontinuation guide (Scott et al., 2013).

A number of tools have been developed to aid clinicians in reviewing potentially inappropriate medicines and can provide structure for clinicians conducting comprehensive reviews of complex medication regimens (Hanlon and Schmader, 2013). The NO TEARS tool was developed to help primary care physicians conduct medication review (Lewis, 2004), while the medication appropriateness index (Hanlon et al., 1992) can score individual medicines for appropriateness (Samsa et al., 1994). Several tools are specifically designed for reviewing potentially inappropriate medicines in older people. These include the Beers criteria (American Geriatrics Society, 2015), while the STOPP/START tool is an evidence-based screening tool of older people's prescription (STOPP) and screening tool to alert to right treatments (START) (O'Mahony et al., 2014). A further tool has been developed for reviewing potentially inappropriate medicines in frail older people, STOPPFrail (Lavan et al., 2017). IMPACT (Improving Medicines and Polypharmacy Appropriateness Clinical Tool) is a tool developed by PrescQIPP, which identifies potential clinical and cost benefits of deprescribing with recommendations for appropriately continuing or discontinuing medicines (PrescQIPP NHS Programme, 2016).

Some tools are also available online and are represented in **Table 1**.

While a comprehensive review of adherence is beyond the scope of this article, a key component of a clinical medication review or deprescribing consultation is to determine what medicines the person is actually taking, rather than what is prescribed and how they manage, or don't manage, their medicines. Consultation technique is important in terms of gaining the person's trust and elucidating information about medicine-taking behaviors but also the person's beliefs, values, and how they can incorporate medicine taking into their daily life.

Various consultation techniques can be used. A coaching approach has been advocated as being beneficial for improving adherence. This incorporates the four Es which are as follows:

Explore the person's knowledge, perceptions, and lifestyle goals
Educate by giving the patient the information they want, rather than what the health-care professional wants to tell them, cover the main points for patient safety, and check the person's understanding.
Empower the person by helping them decide whether they want to take the medicine or not and help them own any decision to take medicines, rather than being told what to do.
Enable the person to work out how they will incorporate medicines into their lives and how they will monitor their adherence and the medicine's effectiveness (Barnett et al., 2013).

Care Home Considerations

Care home or long-term care facility residents need special consideration. The number of care home residents living with severe frailty and multimorbidity including mental health problems has risen over recent years. Care home residents are supported by a multidisciplinary team of people who try to ensure that the resident lives well by maintaining health and quality of life, ages well by managing long-term conditions and that they can die well by ensuring a good quality end of life (National Institute for Health Research, 2017). The World Health Organization (WHO, 2003) recommends that regulatory standards should establish the minimum standards for long-term care facilities including aspects such as the level and qualifications of staff, minimum staffing levels, skill-mix, procedural standards, and infrastructure specifications. Some countries may also wish to regulate the rights of people to long-term care and enforce compliance with standards (WHO, 2003). Residents in care homes should be encouraged to

be involved in decisions about their care and treatment if they choose to, so that the health and life outcomes that the person actually wants are prioritized, using person-centered care (National Institute for Health Research, 2017; Payne and Duerden, 2015; Royal Pharmaceutical Society, 2016). Formal capacity assessments should be used to determine whether patients can make decisions for themselves. Residents with reduced mental capacity should be able to make decisions about the aspects of their care and lives for which they have capacity (National Institute for Health and Care Excellence, 2014). For example, a patient may be able to decide whether they need acetaminophen (paracetamol) or not for pain relief but may not be able to make a decision about long-term anticoagulation. This applies equally to patients with cognitive impairment living in domiciliary settings. Where residents have capacity, they should be asked about whether they want family or supporter peers to be involved in decisions about their care. Where residents lack capacity, the assessment and findings should be formally documented. How often capacity is assessed should depend on the cause, as in some circumstances, lack of capacity fluctuates or is temporary (National Institute for Health and Care Excellence, 2014). Laws around consent and capacity will differ between countries but health-care practitioners must ensure that they adhere to legal frameworks, best practice guidance, and put the best interests of the person without capacity first.

Partners, relatives, or supporter peers of care home residents often support the resident to communicate with the multidisciplinary team in order to voice their individual needs, which is especially important where residents may not be able to voice this themselves, for example, in severe dementia (National Institute for Health Research, 2017; Payne and Duerden, 2015). Care home staff can also provide valuable information to inform decision-making regarding medicines (Payne and Duerden, 2015), for example, on symptom control.

Some residents in care homes will not be able to manage some, or all of their medicines, due to physical or mental illness (Payne and Duerden, 2015). However, care home residents should be able to self-medicate if they are able and wish to do so (National Institute for Health and Care Excellence, 2014; Royal Pharmaceutical Society, 2016), take the medicines how and when they want to, and take nonprescription medicines if needed (Royal Pharmaceutical Society, 2016).

Care home residents may be at greater risk of ADRs due to a combination of multimorbidity, polypharmacy, and frailty. As discussed earlier, the number of medication errors in care homes is high. Patient factors contributing to medication errors include cognitive issues and lack of awareness of medicines, physical difficulties such as arthritis or dysphagia, or practical issues such as staff finding the person when a dose is due to be administered. Other factors relate to processes for prescribing and administration in care homes. These include availability of electronic decision support aids, access to clinical records, availability of medicines, care home policies, procedures and guidelines, accuracy of medicine administration records, staff interruptions, and staff training (Payne and Duerden, 2015). Monitored dosage systems (MDS) are often employed in care homes to speed up drug administration and reduce errors although the CHUMs study found no evidence that MDS reduced administration errors (Barber et al., 2009). Use of MDS also makes it difficult for staff to omit particular medicines (Payne and Duerden, 2015) that are not clinically appropriate on a given day, for example, diuretics in a patient who is dehydrated.

Approximately 80% of people in care homes have regular pain, which reduces quality of life, limits mobility, and can cause behavioral problems, especially in people with dementia (National Institute for Health Research, 2017). While, a review of the treatment of pain is beyond the scope of this chapter, it is important that any review of medicines for a resident of a care home explores pain symptoms and treatment.

While a review of falls and medicines that cause falls is beyond the scope of this chapter, pharmacists should be involving in assessing falls risk from medicines in care home residents (Royal Pharmaceutical Society, 2016). This is also applicable to people in domiciliary settings who are at high risk of falls and/or who are taking a number of medicines that could contribute to falls.

Studies have shown that antipsychotics are more commonly prescribed for those in care homes than those living in domiciliary settings. Pharmacists should play a key role in the multidisciplinary team to ensure oversight of antipsychotics in care homes and to keep prescribing of these agents to a minimum (Royal Pharmaceutical Society, 2016).

Many residents of care homes will end their lives there so pharmacists can give advice about, and access to, end-of-life, and anticipatory care medicines. Pharmacists can also be valuable assets to care home providers in reducing medicines waste, especially if they are given responsibility for the use of medicines in individual care homes. This can be achieved through regular medication review but also by training care homes staff and working in an integrated way with the multidisciplinary team (Royal Pharmaceutical Society, 2016).

Dysphagia

Dysphagia is a swallowing disorder, which is caused by neurological or physical impairment of oral, pharyngeal, or esophageal mechanisms (Barnett and Parmar, 2016). It is usually caused by another condition such as stroke, head injury, or progressive neurological diseases such as Parkinson's (Barnett and Parmar, 2016; PresQIPP NHS Programme, 2015). Dysphagia can also be drug induced. This can be due to ADRs, for example, anticholinergics affect smooth muscle function of the esophagus; some drugs cause xerostomia (dry mouth), which impairs food transport, for example, lisinopril, antihistamines and antidepressants, and antipsychotics can cause extrapyramidal side effects and tardive dyskinesia causing dysphagia. Medicines that reduce alertness can also cause dysphagia, for example, opioids (Balzer, 2000).

Up to two-thirds of stroke patients, two-thirds of people with dementia and a quarter of people with COPD will have dysphagia (Barnett and Parmar P, 2016). Dysphagia can cause dehydration and malnutrition and is associated with increased length of hospital

stay, increased need for long-term residential care, and an increase in health-care costs (Smithard et al., 1996). Dysphagia is also associated with aspiration pneumonia, which is caused by the inhalation of foreign matter such as food and fluids (Barnett and Parmar P, 2016). Patients with dysphagia should have food administered in a form that can be swallowed without aspiration following specialist assessment of swallowing such as provided by a speech and language therapist (SLT) (National Institute for Health and Care Excellence, 2008). Food and fluid intake should be monitored and if indicated, a referral made to a dietician (Scottish Intercollegiate Guidelines Network, 2010). Patients with dysphagia may be unable to take some solid oral formulations of medicines. Formulation should be based on recommendations from a SLT. Pharmacists need to understand appropriate fluid consistency and food texture to advise patients on the safest and most effective form of administration of medicines, to reduce the risk of aspiration pneumonia and choking. It should be noted that some patients with dysphagia can swallow solid dosage forms and that liquids are not necessarily better for these patients. Some thinner liquids can increase the risk of coughing and aspiration in some patients and a thicker liquid or medication mixed with more textured food might be preferable (Barnett and Parmar, 2016). Thickeners are used to thicken both liquids and food to various consistencies to aid swallowing in dysphagia. Thickeners help to slow down transit to allow the person with dysphagia more time to coordinate the swallowing process safely and should be recommended by SLTs. Different brands of thickeners are available, some are starch based and others contain gums. Increasing the viscosity by thickening foods and liquids could theoretically reduce the dissolution, disintegration, and bioavailability of medicines (PresQIPP NHS Programme, 2015). The electrical charge associated with some gum thickeners may also reduce drug dissolution so drug thickener interactions may be reduced by using starch-based products although these are often less stable and palatable (Barnett and Parmar, 2016; PresQIPP NHS Programme, 2015). However, further studies are needed to assess the true effect of thickeners on medicines (PresQIPP NHS Programme, 2015).

Where possible tablets and capsules should be administered whole with the appropriate fluid consistency or food texture. Smaller tablets (<4 mm) can sometimes be safely swallowed whole if mixed with a food of a suitable consistency, for example, a puree. If a patient can't swallow tablets or capsules, a liquid can be used but only if it is thickened to the right consistency. If no suitable liquid is available, pharmacists will need to investigate whether crushing tablets or opening capsules is appropriate for administration with appropriate food or fluids (Barnett and Parmar, 2016). Specialist resources are available to determine whether crushing tablets or opening capsules is feasible (Smith, 2015; White and Bradnam, 2015). The administration of crushed tablets and the contents of opened capsules exposes the patient to the unpleasant taste, potential unpalatability and reduced adherence, and potentially reduced efficacy of the medication, as well as having legal implications for professionals who administer medicines off-label (Barnett and Parmar, 2016). When licensed medicines are used, if a patient is harmed, liability rests with the manufacturer. When medicines are crushed or capsules opened, this renders them unlicensed and greater liability for any patient harm falls on the prescriber, dispenser, and person administering the unlicensed medicine. The prescriber should always be involved in any decision to supply or administer medicines outside of their product license (Wright and Tomlin, 2011; Wright et al., 2015). Some tablets should not be crushed including modified release preparations that will cause dose dumping; enteric-coated medicines that may not then deliver the medicine to an area of the gut from which it can be absorbed and hormonal, cytotoxic, and steroid medicines should not be crushed as they may be dispersed into the air and the person administering the medicine can be exposed to their harmful effects (Wright et al., 2015).

When reviewing or prescribing medicines for patients with dysphagia, the following issues should be assessed:

- Review whether the medicine is still needed (Barnett and Parmar, 2016; UK Medicines Information, 2016)
- Observe medication taking as technique may be at fault and education may rectify the problem (Wright and Tomlin, 2011)
- Check if the tablet/capsule can be swallowed whole with pureed food or yoghurt. If it can, check for drug–food interactions, for example, levothyroxine. Remember to also check SLT recommendations on diet and fluid consistency (Barnett and Parmar, 2016).
- Check if the tablet or capsule can be crushed or opened and administered with thickened fluid, pureed food, or yoghurt (Barnett and Parmar, 2016)
- Check if the tablet or capsule can be swallowed whole when mixed with appropriate consistency food or fluid? Check what size of tablet/capsule the person can comfortably swallow (Barnett and Parmar, 2016).
- Are other routes suitable, for example, transdermal, sublingual, buccal? (Wright et al., 2015)
- Are other licensed formulations available? (UK Medicines Information, 2016)
- If a feeding tube is used to administer medicines, check if there are any interactions with food (UK Medicines Information, 2016)
- Does the person administering the medicine, if it is not the patient themselves, know how to prepare, and administer the medicine?
- If the person with dysphagia is moving care settings, ensure that all the information on their swallow and administration of medicines is communicated (Barnett and Parmar, 2016).

Role of Pharmacist in Health-Care Team Current and Future Trends in Pharmacotherapy and Management

Primary/Community Care

There is good evidence that pharmacists working in community settings can reduce the risk of drug-related problems, improve appropriateness of prescribing, reduce polypharmacy, and reduce drug costs by conducting medication reviews. Patient satisfaction

also improved after community pharmacy medication reviews, but there is mixed evidence on whether this has any impact on hospital admission and no evidence on mortality or other clinical benefits. Medication review may also improve transition of care between providers (Centre for Policy on Ageing, 2014).

Medication reviews in primary care have been studied in a randomized controlled trial in Sweden. Patients 75 years or more who were taking at least 10 medicines and using at least 3 psychotropic's received a pharmacist-led medication review. This included patients in both care homes and domiciliary settings. Two months after the reviews, the number of intervention group patients with at least one potentially inappropriate medicine and the number of patients using ten or more medicines had decreased significantly. There was no significant change for patients in the control group. No changes were seen in the number of patients using three or more psychotropic medicines although dosages of these tended to decrease (Milos et al., 2013). Another Swedish study evaluated structured medication reviews for patients living in nursing homes or patients 65 years and over who were living at home with medication-related community help. This study focused on the clinical significance of recommendations made by clinical pharmacists and ranked these from 1 (adverse significance) to 6 (extremely significant). About 96% of recommendations made by pharmacists in this study were judged to have a significance of 3 of higher and more than half were judged to have a significance of 4 or more. The authors suggest that structured clinical medication review in this population increases prescribing quality and has the potential to contribute to better and safer drug therapy for elderly patients (Modig et al., 2015).

A further study was conducted at two general practice clinics in Australia. Participants were patients who had risk factors for medication-related problems (MRPs), for example, polypharmacy. Patients received a consultation with the pharmacist who reviewed the patient's medication regimen, adherence, and provided education. The median number of MRPs per patient identified by the practice pharmacist was 2. This fell to 0, 6 months after the review, and patients were highly satisfied with the pharmacist consultations. The number of patients who were adherent to their medicines also improved significantly. There was no significant effect on health service use (Tan et al., 2014).

An Australian randomized controlled effectiveness trial evaluated medication reviews in the community. The intervention involved GP education, home visits, pharmacist medication review, primary team conferences, GP implementation of action plans, and consultation with patients and follow-up surgery visits for monitoring. A total of 54.4% of clinical medication review recommendations were enacted, and 23.9% of these were implemented precisely as recommended. About 70.9% had a positive outcome with 15.7% having no effect and 3.7% a negative outcome. The most common problems identified were potential ADRs, suboptimal monitoring, and adherence issues. There were positive trends in clinical outcomes (reduction in adverse drug events and severity of illness) and a trend toward reduced health-care service costs. Subsequently, a domiciliary medication review program was implemented as a national Australian practice where GPs and pharmacists were reimbursed by the Australian government for such services (Sorensen et al., 2004).

In Switzerland, a controlled trial evaluated the Polymedication Check (PMC) in community pharmacies. A significant number of drug-related problems were identified. There was no significant increase in objective adherence perhaps due to the high baseline objective adherence of 87.5% in the study, but subjective adherence was improved by approximately 5% (Messerli et al., 2016).

Clinical pharmacist input into an internal medicine practice has also been evaluated and primary care physicians (PCRs) were studied in terms of their proactive input into medicines optimization as a result of the pharmacist recommendations. This showed that compared to patients who received no pharmacist input, patients of PCRs who received clinical pharmacist recommendations were more likely to have several medicines-related issues addressed including medication nonadherence, untreated indications, suboptimal medication choices, and cost-ineffective drug therapies. However, total medical (excluding Pharmacy) costs for the intervention and comparison groups were not significantly different (Altavela et al., 2008).

Structured pharmaceutical care delivered by community pharmacists, according to a protocol, for patients who were discharged on five or more medicines was studied in Amsterdam. This structured pharmaceutical care resulted in more changes in drug therapy. Home visits cleared redundant home drug supplies and patients were highly satisfied with the counseling at discharge from hospital by their community pharmacist (Hugtenburg et al., 2009).

Secondary Care

A retrospective study of pharmacist interventions was conducted on two older people's wards in Germany to evaluate the clinical significance of medication errors detected. The majority of interventions carried out at admission and discharge were due to an omission of medicines and clinically significant interactions requiring monitoring. About 68.1% interventions were considered significant, 7.2% were clinically serious, and 24.8% were of minor significance. The authors state that the study shows the importance of clinical pharmacist involvement in the optimization of pharmacotherapy in older adults (Cortejosos et al., 2016).

Patients from five internal medicine and two rheumatology departments in Norway were included in a perspective study where clinical pharmacists assessed drug-related problems (DRPs) by reviewing medical records and participating in multidisciplinary team discussions. A quality team assessed the clinical significance of the DRPs. A proportion of patients were randomly selected for interview with pharmacists. Significantly more DRPs were identified among the patients who were interviewed compared to those patients having only usual care examination. A high proportion of the DRPs identified in the interviews were of major clinical

significance. The authors concluded that clinical pharmacists seem to fill a gap ensuring that significant DRPs do not escape detection (Viktil et al., 2006).

A further study in a university hospital in Ireland calculated the cost–benefit of pharmacist interventions made over a 1 year period. The study evaluated the cost benefit of pharmacist interventions as 8.64:1 (Gallagher et al., 2014).

A study evaluated the impact of a specifically developed structured pharmacist review of medication (SPRM) intervention and computerized decision support systems (CDSS) intervention on the appropriateness of prescribing in older Irish hospital inpatients. The acceptance rate of recommendations was also examined. On admission, patients received a SPRM/CDSS intervention that screened DRPs. Any DRPs identified were then communicated to the medical team. Medical records were reviewed to identify the implementation of recommendations and appropriateness of prescribing. The authors concluded that DRPs are prevalent in older, Irish, hospitalized inpatients and the specially developed SPRM intervention supported by CDSS can improve the appropriateness and accuracy of medication regimens of older hospitalized inpatients (O'Sullivan et al., 2014).

A systematic review and metaanalysis of the appropriateness of prescribing in older patients concluded that multidisciplinary and patient care teams involving pharmacists may improve the appropriateness of prescribing in older, hospitalized patients. The overall calculated reduction in the MAI score per patient was 7.45 in the intervention group (pharmacist involvement) versus the control group (Walsh et al., 2016).

A further systematic review looked at 19 randomized controlled trials of pharmacist-led medication reviews in hospitals involving 4805 patients. Overall the rate of readmission and emergency department attendance did not differ between the intervention and control groups although drug-related readmissions had a lower relative risk in the group receiving a pharmacist-led clinical medication review (Renaudin et al., 2016).

Institutional Care

In three Norwegian nursing homes, pharmacists undertook medication review and joined the multidisciplinary team (MDT) meetings aiming to reduce DRPs. Each patient's drug regimen was systematically reviewed by a pharmacist according to the criteria of a Norwegian classification tool, and potential DRPs were identified and classified. On average, the pharmacists identified 5.1 DRPs per patient, 3.5 were acknowledged by physicians and nurses, of which 94% were followed up. Therefore, the MDT intervention was suitable to identify and resolve DRPs in nursing home settings. The authors recommend that systematic medication reviews and involvement in clinical teams should be implemented on a regular basis to achieve and maintain high-quality drug therapy (Halvorsen et al., 2010).

Six Portuguese nursing homes evaluated the need for pharmaceutical care in institutionalized, polymedicated elderly patients. Pharmacists identified DRPs and carried out a structured interview with each patient and consulted patient medical records to gather demographic data, information on health problems, and medications used. A total of 484 DRPs were found. The most common DRPs were nonallergic adverse drug events, drug treatments more costly than necessary, effect of drug treatment not optimal, and unnecessary drug treatment. The authors concluded that these results reinforce the need for implementation of pharmaceutical care services for institutionalized elderly patients to improve medicines efficacy and safety, better clinical outcomes, and cost reduction (Silva et al., 2015).

A study measured the impact of pharmacist-conducted clinical medication review with elderly residents in 65 UK care homes versus usual care. Recommendations were made to general practitioners for approval and implementation. Control patients received usual general practitioner care. The pharmacist reviewed 315 patients in 6 months. The mean number of drug changes per patient was 3.1 for the intervention and 2.4 for the control group. About 75.6% of pharmacist recommendations were accepted by the general practitioner; and 76.6% of accepted recommendations were implemented. There were respectively 0.8 and 1.3 falls per patient in the intervention versus the control group. Pharmacists made substantial changes to patients' medication regimens without change in drug costs. There was a reduction in the number of falls. There was no significant change in consultations, hospitalization, mortality, or mini-mental state examination scores (Zermansky et al., 2006).

A UK project implemented patient-centered, pharmacist clinical medication review in 20 care homes. A total of 422 reviews were completed, and 1346 pharmacist interventions were made. On average, 1.7 medicines were stopped per patient, and the authors calculated that for every £1 invested in the service, £2.28 was saved (The Health Foundation, 2014).

Cross-Sector/Transitions of Care

A study evaluated the effect of transition of care follow-up by a pharmacist. The pharmacist contacted patients over 65 years old by telephone after hospital discharge to perform medication reconciliation, review discharge instructions, and schedule a follow-up appointment. At this follow-up appointment, the pharmacist reviewed the patient's electronic medical record (EMR) and communicated recommendations to a physician. The current standard of care, which does not involve a pharmacist, at a similar local physician practice was used as a comparative group. The difference in 30-day readmission rates did not reach statistical significance, but there was a trending decrease in the percentage of patients readmitted in the intervention versus the control group. There was nearly a statistically significant decrease in readmission rates for those patients who interacted with the pharmacist face to face versus only over the telephone. The authors suggested that pharmacists have a potential role in decreasing 30-day readmissions (Tedesco et al., 2016).

A randomized controlled trial of a Medication Management Review (MMR) program was conducted in Jordon. This was a patient-focused, structured, and collaborative health-care service in a community setting to optimize patient understanding and quality use of medicines. Pharmacists based in an outpatient clinic identified treatment related problems (TRPs) during home visits. They assessed the type and frequency of TRPs and eventual effect of resolving TRPs identified by the pharmacist, and accepted by the physician, on the health status of participating patients. Therefore, home-based medication review for patients with chronic conditions can decrease TRPs and improve self-reported adherence (Basheti et al., 2016).

In the United Kingdom, a study was conducted on patients who were referred from the hospital to community pharmacists for follow-up. This included provision of the New Medicines Service (NMS) and postdischarge Medicines Use Reviews. The NMS is a service for patients started on new medicines for asthma, COPD, hypertension, Type 2 Diabetes Melllitus, or antiplatelets and anticoagulants where patients are followed up by their community pharmacist to support adherence. Patients who had a community pharmacy intervention postdischarge were found to have significantly reduced readmissions to hospital and a shorter length of stay if they were subsequently readmitted, compared to patients who were referred but who did not receive community pharmacy intervention (Nazar et al., 2016).

Person-centered pharmaceutical care bundles were evaluated in a UK hospital setting. The control group was a similar ward with usual clinical pharmacy care. The care bundles were designed for each medication type known to be correlated to admission and were used on socially isolated older people or those on high-risk medicines. Patients were given education and medicine support needs post discharge were assessed. Where patients were eligible for the New Medicine Service or medicines use review service from community pharmacy, they were referred on discharge. Where patients were not eligible, for example, housebound patients, the hospital team provided these services in the community. Length of stay did not differ between the intervention and control groups, but the 30-day readmission rate was reduced from 17% to 22% in the intervention versus the control group although the study was not powered to detect a reduction in readmissions (Blagburn et al., 2015).

In summary, clinical medication review by pharmacists in various settings seems to have positive benefits for people in terms of a reduction in MRPs, improved medication appropriateness, improved adherence, and reduced health-care system costs. Patient satisfaction with such services is high, but the evidence for an effect on other clinical outcomes such as mortality and readmissions isn't strong and further work is needed in this area. There is some evidence that face-to-face clinical medication review is more effective than remote reviews such as those performed over the telephone and some evidence that clinical medication review reduces falls.

While the lack of impact on some clinical outcomes is disappointing, there are multifactorial influences on outcomes such as mortality and readmissions, and therefore, often the link between positive changes to medicines and positive outcomes is difficult to prove. As discussed earlier, polypharmacy is associated with a number of harms. Therefore, this lack of impact on some outcomes shouldn't dissuade pharmacists from person-centered medicines optimization, which has other benefits and may well be shown to have a positive effect on a wider range of clinical outcomes in future trials.

Pharmacogenomic Testing

Pharmacogenomics (PGx) is the investigation of the effects of genetic differences (genome differences) on drug response. PGx aims to use genetic information to inform prescription decision-making and therefore make drug therapy safer and more effective (Rollinson et al., 2017) with better patient outcomes, for example, improvements in disease management, reduced ADRs, and improved quality of life (Elliott et al., 2017). PGx testing identifies genetic variants that influence drug response that can be used to select specific genotype-informed prescriptions. This is called precision, stratified, or personalized medicine. Some genetic variants can influence pharmacokinetics including drug-metabolizing enzymes such as the cytochrome P450 isoforms (CYPs). Genetic variants can also influence drug pharmacodynamic effects (Rollinson et al., 2017).

PGx tests are available that can test various CYPs, which could have clinical relevance in the selection and dosing of medicines metabolized by these CYPs. This has the potential to predict and reduce unnecessary ADRs and has been used in clinical trials in Psychiatry. A small study (Elliott et al., 2017) was conducted in home health management patients with polypharmacy who were over 50 years old in the United States. PGx testing of CYPs with guidance from a clinical decision support tool regarding reduced drug, gene, and interaction risk was used by pharmacists to make medication recommendations to doctors. Compared to usual care, the PGx-tested patients had reduced readmissions to hospital and emergency department visits at 60 days (Elliott et al., 2017).

PREPARE (**Pre**-emptive pharmacogenomic testing for **P**reventing **A**dverse Drug **Re**actions) is a clinical study initiated by the U-PGx (Ubiquitous Pharmacogenomics) consortium to implement and evaluate the impact of PGx testing on therapy outcomes in 7 European centers. The study started recruiting >8000 patients in 2017 and will analyze results in 2020. Patients will have the U-PGx test that tests for >40 clinically relevant PGx markers. For half the study patients, test results will be used to guide drug and dose selection for >40 drugs: the other half will have usual care and treatment (Ubiquitous Pharmacogenomics consortium, 2018).

In summary, PGx testing is in the early stages of development as a tool for people with long-term conditions to improve safer, more effective prescribing and may have a positive impact on patient outcomes such as readmission to hospital.

Glossary

Adherence is defined as the extent to which the patient's action matches the agreed recommendations from the prescriber
Aspiration pneumonia is an infection and inflammation of the lungs and bronchial tubes caused by the inhalation of foreign matter
Care Home is a long-term care facility and covers the provision of 24-h accommodation together with either nonnursing or nursing care
Care Home Staff includes registered nurses and social care practitioners working in a care home
Deprescribing is defined as the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes
Dysphagia is a swallowing disorder cause by neurological or physical impairment of the oral (mouth), pharyngeal (upper throat), and esophageal (lower throat) mechanisms
Frailty is a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves
Long-term conditions are conditions for which there is currently no cure, and which are managed with drugs and other treatment, for example: diabetes, chronic obstructive pulmonary disease, arthritis, and hypertension. LTCs also include defined mental health conditions such as schizophrenia, ongoing conditions such as learning disabilities, symptom complexes such as frailty or chronic pain, sensory impairment such as sight or hearing loss, and alcohol and substance misuse
Medicines Optimization is a process that allows patients to gain the most net benefit from taking medication where medicines are prescribed taking the patient's preferences and characteristics into account
Medication Review is defined as a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems, and reducing waste.
Mental capacity is defined as having sufficient understanding and memory to comprehend in a general way the situation in which one finds oneself and the nature, purpose, and consequence of any act or transaction into which one proposes to enter.
Monitored dosage systems are medication storage devices designed to simplify the administration of solid oral dose medication usually with a separate compartment for each dosage time of the day
Morbidity refers to having a disease or a symptom of disease or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment.
Multimorbidity is the presence of two or more long-term conditions
Pharmacogenomics is the investigation of the effects of genetic differences (genome differences) on drug response.
Polypharmacy is where an individual takes multiple medicines
Appropriate polypharmacy has been defined as the prescribing for an individual for complex conditions or multiple conditions in circumstances where medicines use has been optimized and where the medicines are prescribed according to best practice.
Problematic polypharmacy has been defined as the prescribing of multiple medications inappropriately or where the intended benefit of the medication is not realized

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Websites

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British Geriatrics Society www.bgs.org.uk for information on comprehensive geriatric assessment and medication review process
Deprescribing website www.deprescribing.org for deprescribing resources
Specialist Pharmacy Services (National Health Service in England) website on olypharmacy www.sps.nhs.uk for resources to support pharmacy staff delivering polypharmacy and deprescribing service
National Institute for Health and Care Excellence website www.nice.org.uk for guidance on multimorbidy and managing medicines in care homes
Scottish Government website http://www.polypharmacy.scot.nhs.uk/ for resources on polypharmacy

Prescribing Insulin for People With Diabetes in Secondary Care: Recommendations and Future Direction

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Introduction

Diabetes is a chronic, incurable endocrine condition that is an important cause of mortality, morbidity, and associated healthcare costs worldwide (Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014). The global prevalence of diabetes is increasing; the latest International Diabetes Federation (IDF) estimates suggest that there were 425 million people with diabetes in 2017, which is set to rise to 629 million by 2045 (International Diabetes Federation, 2017). Although the majority of this increase involves people with type 2 diabetes, the number of people being diagnosed with type 1 diabetes is also increasing. Studies have shown that people with diabetes are more likely to be admitted to hospital, on a more frequent basis, and have longer lengths of stay than people without diabetes (Sajjad et al., 2018; De Berardis et al., 2012; Aro et al., 1994; Comino et al., 2015). Given the increase in incidence of diabetes globally, the increase in demand for secondary care services is likely to be sustained.

As the incidence of diabetes increases, so does the number of people with diabetes requiring insulin, with around 150-200 million people using insulin worldwide (Garg et al., 2018; Holden et al., 2014). Insulin is required by all people with type 1 diabetes, but also forms an important part of the management of people with other types of diabetes. It is understood that in type 2 diabetes, insulin secretory capacity decreases over time, therefore many people with this diagnosis may eventually require insulin (Home et al., 2014). Although insulin is vitally important, it is also associated with a significant risk of adverse effects such as hypoglycemia. Furthermore, insulin can be complex to prescribe and administer; as such, there is considerable scope for potentially serious medication errors to occur with its use.

The first section of this chapter includes a brief overview of medication errors involving insulin in hospital, focusing on prescribing errors. Approaches and interventions to help improve insulin safety is outlined and reviewed, and a variety of current recommendations for prescribing insulin in hospitals is summarized. Finally, a short series of case studies from a large teaching hospital in the United Kingdom is presented to illustrate how insulin prescribing safety may be investigated and improved by pharmacy teams at a local level.

Risks Associated With Insulin Use

Insulin is undoubtedly a life-saving medication of paramount importance, particularly to people with type 1 diabetes. It is, however, also classified as a high-alert medication by the Institute for Safe Medication Practices (ISMP) (Institute of Safe Medication Practitices, 2011). High-alert medications confer a heightened risk of causing significant harm when used inappropriately, and require particular safeguards to minimize the risk associated with their use. As insulin facilitates glucose movement from the bloodstream into cells, patients receiving excessive insulin may experience low blood glucose levels (hypoglycemia). Hypoglycemia can result in impairment of cognitive function, seizures, hemiparesis, and even coma. Inpatient mortality rates

and length of hospital stay for people using insulin, experiencing hypoglycemia, are also higher compared with those who do not use insulin (Turchin et al., 2009; Akirov et al., 2017).

Hyperglycemia can also occur when insulin is under-utilized, or when the dose prescribed and administered is not sufficient to control increased blood glucose levels. Hyperglycemia, if untreated, may result in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) for people with type 1 and type 2 diabetes, respectively. These conditions can cause serious harm to patients, and may be fatal if not managed appropriately. People experiencing DKA or HHS face longer hospital stay, require more intensive nursing and monitoring, and potential progression to intensive care (Joint British Diabetes Societies Inpatient Care Group, 2012; Sinclair-Hammersley et al., 2010).

Unfortunately, these adverse effects of insulin therapy are not uncommon, and are often associated with suboptimal or erroneous insulin prescribing and administration in hospitals. In the United Kingdom, an estimated 9600 people required rescue treatment after falling into a coma following a severe hypoglycemic attack, in 2017. During the same year, 2200 people (1 in 25 people with type 1 diabetes) suffered from DKA due to under treatment with insulin (NaDIA HQIP, 2018). There are various types of medication errors involving insulin, and there are many possible causes for these errors. More importantly, all insulin errors have the potential to put patients at serious risk of harm, and should therefore be investigated and mitigated in order to improve patient safety (Cousins et al., 2011; Hellman, 2004).

The impetus to improve the safety of insulin prescribing and administration is currently of great significance to align with the World Health Organization third global patient safety challenge 'Medication without harm', which aims to reduce avoidable medication harm by 50% over 5 years and includes a focus on high risk situations, polypharmacy, and transitions of care, all of which are pertinent to insulin prescribing.

Medication Errors Involving Insulin

Insulin errors have been reported at all stages of the medication use process, including prescribing, transcribing, dispensing, storing, administration, and monitoring. Most errors with insulin have been found to occur at the point of prescribing and administration (Cousins et al., 2011; Cobaugh et al., 2013). Pharmacists are able to help improve insulin safety processes at all of these stages, but here we will focus on the types and causes of insulin prescribing errors in particular.

Insulin Prescribing Errors

The term 'prescribing error' may be defined as "a failure in the prescribing process that leads to, or has the potential to lead to, harm to the patient" (Aronson, 2009). In general, prescribing errors commonly involve incorrect doses, illegible details, or inappropriate interacting medications. There is some debate as to what exactly might be categorized as a prescribing error, however, with some taking the view that errors of omission, or prescribing contrary to local or national guidance would not constitute a prescribing error (Dean et al., 2000). This is further reflected in the variety of definitions of 'prescribing error' in the literature reporting on incidence, causes, or solutions to prescribing errors (Tully et al., 2009).

As a result, some have taken the approach to differentiate 'prescribing faults' from 'prescription errors', where the first encompasses the whole process of writing a prescription (e.g., including clinical decision-making and monitoring processes), and the second relates solely to the act of writing a prescription (Velo and Minuz, 2009). As both 'prescribing faults' and 'prescription errors' can lead to potentially serious consequences with respect to insulin, we will consider them together as essential to tackle in order to improve patient safety.

Types of Insulin Prescribing Errors

Prescribing errors involving insulin may involve the name, frequency, device, concentration, or number of units of insulin doses being omitted, incorrect or unclear, insulin being prescribed at the wrong time of day (e.g., pre-mixed biphasic insulin being prescribed at night), insulin prescriptions not being signed, or insulin being omitted from the prescription altogether (e.g., on admission to hospital as a result of incomplete clerking).

The abbreviation of the word 'units' to 'u' is a well-reported cause of insulin errors, with nursing staff mistaking the 'u' for an extra '0' at the end of the dose, therefore administering a 10-fold overdose (National Patient Safety Agency, 2010). More recently, there is potential for insulin errors to occur where more than one concentration of a particular insulin product exists. If the correct brand and strength is not stipulated, patients may inadvertently receive the wrong dose. The consequence of this depends upon the particular product being prescribed, examples include the introduction of glargine 300 units/mL, which has a different release profile to its 100 units/mL counterpart, compared with lispro and degludec in which the profile is the same. Despite the manufacturers attempt to mitigate errors through use of defined dose pens, patients have inadvertently received the wrong dose due to the inappropriate use of insulin syringes with the pen devices, and consequently received excess or subtherapeutic doses (NHS Improvement, 2016).

Similarly, failure to stipulate the type of insulin device can be a cause of significant confusion, delay, and potential error, with patients receiving the wrong delivery system and in some circumstances, being unable to receive their insulin dose when needed.

Prescribing errors with insulin can occur with both electronic and non-electronic systems in hospital, especially as the functionality of electronic prescribing systems can vary considerably. Clearly, there will be merits to the use of electronic prescriptions for

insulin; for example, prescription clarity may be improved and incorporating standard insulin order sets can encourage more appropriate insulin prescribing. The particular need for variable insulin dosing depending on blood glucose result may, however, pose difficulties to integrate effectively into some electronic prescribing systems. New types of error have also been found to be introduced with electronic prescribing. These include issues like misinterpreting the insulin strength as the dose to be administered and 'picking errors' (where prescribers choose the wrong insulin product from a dropdown list) and the inappropriate continuation of short-acting correctional dose insulin on discharge prescriptions. In particular, insulin device errors have been shown to persist following electronic prescribing system implementation (Goble et al., 2010). The potential causes of insulin prescribing errors like these discussed hereunder.

Causes of Prescribing Errors

The causes of prescribing errors are multifactorial, involving organizational processes, task and environmental conditions as well as individual unsafe acts such as knowledge-based mistakes, violations, slips, and lapses (Tully et al., 2009). In a systematic review of the causes and factors associated with prescribing errors in hospital inpatients, Tully et al. found that active errors were often made as a result of knowledge deficiencies regarding the drug or the patient for whom they are being prescribed. With respect to insulin, this is perhaps particularly pertinent, as studies have shown a particular lack of knowledge and confidence in healthcare professionals with respect to insulin use (Lee et al., 2013; Derr et al., 2007).

These results are somewhat unsurprising as insulin can be particularly complex to prescribe. Many different types of insulin are currently available, and can be described in a number of ways by both healthcare professionals and patients (e.g., long-acting, short-acting, rapid-acting, pre-mixed, human, animal, analogue, basal, bolus, nutritional, correctional, mealtime, cloudy, clear). Insulin also has generic and brand names, which can further complicate its communication and prescribing. Prescribing "insulin glargine", for example would be insufficient to describe exactly the insulin required, with many different preparations potentially available. As such, without sufficient education, experience, and training, prescribers may not have the confidence or competence to prescribe insulin accurately, completely, and safely.

Other causes of error involve rule-based mistakes, whereby prescribers are unsure what rules to apply when prescribing for patients in certain circumstances (Aronson, 2009). With respect to insulin, the inappropriate omission of insulin for people with type 1 diabetes who are nil by mouth, or have a one-off episode of hypoglycemia has been found to be a cause of error in practice. Prescribers may also find prescribing insulin in the perioperative period challenging, including converting patients from intravenous insulin back to subcutaneous insulin.

Violations of rules or guidelines are another cause of prescribing error. This is particularly well reported in studies originating from America and Canada, where hospital prescribers continue to prescribe discouraged retroactive subcutaneous sliding scale insulin monotherapy instead of basal bolus correctional regimens (Newsom et al., 2018; Helmle et al., 2017). Similar errors are recognized in the United Kingdom with the use of variable rate intravenous insulin infusions (commonly referred to as sliding scale infusions) and includes the inappropriate duration of infusion, use of required concomitant basal insulin and safe step down to usual therapy (Joint British Diabetes Societies for Inpatient Care, 2014).

Even with a sufficient knowledge base, and the application of correct rules and guidelines for prescribing insulin, prescribers may make 'slips' or 'lapses' as a result of being busy, tired, or distracted whilst prescribing. These particular causes of prescribing errors are quite common, and may also result in clinically significant errors due to the complexity and high-risk nature of insulin.

On account of the range of insulin prescribing error types and causes, various strategies to reduce errors have been proposed. A number of these strategies will now be outlined, followed by a summary of recommendations for good practice.

Interventions to Improve Insulin Prescribing

Interventions to improve prescribing practice, in general, have been the subject of much study, and are often targeted according to different error types (Aronson, 2009; Velo and Minuz, 2009). A variety of interventions to improve the quality of prescribing insulin for inpatients with diabetes has been recommended by consensus expert panels, including the use of dedicated insulin prescription forms, electronic prescribing systems, insulin order sets, education, and readily available insulin prescribing guidance and protocols (Cobaugh et al., 2013; American Diabetes Association, 2019; Cornish, 2014).

In a recent search of the literature, 35 studies were found to have reported interventions to improve insulin prescribing practice in hospital inpatients, measured as adherence to guidelines, completeness, accuracy, or reduction in insulin prescribing errors (Bain et al., 2018). Most studies (n = 24) reported adherence to the American Diabetes Association (ADA) recommendations to use basal bolus correctional insulin instead of subcutaneous sliding scale insulin. The other 11 studies reported interventions to improve insulin prescribing completeness, accuracy, or reduction in insulin prescribing errors.

Interventions described in the literature include introducing structured diabetes and insulin education sessions (Taylor et al., 2012; Al-Yassin et al., 2013; Horton et al., 2015; Vaidya et al., 2012), dedicated insulin prescribing charts (McIver et al., 2009), electronic insulin order sets (Newsom et al., 2018; Helmle et al., 2017; Yeung et al., 2018; Achtmeyer et al., 2002; Donsa et al., 2016; Guerra et al., 2010; Maynard et al., 2009; Schnipper et al., 2009; Schnipper et al., 2010; Valgardson et al., 2015 Jul; Wexler et al., 2010), incorporating prescribing guidance (Rushmer and Voigt, 2008; Hamilton et al., 2013; Donihi et al., 2006), the introduction of a diabetes specialist nurse prescriber service (Courtenay et al., 2007), implementation of a 'high dose insulin validation guideline' (Dooley et al., 2011), a medicines reconciliation sticker (Tully et al., 2018), and the use of algorithms or electronic software to

calculate required total daily and bolus insulin doses (Donsa et al., 2016). The non-randomized nature of the majority of studies, as well as the lack of consistency with respect to definitions of insulin prescribing errors, study methodology, number of interventions, implementation strategies, and outcome measures made it difficult to compare the results between studies. Despite this, a number of interesting results were found.

For example, the introduction of simple, small focused interventions led to an improvement in the completeness and accuracy of insulin prescribing, particularly when they involved 'hard stops' (such as pre-printing 'units' on dedicated insulin prescription charts to avoid misinterpretation of 'u') (McIver et al., 2009; Rushmer and Voigt, 2008; Hamilton et al., 2013). A small-scale quality improvement project undertaken by Tully et al. used a continuous improvement methodology to design and implement a sticker to prompt accurate and complete prescribing of insulin on admission, resulting in an increase in insulin medicines reconciliation from 64% to 91% (Tully et al., 2018).

In contrast, Newsom et al. describe a large-scale whole-organizational transition to the use of an electronic glucose management system integrated with the hospital's electronic health record. As a result, the prescribing of insulin became simpler and more standardized, and the use of subcutaneous sliding scale insulin monotherapy dramatically reduced from 95% to 4% (Newsom et al., 2018).

Interestingly, the applications of educational interventions alone to improve insulin prescribing were not associated with overwhelmingly significant improvements (Al-Yassin et al., 2013; Horton et al., 2015; Vaidya et al., 2012; Taylor et al., 2012). This may be on account of the non-randomized, uncontrolled before-and-after study design (mostly involving junior doctors), or perhaps more likely, the need for a multi-modal interventional approach involving the whole healthcare team. Indeed, improvement strategies involving system changes that engage multiple stakeholders at various levels were more likely to be effective and sustainable, which is consistent with the principles of total quality management (Pereira and Aspinwall, 1997).

In addition to interventions that have been reported in the literature, a number of international expert bodies have suggested ways in which insulin prescribing safety may be improved in the hospital setting. These will be summarized in the next section, which may provide a useful reference for practitioners and healthcare providers.

Insulin Prescribing Recommendations

The 2019 ADA guidelines for diabetes care in the hospital recommend that physiological, proactive insulin regimens (i.e., basal, bolus/nutritional, correctional insulin) should be used to treat non-critically ill people with diabetes (American Diabetes Association, 2019). The retroactive use of subcutaneous 'sliding scale' insulin is strongly discouraged as it leads to poorer glycemic control, increased length of stay and associated costs (American Diabetes Association, 2019; Umpierrez et al., 2007, 2011). ADA guidelines also state that insulin prescriptions should state the type of diabetes from the point of admission, and should be administered using validated written or computerized protocols that allow dose titration according to blood glucose results. Structured electronic insulin order sets that pre-populate the insulin prescription based on a template are also recommended because they are associated with improved glycemic control (American Diabetes Association, 2019).

The ISMP and the American Society of Health-System Pharmacists (ASHP) have developed practical recommendations for prescribing subcutaneous insulin in hospitals, which are included in **Table 1** (Cobaugh et al., 2013; Institute for Safe Medication Practices, 2017; American Society of Health- System Pharmacists, 2006). In the United Kingdom, the National Institute for Health and Care Excellence (NICE) published a document called 'safer insulin prescribing' in 2017 (National Institute for Health and Care Excellence, 2017). This was followed by a report from the charity 'Diabetes UK' in 2018 (Watts and Rayman, 2018). Both contain recommendations for insulin prescribing, which are outlined in **Table 2**.

Despite these comprehensive recommendations, insulin prescribing errors remain a significant and clinically important problem in hospitals (Cornish, 2014). It is appreciated that due to the variety of complex risk factors and causes of insulin prescribing errors, a rigorous and mutli-pronged approach will be needed by institutions in order to successfully and sustainably improve prescribing safety. The next section illustrates how pharmacists from a large teaching hospital in England approached the evaluation and improvement of insulin prescribing practice at a local level.

Case Study from a Teaching Hospital in the United Kingdom

Prevalence and Types of Insulin Errors Locally

Sheffield Teaching Hospitals NHS Foundation Trust (STHFT) is one of the largest and busiest NHS hospital trusts in England, operating across five hospitals and 40 community sites. Over 2.3 million patients a year are seen at STHFT, 15% of whom have a diagnosis of diabetes. Insulin, consistently, features as one of the top medicines responsible for safety incidents reported at the trust, despite the introduction of e-learning modules, specialist diabetes and link nurses, insulin prescription, administration, monitoring, and guideline charts and foundation doctor training. The safe use of insulin in hospitals is of concern for patients at STHFT, with local diabetes patient public involvement groups expressing interest in being involved with insulin prescribing safety initiatives.

During 2015, the UK National Diabetes Inpatient Audit (NaDIA) revealed that 28.1% of patients prescribed insulin had at least one medication error involving their insulin in 2015 at the main acute hospital in STHFT, compared with 18.5% in 2013.

Table 1 International recommendations for safe insulin prescribing from the ISMP and AHSP

Institute for Safe Medication Practices (2017)	*American Society of Health System Pharmacists (2006, 2013)*
The indication for insulin use is clearly documented in the health record and is readily accessible and visible to all clinicians during insulin order entry, verification, and administration.	Insulin prescriptions should include: • At least two patient identifiers • Indication for insulin and appropriate terminology for type of insulin used (e.g., basal, prandial) • Target blood glucose range • Both generic (e.g., glargine) and brand name (e.g., Lantus) • Dose(s) for each insulin type • Specific time of administration, either clock hour or as time prior to or with food or meals • Blood glucose monitoring regimen specified by time of day and/or as time prior to food or meals • Specific insulin dose regimen adjustment based on dietary intake and/or BG results. • Route of administration • Orders for management of Hypoglycemia • Description of the role of the patient in management of insulin therapy • Patient-specific issues and care needs
Organizations develop and utilize evidence-based insulin protocols and/or evidence-based insulin order sets with decision support capabilities, when appropriate. These should cover situations that involve, for example, transitions from intravenous to subcutaneous insulin, calculations and communication of basal, nutritional and correctional insulin doses, insulin prescribing with respect to nutritional intake, concentrated insulin, concomitant glucocorticoid use, pregnancy, hypoglycemia and post-discharge insulin management	Develop protocol-driven and evidence-based order sets for specific uses of insulin such as transition of administration route from intravenous to subcutaneous, administration via subcutaneous insulin pumps, post-discharge dosing, diabetic ketoacidosis, hyperosmolar states, hyperkalemia, and post-cardiac surgery care. Order sets should include orders for glucose monitoring and decision-support tools to guide insulin use, including the management of hypoglycemia.
Organizational policies are in place to guide the care of patients with a personal subcutaneous insulin pump.	Verbal and telephone orders for insulin should be minimized and used only when necessary in urgent medical situations.
The prescriber identifies the target glucose range in the patient's health record.	All patients receiving insulin should have their blood glucose monitored at appropriate times and evaluated at least daily.
Eliminate the use of sliding scale insulin doses based on blood glucose values as the only strategy for managing hyperglycemia.	Eliminate the routine prescription of correction/sliding scale insulin monotherapy.
Insulin orders are free of error-prone abbreviations and dose expressions.	The word "units" must be written in full. Leading zeroes should be used before all decimal points when insulin is ordered. No "trailing" zeroes should be used following decimal points. No "prohibited" abbreviations as determined by the organization should be used. Eliminate the use of "free text" insulin orders in electronic and paper medical records.
Strategies such as tall man lettering with bolded text for the unique letter characters are used to help distinguish look-alike insulin names (e.g., HumaLOG and HumuLIN)	When used, electronic prescribing systems include appropriate alerts to reduce risk of error in insulin prescribing and should prompt use of organization-specific protocols and orders for blood glucose monitoring.
Communicate all patient-specific information related to diabetes care in one designated place in the health record.	Approved insulin protocols should not require or should minimize the use of calculation.
An endocrinologist or practitioner trained in insulin management is consulted for patients with hospital-defined uncontrolled hyperglycemia or hypoglycemia.	

Source: Adapted from American Society of Health System Pharmacists (2006); Cobaugh et al. (2013); Institute for Safe Medication Practices (2017).

In order to improve insulin safety at the trust, further investigation into the nature and prevalence of errors was required. A retrospective review of incidents reported to the trust on existing patient safety software (DATIX) was undertaken to identify and review insulin-related errors over the past 24 months. Results revealed that 160 medication errors were reported relating to insulin use in inpatients, which varied considerably with respect to severity and type. Prescription and administration errors were most commonly reported, as well as errors related to the use of IV insulin, and errors as a result of unclear discharge letters (which, at STHFT, incorporate prescriptions).Considering the limitations of data retrieved from the trust's incident reporting software (the reports are highly configurable, and there is a high-rate of under-reporting for prescribing errors), a prospective cross-sectional audit was undertaken to gain a snapshot of the problem. All inpatients prescribed insulin at the trust were identified during the NaDIA data collection. A single pharmacist then reviewed their medical notes to identify and document any insulin errors that had occurred during their admission. Insulin errors were then quantified and thematically analyzed to determine the nature and prevalence of insulin medication errors. Errors were categorized as either prescription errors, administration errors, errors involving

Table 2 Recommendations for safe insulin prescribing in the United Kingdom from NICE and Diabetes UK

National Institute of Health and Care Excellence (2017)	*Diabetes UK (2018)*
Ensure that people with diabetes who are receiving insulin therapy are given information about awareness and management of hypoglycemia.	All patients with a diagnosis of diabetes should be supported to self-manage their diabetes, wherever appropriate. Hospitals should have systems and training in place to supports this.
Be aware of 'sick-day' rules and ensure that people with diabetes who are receiving insulin therapy are given appropriate information about these.	Basic training on the safe use of insulin and the main diabetes harms and how they can be prevented should be mandatory for all healthcare professionals, caring for people with diabetes.
Several new insulin products have been launched recently, including high-strength, fixed combination and biosimilar insulins. Be aware of the differences between these products and ensure that people receive appropriate training on their correct use.	Effective electronic prescribing system for detecting, recording, and avoiding insulin errors should be used across hospitals.
Give adults who are using insulin therapy a patient information booklet and an "Insulin Passport" *(a booklet in which patients and healthcare providers can document contemporaneous information about the currently used insulin regimen).*	Hospitals should agree on local key indicators, such as insulin errors, to audit and to have methods in place that ensure data collection is robust and the data is subjected to rigorous analysis.

Source: Adapted from National Institute for Health and Care Excellence (2017); NaDIA HQIP (2018).

IV insulin or insulin monitoring errors. Relationships were found between errors and clinical areas, as well as administration status and diabetes team involvement.

As a result of data analysis, it was found that most prescribing errors involved the number of insulin units and device. We also found that surgical and admission wards had a greater volume of patients with diabetes and a greater number of insulin errors. Patients who self-administrated their insulin seemed to encounter fewer errors than with patients whose insulin was administered by nursing staff.

The introduction of electronic prescribing at the Trust, which included the prescribing of subcutaneous insulin, was anticipated to influence the number and types of errors, however a retrospective thematic analysis of the error reporting system did not support this. The error themes aligned with those of pre-electronic prescribing implementation. Cases where electronic prescribing could have impacted in the error were identified as combined use of the electronic and paper system. Unintended 'when required' (PRN) doses, and lack of cross referencing of other charts including monitoring and intravenous insulin prescriptions.

Undertaking these baseline audits allowed us to identify specific problem areas that could be targeted for further examination and improvement. These areas included the prescribing of insulin at the point of care transfer (hospital admission and discharge) and the promotion of patient self-administration of insulin.

Insulin Prescribing on Admission

Previous studies have shown that medication errors in hospitals are most common at the time of admission to hospital, pharmacists can help improve insulin prescribing on admission by undertaking medicines reconciliation (Dornan et al., 2010; Breuker et al., 2017a; Breuker et al., 2017b). Following results of the aforementioned local audits, we aim to establish the nature and prevalence of insulin prescribing errors, information discrepancies, and pharmacy interventions at the time of hospital admission at STHFT. We sought to assess the timeliness of medicines reconciliation for patients with insulin-treated diabetes, identify and characterize insulin prescribing errors and pharmacy interventions documented on admission, and investigate discrepancies between insulin information recorded by doctors on clerking documentation and pharmacy medicines reconciliation charts.

Pharmacists visited 3 medicines admissions and surgical wards on 4 non-consecutive weekdays each week for 3 weeks during January 2017 to identify recently admitted patients with insulin-treated diabetes. Medical records and prescription charts were reviewed to identify insulin prescription errors, information discrepancies, and details of any pharmacy interventions.

We found that insulin prescribing errors and information discrepancies were common at the time of hospital admission. From a sample of 25 patients, 86% experienced at least one insulin prescription error or information discrepancy at the time of admission to hospital. A total of 69 insulin prescription errors or information discrepancies were identified. The 50 insulin prescription errors included insulin device (n = 26), dose (n = 11), time (n = 4), and frequency (n = 3), with 47 (94%) being rectified by pharmacy intervention. Information discrepancies involved the complete omission of insulin from the clerking drug history (n = 13) or insufficient information documented during clerking to prescribe insulin (n = 6). Medicines reconciliation was completed by pharmacy staff within 24 h of admission for 100% of the patients on admissions wards and for 86% of the patients on the surgical wards.

By undertaking medicines reconciliation, which includes all the necessary details for complete and accurate insulin prescriptions on admission, ward-based pharmacists at STHFT demonstrated the value of their service in improving quality and safety through identifying and rectifying potentially harmful insulin errors and information discrepancies. The introduction of an insulin summary card that encompasses pertinent clinical details for the commonly used insulin products,

including type of insulin, dose timings and likely regimens, was utilized to support the clinical review aspect of the medicines reconciliation process.

Insulin Prescribing on Discharge

Medication errors at the point of discharge have previously been reported as 'common' (WHO Collaborating Centre for Patient Safety Solutions, 2007; Vira, 2006) and can include unintended omission of medication, continuation/re-prescribing of an intentionally stopped medication, or an error in medication dose, frequency or formulation (Callen et al., 2010; Herrero-Herrero et al., 2011; Riordan et al., 2016). Such errors have been found to persist post-discharge and may pose a greater risk to patient care than those identified on admission (Pippins et al., 2008). In response to local audit data that documented a number of patient safety incidents relating to insulin discharge prescriptions, we sought to investigate the nature and prevalence of insulin-related medication discrepancies documented in the hospital discharge summaries for patients with diabetes at STHFT. We also aimed to establish the timelines and completeness of relevant information regarding insulin therapy provided on discharge summaries.

We made use of the National Diabetes Inpatient Audit (NaDIA) to identify all inpatients at STHFT, who were prescribed insulin on one day in October 2016. We then undertook a retrospective analysis of their discharge summaries, auditing compliance to criteria for discharge prescriptions based on previous national guidance (Joint British Diabetes Societies for inpatient care, 2017; National Prescribing Centre, 2008).

A total of 42 patients were included, of which 33 (79%) had changes made to their insulin regimen during hospital admission. Eighteen (43%) patients were identified as having an error or discrepancy relating to insulin on their discharge summary. A total of 27 insulin errors or discrepancies were identified on discharge, most commonly involving non-communication of an insulin dose change ($n = 8$) and wrong insulin device ($n = 7$). Seventeen issues relating to completeness of insulin information were identified, including the particular time of insulin dose ($n = 10$) and unexplained insulin dose change ($n = 4$). Although not proof of causation, we found that 2 patients who had insulin-related errors identified on their discharge summaries, were readmitted to the hospital within 30 days of discharge, and this was due to poor diabetic control.

Following discussion of these results with the multidisciplinary inpatient diabetes team, pharmacists sought to improve insulin prescribing on discharge using a continuous quality improvement approach involving cycles of iterative change. Locally-tailored insulin discharge prescribing guidance was formed by consensus with the multi-disciplinary project team. A diabetes ward that had experienced a number of insulin discharge prescription errors in recent months (identified by further review of the trust's incident reporting system) piloted the planned improvement project. Electronic discharge prescriptions involving insulin from the ward during Monday to Friday of each week were examined retrospectively, and their adherence to the guidance was measured and analyzed. After baseline measurement, three cycles of iterative change, involving input and feedback from multiple healthcare professionals in the ward, were undertaken over a three-week period to introduce the guidelines and improve the quality of discharge prescriptions.

After the introduction of the guidelines in the form of a poster, and later a nursing checklist, the adherence to guidelines rose from an average of 50% to 99%. Qualitative data suggested that although it took pharmacists slightly longer to clinically verify discharge prescriptions, the interventions comprised a simple, clear, and helpful reminder to help improve discharge quality for the benefit of patient safety. In conclusion, pharmacists were able to demonstrate that small, low-cost, iterative changes made by a multi-disciplinary team could result in substantial improvement in the quality of insulin discharge prescriptions.

Self-Administration with Insulin

Following the publication of the Joint British Diabetes Societies recommendations for the self-management of diabetes during hospital admission (Joint British Diabetes Societies for Inpatient Care Group, 2012), STHFT amended its policy to allow people to continue to self-administer their insulin in the hospital setting. However, experience indicated that barriers, including patient access to insulin for self-administration, still existed. Discussions with the local Diabetes UK group revealed that the main points of concern for people with diabetes being admitted to hospital were not having access to their insulin and doses being given at the wrong time. The pharmacist, therefore led a series of projects, including audits, incident reviews, and service user interviews in order to facilitate self-administration of insulin in the hospital setting.

The trust's patient safety software was reviewed specifically for insulin self-administration or misappropriation incidents. Results identified cases where the patient self-administered the correct dose of insulin despite a wrong prescription, and 20 incidents that could have been prevented if the patient had been self-administering. A baseline trust-wide cross-sectional audit was then undertaken to assess insulin storage and self-administration status at home and in the hospital. Results showed that 58% (41/71) patients self-administered at home, 30 of which continued to do so in hospital (4 were deemed not suitable to do so whilst in hospital). Although policy stipulated that patients did not have access to their insulin, 23 patients who were self-administering had insulin access. Further risk assessments and options appraisals were undertaken, and the trust policy was amended to allow patients to maintain possession of their own insulin and continue self-care whilst in hospital.

After the policy change, a pharmacist-led service assessing and documenting the suitability of self-administration for people with type 1 diabetes admitted to hospital was successfully implemented to further support patients to self-administer.

Following these projects, pharmacists at STHFT are seeking to deeply explore the barriers and facilitators to the safe insulin prescribing for inpatients by the use of qualitative methodological approaches such as focus groups discussions and patient interviews. In line with the ethos of continuous improvement at the trust, further improvements and interventions will be designed and developed in order to help make insulin prescribing safer for patients in hospital.

Conclusion

Insulin prescribing is a process that is of critical importance, but is prone to risks. Pharmacists have the opportunity to help improve insulin prescribing safety in hospitals by the use of continual audit, implementation of decision-support tools such as dedicated insulin prescribing charts and algorithms, utilization and optimization of electronic prescribing software, and the development of locally-tailored, evidence based guidance. By integrating into the wider diabetes team, pharmacists have the potential to offer cost-effective interventions to improve insulin prescribing and patient safety. By prioritizing issues that are important to patients, pharmacists can make a positive contribution to the overall care and experience of patients, who use insulin in the hospital setting.

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Pharmacotherapy and Deprescribing

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Background

Effective and safe use of medicines is essential for achieving positive health outcomes and minimizing harms to individuals while also managing appropriate allocation of health-care resources. On the individual level, appropriate use of medicines involves the prescription of medications where the benefits outweigh the harms. Other considerations in determining appropriateness include whether there is a better alternative (e.g., safer or less expensive) and alignment with patients' goals of care, preferences, and values (Garfinkel et al., 2015; Scott et al., 2015; Spinewine et al., 2007). Older adults, who are frequently exposed to polypharmacy, are at a greater risk of harm from medication use due to the potential for drug–disease and drug–drug interactions, reduced physiological reserve, and changes in pharmacokinetics and pharmacodynamics (Reeve et al., 2015c; Scott et al., 2015). These concepts are covered in greater detail in Section "Geriatrics."

Potential benefits and harms of medications can both change in an individual over time, which means that a medication that was once appropriate can become inappropriate. For example, likely benefit may reduce if the medication is continued longer than the recommended duration, if onset of new diseases intervenes, or if there are changes in care goals, while harm may increase due to the aging process or prescription of a new interacting agent (Reeve et al., 2014a).

Polypharmacy (use of multiple medications) and inappropriate medication use are common, especially among older adults. Approximately half of adults aged greater than 65 years are taking five or more regular medications, with as many as one out of every five of these medications being potentially inappropriate (Hubbard et al., 2015; Opondo et al., 2012; Spinewine et al., 2007). Polypharmacy and inappropriate medication use have been associated with a number of negative health outcomes in older adults including adverse drug events (ADEs), reduced quality of life, hospitalization, falls, and mortality (Muhlack et al., 2017; Olsson et al., 2011; Passarelli et al., 2005; Steinman, 2016; Wallace et al., 2017). Therefore, quality use of medicines involves both initiating and continuing medications that are appropriate and will lead to a benefit and withdrawal of medications that are inappropriate.

What is Deprescribing?

The term "deprescribing" (or "deprescribing") first appeared in the English health literature in 2003 in an article published in an Australian hospital pharmacist journal (Woodward, 2003). The article outlined the principles considered essential for deprescribing:

1. Reviewing all current medications,
2. Identifying medications to be ceased, substituted, or reduced,
3. Planning a deprescribing regimen in partnership with the patient and
4. Frequently reviewing and supporting the patient

A systematic review conducted in 2014 investigated the definition of deprescribing provided in English language articles (Reeve et al., 2015b). Based on the results of the review and clinical considerations, the authors of the systematic review proposed the following definition for deprescribing:

> "Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."

A manuscript by Scott and colleagues, which is the most highly cited manuscript using the term deprescribing, contains the following definition:

> "The systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences."(Scott et al., 2015)

While Thompson and Farrell provide the following definition (also highly cited):

> "Deprescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes."(Thompson and Farrell, 2013)

The components of these definitions and others are debated in the literature. First, there is not a consistent definition of "inappropriate medications," with some academics using the term only for high-risk medications. In the definitions above, it is used in the broad sense of any medication that is not appropriate in the individual at the time (i.e., where the potential harms outweigh the potential benefits in the individual or where use of the medication does not match care goals). Also, whether dose reduction can be categorized as deprescribing is contentious. The authors of the systematic review suggest dose reduction may be more appropriately considered as optimal prescribing rather than deprescribing, although mention that dose reduction may be an appropriate and beneficial outcome in many cases (Reeve et al., 2015b). Yet, it is included in other definitions of deprescribing.

It should be noted that this discussion is limited to the English language (as definition of a word is unique to the language in which it is used), although the concept crosses language boundaries. The term "deprescription" has been used in French literature as early as 2007 (Queneau et al., 2007). The concept of withdrawing medications that are no longer appropriate was around long before the term deprescribing became widespread. There are, however, several reasons why use of this term has increased and why it is beneficial for the end goal of improving care of older adults.

The first systematic review using the term deprescribing was conducted by Iyer and colleagues in 2008, who reviewed the outcomes of medication withdrawal trials in older adults (Iyer et al., 2008). However, they reported in their methods, "After a preliminary search using a number of different search strategies it was evident that there was no standard terminology for classifying clinical studies on cessation of drug therapy or medication withdrawal." As such they used a combination of different search strategies to inform their review. Alternative terms used in systematic reviews may cover broader concepts (such as rationalization or deescalation) or may be more simplistic (such as withdrawal, cessation, or discontinuation). This results in a large number of results to search through (time intensive) and may also mean that relevant articles are missed. This difficulty in identifying relevant research for synthesis and knowledge translation is one reason to advocate for use of the term deprescribing.

A consistent definition of deprescribing has both research and clinical applications. In research, determining the feasibility as well as the outcomes or success of deprescribing will depend on its definition and allow comparison of independently conducted studies. Where there is not yet international consensus (e.g., on dose reduction), it is important for pharmacists reading studies to be aware of what constituted deprescribing in that individual study. Clinically, the definition of deprescribing will have implications for guiding best practice and communications between health-care professionals (e.g., what does a recommendation of deprescribing from a pharmacist to a general practitioner mean?) As such, it is important that guidelines, training about deprescribing, and communication between health-care professionals are clear and descriptive in their messages. However, regarding the aim of improving patient care through optimization of medication use, the specific definition may be less important. In pursuit of optimizing therapy, deprescribing is part of good prescribing and the wider field of safe and appropriate medication use (Scott et al., 2015). However, there are a number of studies that support the need to discuss and conduct research with a focus on deprescribing. The high prevalence of inappropriate medication use shows that deprescribing is not occurring as often in practice as it should be (Opondo et al., 2012; Spinewine et al., 2007), the reasons for which are discussed below.

Overall, the core of definition is that deprescribing involves withdrawal of a medication to improve the risk:benefit ratio of medication use in an individual. It is a positive action done for the benefit of the patient and does not deny them potentially beneficial treatment. Generally, deprescribing is discussed as a patient-centered process that requires shared decision-making, informed consent, and monitoring throughout the process and after cessation. While there are inherent uncertainties of the benefits and risks of deprescribing in an individual, the same is true for initiating, or indeed continuing therapy.

Evidence of Outcomes of Deprescribing

The outcomes of deprescribing interventions can be assessed and categorized in various ways depending on the type of intervention and the outcome of interest.

- Indirect (or system level) deprescribing interventions are programmatic strategies aimed at populations of clinicians such as professional education programs, decision support tools, and prescribing policies.
- Generic direct interventions involve deprescribing on an individual patient level, but without the use of prespecified, structured, or explicit criteria, such as pharmacist-led medication reviews and comprehensive geriatric assessment.
- Structured direct (or patient level) interventions use explicit, systematic processes (such as using an algorithm or a structured deprescribing framework or guide) applied by individual clinicians to the medication regimens of individual patients. These can be medication class specific or directed to all medications.

Clearly, indirect and direct deprescribing can overlap and complement one another. Outcomes may be medication-centric, i.e., number of medications overall or of a specific class taken by either a broad population or specific patient groups; or patient-centric (including clinically relevant outcomes), i.e., drug-related burden, ADEs, hospitalizations, deaths, physical or mental impairment, costs, and inconvenience.

Effects of Indirect and Generic Direct Deprescribing Interventions

A number of systematic reviews have been conducted on indirect interventions and generic direct interventions. The studies have generally been of low to moderate quality, measuring medication- rather than patient-centric outcomes, of short duration, and have produced mixed results (Kaur et al., 2009). A review of 30 studies, 10 randomized, including pharmacist and physician-led reviews, multidisciplinary interventions, computer feedback, and educational interventions found significant reductions in number of medications in most controlled studies, although mixed results in randomized studies. Only 15 of the studies reported on clinical endpoints, of which only six reported benefits such as reduction in serious ADEs (Gnjidic et al., 2012). Similarly, more recent reviews (Cooper et al., 2015; Johansson et al., 2016) found interventions generally led to reduced use of potentially inappropriate medications (PIMs), although improvements in clinical end-points were not confirmed.

Reviews examining specific intervention types, patient populations, and settings have found similar results, generally concluding benefits to medication-centric outcomes (reduction of number of medications or PIMs) with scarce evidence on patient-centric outcomes. A review of 20 trials of pharmacist-led medication reviews, both inpatient and outpatient, saw the mean number of prescribed medications per patient reduced by 0.48, but with no effects on outcomes except for reduced hospitalizations in heart failure patients (Thomas et al., 2014). A review of 15 studies of academic detailing of family physicians saw a modest reduction in the number of inappropriate medications of certain classes (benzodiazepines and nonsteroidal anti-inflammatory drugs) (Chhina et al., 2013). In a recent systematic review of different interventions targeting frail older patients in various settings, 22 of 26 quantitative studies reported significant reductions of 3 to 20 percentage points in the proportions of medications deemed unnecessary (defined using various criteria) (Tjia et al., 2013). Another review of 8 randomized trials of various interventions involving nursing home patients showed more frequent identification and resolution of medication-related problems and improved medication appropriateness (Alldred et al., 2013). Individual studies do point toward clinically relevant outcomes. In two randomized trials conducted in aged care facilities that featured educational interventions aimed at either prescribers (García-Gollarte et al., 2014) or nursing staff (Pitkälä et al., 2014), the number of PIMs and days in hospital were significantly reduced, and declines in health-related quality of life were slower (García-Gollarte et al., 2014).

Effects of Structured Direct Deprescribing Targeting Specific Classes of Medications

The evidence base for structured, direct patient-level deprescribing is more rigorous as it often pertains to specific classes of medications. This allows recruitment of specific populations (such as those in whom the medication is inappropriate) and monitoring of clinical outcomes that are relevant to the medication of interest (such as known adverse drug reactions, for example, falls). A systematic review of 31 trials (15 randomized) that withdrew a single (targeted) class of medication in older people demonstrated that, with appropriate patient selection and education coupled with close monitoring during withdrawal, antihypertensive agents, psychotropic medications, and benzodiazepines could be discontinued without harm in 20%–100% of patients. However, psychotropics and to a lesser extent antihypertensives showed high posttrial rates of recommencement. Several of the studies indicated a benefit (such as a reduction in falls and improvement in daily function) from withdrawal of

psychotropics (Iyer et al., 2008). Another review of 9 randomized trials showed that antipsychotic agents used to control behavioral and psychological symptoms of dementia could be withdrawn in more than 80% of subjects. Their meta-analysis revealed no significant difference in symptoms between groups that continued versus discontinued (Declercq et al., 2013). In an observational study, cessation of inappropriate antihypertensives was associated with fewer cardiovascular events and deaths over a 5-year period (Ekbom et al., 1994). A randomized trial of statin withdrawal in patients with advanced illness, half of whom died within 12 months, demonstrated improved quality of life and no increased risk of cardiovascular events over the following 60 days (Kutner et al., 2015). In a randomized trial, direct patient education through distribution of an empowerment brochure by community pharmacists reduced benzodiazepine use by 77% among chronic users at 6 months with no withdrawal seizures (Tannenbaum et al., 2014).

Effects of Structured Direct Deprescribing Targeting All Medications

The evidence for direct deprescribing of all medications using explicit tools or structured processes is limited by relatively few high-quality randomized trials, small patient samples, short duration of follow-up, selection of specific subsets of patients, and the absence of comprehensive represcribing data and clinical outcomes. However, studies of these kinds suggest a benefit to patient-centric outcomes. In a controlled trial involving 190 patients in aged care facilities, the Good Palliative–Geriatric Practice algorithm resulted in, on average, 2.8 medications per patient discontinued, and a halving in both annual mortality and acute referrals to hospitals (Garfinkel et al., 2007). In a prospective cohort study, the same approach identified an average of 4.4 PIMs per patient ($n = 64$), of which 81% were successfully discontinued, with 88% of patients reporting global improvements in health (Garfinkel and Mangin, 2010). In another prospective cohort study of 50 older hospitalized patients receiving a median of 10 regular medications on admission, a formal deprescribing process led to cessation of just over 1 in 3 medications by discharge, representing 4 fewer medications per patient with less than 5% of ceased medications recommenced for relapsing symptoms over the following 2.5 months (McKean et al., 2015). A multidisciplinary hospital clinic for older patients achieved cessation of 22% of medications in 17 patients over 3 months without ill effect (Mudge et al., 2015). Of two randomized studies of older hospital patients that applied the Screening Tool of Older People's Prescriptions (STOPP), both reported significant reductions in PIMs at discharge but without any impacts on hospital admission, falls, or mortality (Dalleur et al., 2014; Gallagher et al., 2011). Recently, a randomized trial involving aged care residents saw a deprescribing intervention result in successful discontinuation of 207 (59%) of 348 targeted medications, and a mean reduction of two medications per patient at 12 months compared to none in controls, with no differences in mortality or hospitalizations (Potter et al., 2016). In a cohort of 240 patients receiving hemodialysis, a deprescribing tool led to 31 of 40 (78%) target medications being deprescribed, with only 5 recommenced 6 months later (McIntyre et al., 2017).

Other Potential Benefits of Deprescribing

Use of inappropriate medications is associated with significant financial costs to the individual and government funding bodies. Costs may occur not only through the purchase of such medications but also from the treatment of ADEs such as hospitalization. Therefore, deprescribing may result in the reduction of costs to the individual and release of funding to governments, which can be spent on more cost-effective services and/or treatments. There is some research to support this; however, the cost-effectiveness of the different deprescribing intervention types has not yet been fully explored (Gnjidic et al., 2012; Tannenbaum et al., 2017; Thompson et al., 2016). Deprescribing also has the potential to lead to improved adherence to the individual's remaining medications (Reeve et al., 2014).

Safety of Deprescribing

There is little evidence that judicious discontinuation of drugs with close monitoring is unsafe (Reeve et al., 2018b). Serious harm due to withdrawal syndromes is rare (Graves et al., 1997; Marcum et al., 2012; Paquin et al., 2014), with cardiovascular and central nervous system medications being most implicated in the absence of slow tapering of dose. For conditions such as hypertension, diabetes, or asthma, early detection of relapsing disease can be identified using surrogates, enabling rapid resolution by recommencing the drug. For diseases with no surrogates (e.g., gastroesophageal reflux), close monitoring for recurrent symptoms appears sufficient to prevent serious harm. For preventive medications with more distant end-points, determining the risk of relapse or complications is harder to assess and highly dependent on the disease and medication in question. For example, discontinuation of cholinesterase inhibitors in dementia does not worsen disease in some studies and populations, but does in others (Herrmann et al., 2016; O'Regan et al., 2015). While there is a concern that short-term discontinuation of these medications leads to irreversible worsening of the condition (Doody et al., 2001), not all studies support this (Pariente et al., 2012), and there are important limitations to the studies such as natural progression of the disease and lack of an active comparator group. In the case of deprescribing proton pump inhibitors, deprescribing reduces pill burden but may lead to more people experiencing an increase in dyspepsia and regurgitation versus those who continue (Boghossian et al., 2017). In frail, older patients with limited prognosis, many preventive drugs can be discontinued without risk (Lavan et al., 2017).

Summary

A recent systematic review of 132 studies (Page et al., 2016a), which aimed to summarize the evidence on the feasibility and outcomes of deprescribing, concluded that deprescribing is feasible and may lead to improved outcomes. Overall, there is sufficient evidence from this and other reviews that deprescribing of inappropriate medications appears to be safe and effective at reducing medication-centric outcomes, with some indication of benefit to patient-centric outcomes (depending on the intervention, population, and medication deprescribed).

Barriers to and Enablers of Deprescribing

Patients and Caregivers

Patient involvement in deprescribing is important for many reasons: they are the one in control of what they take, they have knowledge about their medications and past medical history as well as their treatment goals, it is in accordance with the ethical principle of autonomy, and patient-centered care leads to improved outcomes (Reeve et al., 2017). Quantitative studies have found that 71%–93% of individuals would be willing to stop one or more of their medications if their doctor said it was possible (Galazzi et al., 2016; Kalogianis et al., 2016; Ng et al., 2017; Qi et al., 2015; Reeve et al., 2013b; Sirois et al., 2017). It is important, however, to understand the potential patient barriers to and enablers of deprescribing in order to optimize deprescribing in practice.

Belief in the appropriateness of a medication that they are taking can act as a barrier if patients feel that it is appropriate. For example, they may feel that a medication is still needed for their condition or may recall the benefit it provided when it was started. Conversely, belief that the medication is inappropriate may enable deprescribing, such as if they are experiencing a side effect or do not think that it is needed anymore. Fear of a withdrawal reaction, return of their condition, and a nonspecific fear of how they would be without the medication have been described as barriers to deprescribing. The process of deprescribing (or lack thereof) and external influences can also both act as barriers to or enablers of deprescribing. For example, knowing that medication withdrawal is a trial and the medication can be restarted if necessary, and also being aware of the process and what to do if they get any symptoms may increase comfort with deprescribing. The primary external influence is that of their GP and can be toward or against deprescribing (Bokhof and Junius-Walker, 2016; Linsky et al., 2015; Luymes et al., 2016; Reeve et al., 2013a, 2016). Other external influences include family members, friends, media, and family history of disease (Luymes et al., 2016; Reeve et al., 2013a, 2016). The final enablers to deprescribing reported by patients relate to a dislike of medications including inconvenience and cost associated with medication use. These barriers and enablers do not work in isolation; individuals have reported belief in the benefits and/or necessity of their medications while also having a desire to reduce medication use and being concerned about adverse outcomes (Linsky et al., 2015; Moen et al., 2009). Patients appreciate discussing their doubts about their medications and also concerns that they may have about deprescribing with their GP (Luymes et al., 2016). In the setting of palliative care patients, being accepting of their disease trajectory led individuals to have reduced fears surrounding medication cessation (Todd et al., 2016).

Similar barriers to and enablers of deprescribing have been reported by caregivers of older adults. Additionally, acting as a surrogate decision maker may be difficult and complicated by feelings of guilt and responsibility if their care recipient's condition worsens (Post et al., 2001; Reeve et al., 2016).

Health-Care Professionals and the Health-Care System

Barriers

Deprescribing medications that patients may have been taking for many years is not always easy. Both doctors and patients often lack confidence about when and how to cease medications. In a recent systematic review of studies, mostly performed in primary care settings, which looked at barriers to deprescribing from the prescriber perspective, four themes emerged (Anderson et al., 2014).

First, prescribers may be unaware of what constitutes potentially inappropriate prescribing within their own practice until this is pointed out to them. Clinicians often overestimate the benefits and underestimate the harms of treatments (Hoffmann and Del Mar, 2017).

Second, after becoming aware, there is clinical inertia toward maintaining the status quo as deprescribing is viewed as a risky affair (Anderson et al., 2017; Reeve et al., 2014b). Doctors are fearful of provoking withdrawal syndromes or disease complications and damaging their reputation and relationships with patients or colleagues in the process. Commission or regret bias arising from ill-fated action may partly explain a clinician's hesitancy to proactively manage inappropriate polypharmacy (Bornstein and Emler, 2001), especially when patients appear to have not suffered any ill effects from PIMs to date. However, the reluctance of many patients to divulge noncompliance with medications because of side effects may perpetuate the false impression of prescribers that all is well. In older patients, there is a pervasive under-recognition of medication-related geriatric syndromes on the part of doctors and pharmacists (Klopotowska et al., 2013). For example, falls or incontinence may be viewed as signs of aging and not identified as side effects of medications.

Third, lack of self-efficacy—feeling ill-equipped, in terms of the necessary knowledge and skills to deprescribe appropriately—may pose a barrier, even if the need for deprescribing is accepted (Anderson et al., 2014). Lack of readily accessible and valid information about benefit–harm trade-offs of particular drugs in older, frail, multimorbid patients, and what may be reasonable alternative treatments (both drug and nondrug), is a major barrier (Fried et al., 2010). The uncertainty of benefit and harm mandates shared decision-making between clinician and patient and, where appropriate, between clinician and caregiver (Jansen et al., 2016). This process can be rendered more difficult for patients with cognitive impairment or limited health literacy. Confidence to deprescribe is further undermined by the lack of clear documentation regarding the indications for which drugs were originally prescribed by other doctors, outcomes of past trials of discontinuation, and current patient care goals.

Fourth, several external or logistical constraints may hamper deprescribing efforts such as patient unwillingness (real or perceived) to deprescribe certain medications, lack of prescriber time, poor remuneration (or lack of incentives), difficulty accessing services, and community and professional culture and attitudes toward more rather than less use of medications (Anderson et al., 2014).

Another complicating factor is that while doctors, pharmacists, nursing staff, and even patients and their families may be in broad agreement that deprescribing is worthwhile, they often differ in their perspectives on what takes priority in selecting medications for deprescribing in individual patients and how it should be done and by whom (Page et al., 2016b; Turner et al., 2016).

Enablers

While deprescribing presents challenges, several strategies can facilitate it at the level of individual clinical encounters.

First, patients should be empowered to ask their doctors and pharmacists when, and under what circumstances, might it be reasonable to stop a medication. Periodic review of the benefits versus harms of specific medications should be undertaken as a patients' health status and comorbidity burden evolve over time. Rechecking medications should be seen as akin to rechecking blood pressure or lipid levels. In turn, doctors and pharmacists should ask in a nonjudgmental fashion, at every encounter, whether patients are experiencing any side effects, administration and monitoring problems, or other barriers to adherence associated with any of their medications.

Second, deprescribing should be framed as an attempt to alleviate symptoms (of drug toxicity), improve quality of life (from drug-induced disability), and lessen the risk of morbid events (especially ADEs) in the future.

Third, compelling evidence that identifies circumstances in which medications can be safely withdrawn while reducing the risk of ADEs needs to be emphasized (Bennett et al., 2014). In language they can understand, patients should be informed of the benefit–harm trade-offs specific to them of continuing or discontinuing a particular medication, as far as these can be made explicit. Patients, like clinicians, often overestimate the benefits and underestimate the harms of treatments (Hoffmann and Del Mar, 2015). Providing such personalized information can substantially alter perceptions of risk and change attitudes toward discontinuation (Martin et al., 2013).

Fourth, onset of ADEs or onset of newly diagnosed diseases or deterioration in existing comorbidities, which all increase the risk of ADEs, serves as tipping points toward deprescribing which prescribers can make full use of (Anderson et al., 2017).

Fifth, a range of decision-making strategies to reconcile therapeutic uncertainty in multimorbid patients can be employed (Sinnott et al., 2015) and various tools, structured guides, guidelines, and algorithms are available (these are discussed further in the Section "Process of Deprescribing").

Sixth, pharmacists, nurses, and other health-care professionals can be creatively engaged to systematize the process of deprescribing and monitoring and follow-up, complementing the role of the doctor (Steinman et al., 2011). Interactive case conferences involving multidisciplinary teams can provide support, seek consensus, and share the risk and responsibility for deprescribing recommendations (Bregnhøj et al., 2009). Other organizational changes such as targeted funding for annual medications review, computer prompts (Anderson et al., 2016), improved information flows between prescribers, improved access to expert advice, regulatory changes, and increased availability of nonpharmaceutical therapies can further support deprescribing at scale (Wallis et al., 2017).

Finally, specialists can play a sentinel leadership role in advising and authorizing other health professionals to deprescribe in situations where current harms of medications they have prescribed some time ago are no longer outweighed by current benefits (Luymes et al., 2016; Scott and Le Couteur, 2015).

The Process of Deprescribing

Understanding of the enablers of and barriers to deprescribing as well as the principles of good clinical care have informed the process of how to undertake deprescribing in practice. Several models of the deprescribing process have been developed and several have been assessed in research studies (McKean et al., 2015; Reeve et al., 2014a, 2015a; Scott et al., 2015). All the processes contain similar steps, which are generally in concordance with the steps first proposed by Woodward in 2003 (Woodward, 2003). The key features of the processes are firstly obtaining a complete medication history with knowledge of their medical history. This includes what medications the person is taking (including dose and frequency), the indications for the medications, how long they have been taking them, and any evidence of benefit or of harm from the medication. The next step is to evaluate patient factors that may impact

on the decision to deprescribe a medication including the patient's goals of care and their prognosis/life-expectancy. Each drug on the patient's medication list should then be reviewed in view of these patient factors, and the other medications that the person is taking, and a decision reached in consultation with the patient, on whether it could be ceased. This will depend on the current risk: benefit ratio for the individual. Medications should be ceased one at a time if possible, aiming to start with those conferring greatest harm and least benefit as decided in consultation with the patient and family. Medications may be able to be ceased simultaneously where there is a very low risk of withdrawal reactions or return of conditions (e.g., vitamins that are not needed). The plan for withdrawal of each medication may be cessation or gradual tapering, depending on the pharmacology of the drug, how long the patient has been taking it, at what dose, and their current adverse effects. Monitoring for withdrawal symptoms and return of disease condition, support for the patient (which may include advice on nonpharmacological treatment or referral to other health-care professionals), and documentation of the outcome are the final steps. If withdrawal symptoms occur, then the tapering/withdrawal process can be slowed down, and if there is clear return of condition (after exclusion of other causes), then the medication can be restarted or continued at the lowest effective dose.

The process of identifying inappropriate medications that are suitable for deprescribing can be difficult in the older comorbid population. However, several tools, algorithms, and guidelines have been developed to assist health-care professionals with this step. Structured but implicit guides and algorithms (i.e., still requiring clinical experience and expertise) can be used to identify medications that are eligible candidates for deprescribing (Garfinkel et al., 2007; Scott et al., 2015, 2017). A number of explicit screening tools have been developed to help clinicians consider the risks and benefits of medications in older patients. Some tools, such as the updated Beers Criteria from the United States ("American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults," 2015), identify PIMs for older adults overall and those with particular clinical characteristics, based on expert consensus review of the literature. Others, such as the STOPP/START Criteria version 2 from the United Kingdom (O'Mahony et al., 2015), use similar principles to generate lists of drugs that should and should not be used in specific circumstances, with a version for frail patients with limited life expectancy, which was published recently (Lavan et al., 2017). Pharmacological risk-assessment tools, which measure an individual's total exposure to specific drug classes, can inform the risk side of the risk:benefit ratio and identify patients and drug targets for possible deprescribing. These include many measures of anticholinergic burden (Kouladjian O'Donnell et al., 2017), the Drug Burden Index (which measures cumulative exposure to medications with anticholinergic and sedative effects) (Hilmer et al., 2007), central nervous system medication use (Wright et al., 2009), and consideration of cumulative serotonergic or hypotensive load. Algorithms on the number needed to treat vs number needed to harm for specific medications and indications as well as disease prediction tools (reviewed in a number of websites, see end of chapter) can help assess and discuss benefit and risk. Estimates of patient prognosis such as the "surprise question" and others (Moss et al., 2010; Yourman et al., 2012) can be useful to determine whether the patient is likely to have enough time to benefit from a preventative treatment. A number of practical guides have been developed on when and how to deprescribe medications, these are listed at the end of the chapter (useful websites). In particular, several drug class specific deprescribing guidelines have been developed over the past few years (Bjerre et al., 2018; Farrell et al., 2017a, 2017b; Reeve et al., 2018a). These have been developed according to robust clinical practice guideline standards (Farrell et al., 2016) and provide recommendations on when and how to deprescribe the medications including recommendations about tapering and monitoring.

As the evidence for deprescribing grows, efforts are being made to implement the deprescribing process, supported by some of the tools described above, into clinical practice (Hilmer and Gnjidic, 2018). Strategies are required to address barriers and enablers specific to different health-care settings (community, nursing home, hospital) and practitioners (primary and specialist, medical, pharmacy, and nursing), with an emphasis on communication between different settings and practitioners. Interventions have been tested that directly target consumers (e.g., EMPOWER, Tannenbaum et al., 2014) or are initiated by health-care professionals, often working as multidisciplinary teams (Wouters et al., 2017). Technology may be able to support the deprescribing process, through software packages that guide and support the process, which may be either stand-alone or integrated with electronic health records and medication management systems (Saddiq and Kauser, 2017). To be effective, the deprescribing process must be patient-centered (Reeve et al., 2014a), ensuring that decisions about medication management are consistent with patient goals and prognosis, are agreed to by the patient, and move with the patient between different health-care settings and providers. However, the most effective, efficient, cost-effective, and sustainable solution to implementing a robust deprescribing process into practice is yet to be determined.

Pharmacists' Involvement in Deprescribing

There is the potential for pharmacists to be involved throughout the deprescribing process as outlined above. However, there are specific components for which pharmacists are well placed to undertake. For example, taking a comprehensive medication history is a key part of pharmacist training. In fact, a pharmacist-acquired medication list on admission to hospital has been associated with reduced medication costs, length of stay, medication errors, ADEs, and mortality (Bond and Raehl, 2007; Nester and Hale, 2002). Additionally, pharmacists have pharmacokinetic and pharmacodynamic knowledge required for planning medication tapering and monitoring. They also have training in communication techniques (McConnell et al., 2008; Tannenbaum and Tsuyuki, 2013).

Pharmacist Attitudes Toward Deprescribing

The attitudes of pharmacists toward deprescribing, including their potential involvement, have been explored in several studies in Australia. Pharmacists have identified barriers to deprescribing in practice similar to those reported by medical doctors (Anderson et al., 2017; Kouladjian et al., 2016; Palagyi et al., 2016; Turner et al., 2016). The main barriers specific to pharmacists' involvement in deprescribing (as reported by pharmacists) are not being sure whose responsibility it is, or devolving of responsibility (Kouladjian et al., 2016), the need for GPs to play a key role in all deprescribing activities (Palagyi et al., 2016), not having a previously established relationship with the patient, a lack of avenues to provide follow-up/continuing care after deprescribing (Anderson et al., 2017; Palagyi et al., 2016), and being cautious where there is uncertainty of evidence (leading to inaction) (Anderson et al., 2017).

In a quantitative study conducted in Australia, hospital pharmacists responded to a survey about optimizing statin use in older adults (Wu et al., 2017). Over 90% felt that they had an important role in providing advice to doctors regarding initiation, continuation, and/or cessation of statins. Approximately two-thirds were confident in their ability to identify patients in whom statin therapy should be deprescribed, but only about half reported that they regularly made recommendations about deprescribing in older adults.

Consumer Attitudes Toward Pharmacists' Involvement in Deprescribing

In studies in Australia, Canada, and Singapore between 51% and 66% of older adults reported that they would be comfortable if a pharmacist was involved in deprescribing one of more of their regular medications including providing follow-up (Ng et al., 2017; Reeve et al., 2013b; Sirois et al., 2017). In a focus group study with older adults and caregivers of older adults regarding deprescribing, experiences, and attitudes toward pharmacists appeared to be limited to the retail community pharmacy setting (Reeve et al., 2016). Pharmacists were acknowledged as experts in medications (such as in identifying drug–drug interactions) and certain individuals recalled times where their pharmacist had been very helpful. However, there was a limited understanding of the scope of the pharmacists' work and their potential role in deprescribing.

Health-Care Professionals' Attitudes Toward Pharmacists' Involvement in Deprescribing

GPs have identified the potential benefits of involvement of pharmacists in deprescribing as part of a multidisciplinary team (Ailabouni et al., 2016; Palagyi et al., 2016; Schuling et al., 2012). However, GPs have expressed concerns that pharmacists may recommend deprescribing that is not appropriate, as they may not be familiar with the patient's complete medical history (Ailabouni et al., 2016; Palagyi et al., 2016). They have also cited a lack of resources to specifically support multidisciplinary meetings with pharmacists as a barrier (Ailabouni et al., 2016). Success of pharmacists' involvement in deprescribing will likely depend on the relationship between the GP and the pharmacist (Palagyi et al., 2016). This has been demonstrated in quantitative studies where pharmacist recommendations are more likely to be accepted and implemented by the GP where there was a preexisting working relationship (Sorensen et al., 2004; Spinewine et al., 2012). Pharmacists embedded within GP clinics are a promising model for enhancing deprescribing in primary care. This would not only lead to trust between professionals but also gives pharmacists access to complete medical records (Anderson et al., 2015; Freeman et al., 2012). Models such as this are currently being investigated to determine clinical benefits and cost-effectiveness (Freeman et al., 2016; Tan et al., 2014).

In the hospital setting, junior doctors have reported that it is not their responsibility to conduct medication reviews and deprescribe inappropriate medications. Instead, they looked to pharmacists (as well as consultants and the patient's regular GP) to conduct these activities (Jubraj et al., 2015). In a survey conducted among nurses working in residential aged care facilities, they recognized the benefit of involvement of a pharmacist in deprescribing. Similar to GPs, however, some questioned whether the pharmacist had sufficient knowledge of the patient to recommend changes (Ailabouni et al., 2017).

Future Directions of Pharmacists' Involvement in Deprescribing

Multidisciplinary interventions (such as those including a pharmacist) appear to be the most effective at achieving deprescribing (Cooper et al., 2015; Gnjidic et al., 2012). Pharmacist-led interventions in a variety of settings can lead to improvements in medication appropriateness and reduction of polypharmacy with some evidence to support improved clinical outcomes such as reduced hospitalization (Jokanovic et al., 2016; Viswanathan et al., 2015; Walsh et al., 2016).

Further investigation into how to best utilize the skills and experience of pharmacists in deprescribing activities is required. There is some evidence to suggest that interventions which do not include the patient's GP are less effective (Ostini et al., 2011; Reeve et al., 2014a), and as such pharmacist deprescribing should not be an isolated function. Lack of communication between health-care professionals and different levels of care is a concern for medication management internationally. Therefore, it is important to ensure that pharmacist deprescribing activities involve good communication and coordination with other health-care providers (Duncan et al., 2017). To address this concern, a communication template for conveying evidence-based deprescribing information from pharmacists to physicians is being investigated (Martin and Tannenbaum, 2018).

Limited time of GPs has been cited as a reason for pharmacists' involvement in deprescribing. Many health-care systems have mechanisms for community pharmacists to conduct medication reviews, which can result in deprescribing recommendations

(Chen, 2016; Duncan et al., 2017). However, these existing schemes may not overcome several of the barriers discussed, such as not being able to do follow-up visits. Further investigation into the differences in pharmacists' roles, scopes of practice, and remuneration schemes across different settings is required to determine how to best use the skills and experiences of this profession to optimize deprescribing practices (Anderson et al., 2015, 2017).

As an accessible and trustworthy member of health-care teams, it appears to be imperative to have pharmacists involved in deprescribing activities on an individual patient level as well as being involved in advocating, educating, and communicating about deprescribing to both other health-care providers as well as the community around them.

Conclusions

In the 15 years since the term "deprescribing" was first published, evidence on its safety, efficacy, and implementation has grown enormously. While deprescribing is a long-standing component of the practice of geriatric medicine, with the ageing of the population and increased use of medicines, it has expanded to primary care and other areas of specialist practice. This has resulted in opportunities for pharmacists to inform and support all stages of the deprescribing process, across primary care, nursing home, and hospital settings. The 2018 WHO 3rd Patient Safety Challenge: Medication Without Harm highlights the importance of addressing inappropriate polypharmacy for the ageing populations across the developed and developing world.

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List of Relevant Webpages

Please note: The resources and tools contained in the websites listed below have been developed using a variety of methods including unstructured and structured literature reviews, expert consensus, and external peer-review. The robustness of development and validity of the content have not been formally assessed by the authors of this chapter.

Websites with prognostic tools:

www.thennt.com
http://eprognosis.ucsf.edu
http://www.medal.org/

Practical guides and resources for deprescribing:

https://deprescribing.org/
https://www.deprescribingnetwork.ca/
http://www.nhshighland.scot.nhs.uk/publications/documents/guidelines/polypharmacy%20guidance%20for%20prescribing%20in%20frail%20adults.pdf
www.bpac.org.nz/magazine/2010/april/stopGuide.asp
http://www.prescqipp.info/projects/polypharmacy-and-deprescribing
https://www.primaryhealthtas.com.au/resources/deprescribing
http://medstopper.com/
http://rxisk.org/

Management of Cardiovascular Disorders and the Pharmacist's Role: Hypertension

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Learning Objectives

At the end of this chapter, the reader should be able to:

1. Describe the epidemiology, etiology, risk factors, and pathophysiology of hypertension.
2. Discuss the screening, diagnosis, and investigations involved in the management of hypertension.
3. Discuss the non-pharmacologic management of hypertension.
4. Discuss the general pharmacologic approach and compare different evidence-based guidelines for the management of hypertension.
5. Describe the current and emerging roles of the pharmacist in the management of hypertension.

Take-Home Messages and Summary

1. Hypertension is a persistent elevation of blood pressure. Guidelines differ in the level of blood pressure that should be considered as "hypertension" and the different goal targets for those diagnosed as hypertensive.
2. The American College of Cardiology and American Heart Association redefined hypertension in 2017 Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults, which resulted in an increase in the number of adults who have hypertension based on this definition.
3. Globally, the prevalence of hypertension is increasing. WHO global estimates in 2010 indicate the prevalence of hypertension to be around 1.39 billion people.

4. Hypertension can be classified as primary or essential hypertension and secondary hypertension. While the cause of essential hypertension is largely unknown, genetic factors and diet play a key role in its development.
5. Secondary hypertension occurs commonly due to endocrine causes, such as hyperaldosteronism and renovascular causes.
6. Several classes of drugs, such as non-steroidal anti-inflammatory drugs, steroids, anti-cancer drugs, and others can cause increase in blood pressure.
7. Increasing age, male gender, black race, and positive family history of hypertension are non-modifiable risk factors for the development of hypertension. Modifiable risk factors for hypertension include consumption of excess salt, alcohol, sedentary lifestyle, and lack of physical activity.
8. Routine laboratory investigations, such as complete blood count, serum electrolytes, and creatinine must be performed during screening and diagnosis. Other specialized tests, such as measurement of plasma aldosterone and urinary metanephrines may be necessary for the diagnosis of hyperaldosteronism or pheochromocytoma.
9. Pharmacists play an important role in the management of cardiovascular diseases (CVDs) as part of the healthcare team. They manage one or more of the risk factors for CVDs independently or as part of a multi-disciplinary team.
10. Pharmacists have a significant role in managing medications and monitoring blood pressure in patients with hypertension. Furthermore, the evidence has proven the benefit of pharmacist's interventions in improving outcomes among patients with hypertension.
11. Pharmacists can play a vital role in several aspects of patient management, such as assessment, screening, and counseling on risk factors for CVDs, medication review and education on adherence, and modification of drug therapy.

Introduction

Hypertension is a persistent elevation of blood pressure (BP). Meeting one or more of the following criteria is defined as having hypertension: (1) a systolic blood pressure (SBP) of 140 mmHg or greater; (2) a diastolic blood pressure (DBP) of 90 mmHg or greater; (3) taking antihypertensive medication or; (4) having been told at least twice by a physician or other health professional that one has hypertension (McConnell and Baker, 2013; Williams et al., 2018). According to the American Heart Association (AHA) 2017 guidelines, hypertension is classified as Stage 1 when the BP range is 130–139 mmHg systolic or 80–89 mmHg diastolic and as Stage 2 when the BP is ≥140 mmHg systolic or ≥90 mmHg diastolic (Whelton et al., 2017; Basile and Bloch, 2018).

Epidemiology

The World Health Organization (WHO) estimate of the global prevalence of high BP among adults above 25 years of age was about 40% in 2008 (WHO, 2017). Accordingly, almost 1 billion people had uncontrolled hypertension worldwide in 2008. According to other estimates in 2010, the global prevalence of hypertension was 1.39 billion affecting about 31% the adult population. This is a 5.2% increase in global prevalence between 2000 and 2010 (Basile and Bloch, 2018). According to estimates by the AHA, 41% of the US adult population could be diagnosed with the hypertension by 2030 (McConnell and Baker, 2013). The highest prevalence of hypertension of 46% is observed in Africa, while the lowest prevalence of 35% is found in the Americas (WHO, 2017). High BP is estimated to cause 7.5 million deaths worldwide that represents about 12.8% of total deaths.

Etiology of Hypertension

Hypertension can be classified as primary/essential hypertension or secondary hypertension. Essential hypertension is the most common form of hypertension that accounts for over 90% of all causes of hypertension. While the exact cause of hypertension is unknown, it could be attributed to several factors, such as over activation of sympathetic nervous system, excess salt intake and genetic factors (Leung et al., 2017). However, secondary hypertension most commonly occurs due to renovascular diseases or endocrine causes, such as hyperaldosteronism or Cushing's syndrome. In addition to renal and hormonal causes, several medications can increase BP. Oral contraceptive pills, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, decongestants, anticancer drugs, and weight loss medications can increase BP and long-term intake can cause hypertension (Basile and Bloch, 2018).

Risk Factors for Hypertension

Factors that increase the risk of developing essential (primary) hypertension can be classified as modifiable and non-modifiable risk factors (Leung et al., 2017). Age, gender, race, and family history are non-modifiable risk factors. The risk of systolic hypertension increases with advancing age. Men are at a higher risk of developing hypertension until about 45 years after which the risk in women increases due to menopause (Martins et al., 2001). Blacks have a higher risk of developing early onset and severe hypertension compared to the white population. In addition, genetic factors also contribute to the risk of developing hypertension. Therefore, individuals with a family history of hypertension are likely to develop hypertension.

Modifiable risk factors of hypertension include high-sodium diet, obesity, sedentary lifestyle, and excessive alcohol consumption. The INTERSALT study established the positive relationship between sodium intake and BP. While there has been a debate regarding the allowable limit of salt intake, it is agreed that salt intake in excess of 3 g/day could increase the risk of hypertension (INTERSALT, 1988). Obesity and physical inactivity also contribute to a rise in BP and that loosing body weight improves hypertension. Alcohol consumption of more than 14 and 9 standard drinks for men and women, respectively poses the risk of developing hypertension.

Pathophysiology of Hypertension

One of the key mechanisms of essential hypertension is over activation of the sympathetic nervous system (Bolivar 2013; Grassi, 2015). BP is the product of cardiac output (CO) and total peripheral resistance (TPR). Therefore, SNS-induced increase in CO or TPR changes increases the BP. One mechanism of increase in CO and TPR is the renin-angiotensin-aldosterone system. While angiontensin II causes an increase in TPR via vascoconstriction, aldosterone promotes sodium and water retention by the kidneys resulting in an increase in plasma volume and therefore an increase in CO. In addition, increase in sodium intake can also cause increase in intracellular calcium levels in vascular smooth muscle cells promoting vasoconstriction and increase in TPR. In secondary forms of hypertension, the cause of increase in plasma volume or TPR is known and is attributed to renal diseases or changes in hormonal levels such as aldosterone or cortisol.

Complications of Hypertension

Hypertension is the most important modifiable risk factor for a number of cardiovascular adverse events, such as stroke and ischemic heart diseases (Basile and Bloch, 2018). For every 20 mmHg higher SBP and 10 mmHg higher DBP, the risk of death from heart diseases or strokes doubles. Therefore, the complications of hypertension include ischemic and hemorrhagic stroke, myocardial infarction, left ventricular hypertrophy, heart failure, and chronic kidney disease.

Investigations, Screening, and Diagnosis of Hypertension

Accurate measurement of BP is essential for the diagnosis of hypertension and monitoring response to therapy (Leung et al., 2017). Four approaches can be used for the measurement of BP: (1) automated office BP (AOBP), (2) non-AOBP, (3) ambulatory BP monitoring (ABPM), and (4) home BP monitoring (HBPM). According to the Canadian Hypertension Education Program (CHEP) 2017 guidelines, using AOBP, mean SBP ≥135 mmHg or DBP ≥ 85 mmHg is considered high. However, using non-AOBP, mean SBP ≥140 mmHg or DBP ≥ 90 mmHg is considered high. HBPM is suggested for routine self-monitoring of BP or when there is discrepancy between other approaches using a validated device. A mean SBP ≥135 mmHg or DBP ≥ 85 mmHg is considered high. ABPM is considered as the gold standard for the diagnosis of hypertension. Having a mean awake SBP ≥135 mmHg or DBP ≥ 85 mmHg or the mean 24-h SBP ≥130 mmHg or DBP ≥ 80 mmHg is considered hypertension. Furthermore, laboratory tests should be performed in patients with hypertension at diagnosis and monitored at intervals, as medically necessary. Complete blood count, serum electrolytes including creatinine, urinalysis, blood glucose or HbA1C, serum lipid levels, thyroid stimulating hormone (TSH), and electrocardiogram (ECG) should be assessed in a patient screened for or diagnosed with hypertension (Basile and Bloch, 2018).

The common causes of secondary hypertension are endocrine conditions, such as hyperaldosteronism, pheochromocytoma (tumor of adrenal medulla), and renovascular hypertension (Leung et al., 2017). Screening for secondary causes of hypertension should be undertaken in early onset hypertension or hypertension that is resistant to treatment with three or more antihypertensive medications. Additionally, screening for hyperaldosteronism should be considered in patients with hypokalemia or hypertension resistant to treatment with three or more medications. Measurement of plasma potassium levels, aldosterone, renin levels, or renin activity is necessary for the diagnosis. Patients with sudden onset severe labile hypertension with BP≥180/110 mmHg and symptoms of sympathetic overactivation should be screened for pheochromocytoma. Measurement of 24-h urinary collection for catecholamines and metanephrine is necessary for diagnosis. Renovascular hypertension should be suspected in patients with sudden onset or worsening of hypertension, patients whose serum creatinine levels increase more than 30% after initiation of ACE inhibitors or resistant hypertension. Captopril-enhanced radioisotope renal scan and investigations for fibromuscular dysplasia should be performed for diagnosis.

Management of Hypertension

Non-pharmacologic Therapy

Various guidelines have recommended the following non-pharmacologic and lifestyle interventions for the management of hypertension in adults:

- Physical exercise: It is recommended by several guidelines for patients with hypertension to do physical exercise due to its multiple beneficial effects on overall health. Physical activity in patients with hypertension is associated with BP reduction. For non-hypertensive individuals, physical activity is recommended to reduce the risk of becoming hypertensive. Clinicians can prescribe the accumulation of 30–60 min of moderate intensity dynamic exercise (e.g., walking, jogging, cycling, or swimming) 4–7 days/week, in addition to the routine activities of daily living (Leung et al., 2017; Williams et al., 2018).
- Weight reduction: Body weight control is indicated to avoid obesity (BMI >30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m^2) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk (Leung et al., 2017; Williams et al., 2018). All overweight individuals with hypertension should be advised to lose weight (Williams et al., 2018).
- Alcohol consumption: The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) guidelines provide some details about alcohol consumption in patients with hypertension. The guidelines recommend that patients who drink alcohol should limit their alcohol consumption to 14-units/week for men and to 8-units/week for women (1 unit is equal to 125 mL of wine or 250 mL of beer). Alcohol-free days during the week are generally advised (Williams et al., 2018). Canadian Hypertension guidelines recommend all individuals to limit their alcohol consumption to two drinks or less per day, and that consumption should not exceed 14 standard drinks/week for men and 9 standard drinks/week for women (Leung et al., 2017).
- Diet: Dietary Approach to Stop Hypertension (DASH) diet is recommended by most guidelines (NICE, 2013; Leung et al., 2017; Whelton et al., 2017; Williams et al., 2018). DASH is a flexible and balanced eating plan that helps create a heart-healthy eating style for life. The DASH eating plan requires no special foods and instead provides daily and weekly nutritional goals. This plan is generally based on the following points: eating vegetables, fruits, and whole grains, fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils, limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils, such as coconut, palm kernel, and palm oils, and limiting sugar-sweetened beverages and sweets. In addition to these, patients should be encouraged to increase the consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); and to consume low amounts of red meat and full-fat dairy products (Leung et al., 2017; Whelton et al., 2017; Williams et al., 2018). A heart-healthy diet that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension (Whelton et al., 2017).
- Sodium intake: There is a consensus across clinical practice guidelines to educate patients to reduce their sodium intake toward 2 g (5 g of salt or 87 mmol of sodium) per day (NICE, 2013; Leung et al., 2017; Whelton et al., 2017; Williams et al., 2018).
- Potassium intake: In patients not at risk of hyperkalemia, increasing dietary potassium intake may be recommended to reduce BP (Leung et al., 2017; Whelton et al., 2017; Williams et al., 2018). However, some guidelines recommend against the use of potassium supplement as a method of BP reduction to avoid putting the patient at the risk of hyperkalemia (NICE, 2013).
- Stress management: In patients with hypertension in whom stress may be contributing to high BP, stress management should be considered as an intervention (Leung et al., 2017). However, there is no evidence to confirm the beneficial effect of this approach in the management of hypertension (Whelton et al., 2017).

Pharmacologic Therapy

Initiation of Drug Therapy

Antihypertensive therapy should be prescribed for average DBP measurements of 100 mmHg or higher or average SBP measurements of 160 mmHg or higher in all patients even without macrovascular target organ damage or other cardiovascular risk factors (NICE, 2013). Antihypertensive therapy should be strongly considered for patients aged under 80 years with an average DBP reading of 90 mmHg or higher or for an average SBP reading of 140 mmHg or higher in the presence of any of the following factors: target organ damage; established CVD; renal disease; diabetes and; a 10-year cardiovascular risk equivalent to 20% or greater.

For patients with average DBP measurements of 90–99 mmHg or average SBP measurements of 120–139 mmHg, without any other complications, lifestyle interventions are recommended to determine, if this will normalize BP first (NICE, 2013; Leung et al., 2017; Whelton et al., 2017). This recommendation is slightly different from what JNC 8 guideline recommends. In JNC 8, it is recommended for general population aged ≥60 years, to initiate pharmacologic treatment to lower BP at SBP ≥150 mmHg or DBP ≥90 mmHg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg (James et al., 2014).

Blood Pressure Goals and Targets Among Individual Patients

The ultimate goal of antihypertensive therapy is a reduction in cardiovascular events risk. The higher the cardiovascular risk, the more likely it is that a patient will benefit from a more aggressive BP goal. However, it is important to keep in mind that the risk of adverse effects, cost, and patient inconvenience increases as more medications are added. Target BP is based on individual patient's characteristics and comorbid conditions. BP goals are slightly different across different guidelines. **Table 1** summarizes the goals and targets presented in the main guidelines used for the treatment of hypertension.

Uncomplicated Hypertension

Since the overall goal of treatment should be reduction in BP, in the context of underlying CVD risk, randomized control trials focused on identifying medication classes that can prevent CVDs. Numerous classes of antihypertensive agents are available to treat high BP. Five drug classes have been shown, in high-quality randomized controlled trials, to prevent CVDs: diuretics, ACE inhibitors,

Table 1 Blood pressure goals recommendations by different clinical practice guidelines.

Guideline	*Year*	*Population and BP targets*
ESC/EHS (Williams et al., 2018)	2018	• The first objective is to lower BP to <140/90 mmHg in all patients and, if well-tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. • In patients <65 years, SBP should be lowered to 120–129 mmHg in most patients. • SBP target of between 140–150 mmHg for older patients (65–80 years). • DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.
JNC 8 (James et al., 2014)	2014	• Adults age < 60 years and those >18 with diabetes or chronic kidney disease: <140/90 mmHg • Adults age ≥60 years: <150/90 mmHg
American College of Cardiology/American Heart Association (ACC/AHA) (Whelton et al., 2017)	2017	• All adults: <130/80 mmHg
American Diabetes Association (ADA) (American Diabetes Association, 2017)	2017	• Adults with diabetes <140/90 mmHg Targets <130/80 mmHg, may be appropriate for individuals at high risk of CVD
Canadian Hypertension guidelines (Leung et al., 2017)	2017	• For patients with non-diabetic chronic kidney disease, target BP is < 140/90 mmHg. Patients with diabetes: <130/80 mmHg

ARBs, CCBs, and beta-blockers (Whelton et al., 2017; Williams et al., 2018). Agents that have been shown to reduce clinical events should be used preferentially. Therefore, the primary agents used in the treatment of hypertension include thiazide diuretics, ACE inhibitors, ARBs, and CCBs. (Whelton et al., 2017).

When the initial drug treatment of high BP is being considered, several different strategies may be contemplated. Many patients can be started on a single agent, but consideration should be given to starting with two drugs of different classes for those with stage 2 hypertension (James et al., 2014; Whelton et al., 2017; Leung et al., 2017). Two-drug approach can be provided as either two different pills or combination of two medications. Two antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line agents. Useful options include a thiazide/thiazide-like diuretic or CCB with either an ACE inhibitor, ARB or a beta-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a beta-blocker. In addition, the combination of an ACE inhibitor and an ARB is not recommended (James et al., 2014; Leung et al., 2017).

Resistant Hypertension

Resistant hypertension is defined as resistance to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, and the inadequate control of BP is confirmed by ABPM or HBPM in patients whose adherence to therapy has been confirmed (Whelton et al., 2017). Resistant hypertension is associated with older age (especially >75 years), male sex, African origin, high initial BP at diagnosis of hypertension, highest BP ever reached during the patient's lifetime, frequent outpatient visits, obesity, diabetes, atherosclerotic disease, hypertension-mediated organ damage (HMOD), chronic kidney disease (CKD), and a Framingham 10-year coronary risk score >20% (Whelton et al., 2017). Patients with resistant hypertension are at higher risk of HMOD, CKD, and premature cardiovascular events. The recommended treatment strategy for resistant hypertension should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs, including a diuretic, an ACE inhibitor or an ARB, and a CCB (Whelton et al., 2017; Carey et al., 2018).

Effective treatment for resistant hypertension should combine lifestyle changes (especially the reduction of sodium intake), discontinuation of possible causes of BP elevation, and the sequential addition of antihypertensive drugs to the initial triple therapy (Whelton et al., 2017). The optimal drug treatment of resistant hypertension has been poorly studied. The most effective strategy seems to be addition of diuretic treatment to decrease volume overload, together with the restriction of salt intake, particularly in patients with CKD (Whelton et al., 2017).

Furthermore, BP control may be improved by increasing the dose of the existing diuretic or by switching to a more potent thiazide-like diuretic (e.g., chlorthalidone or indapamide). A loop diuretic should replace thiazides/thiazide-like diuretics if the patient's eGFR is <30 mL/min. Although resistant hypertension may show a BP reduction if the existing diuretic dose is further increased, most patients would require the administration of additional drugs (Whelton et al., 2017; Williams et al., 2018). Also, there is growing evidence to suggest that the fourth-line treatment should involve the blockade of the biological effects of aldosterone through the use of spironolactone up to 50 mg/day (Whelton et al., 2017; Williams et al., 2018).

Hypertensive Urgency and Emergency

Hypertensive emergencies are defined as significant elevation in BP (>180/120 mm Hg) associated with evidence of new or worsening target organ damage. Examples of target organ damage include hypertensive encephalopathy, intracranial hemorrhage,

Table 2 Antihypertensive medications for the treatment of hypertensive emergencies (Williams et al., 2018)

Cardiovascular event	*First-line drug*	*Alternative drugs*
Acute aortic dissection	Esmolol and nitroprusside or nitroglycerine or nicardipine	Labetalol OR metoprolol
Acute cardiogenic pulmonary edema	Nitroprusside or nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute coronary event	Nitroglycerine, labetalol	Urapidil
Preeclampsia, Eclampsia, and HELLP syndrome	Labetalol or nicardipine and magnesium sulfate	Consider delivery
Hypertensive emergency	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Labetalol, nicardipine	Nitroprusside

HELLP = Hemolysis, Elevated Liver enzymes, and Low Platelets

acute ischemic stroke, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina, and eclampsia (Whelton et al., 2017; Leung et al., 2017). The one-year death rate associated with hypertensive emergencies is greater than 79%, and the median survival is 10.4 months, if the emergency condition is left untreated (Whelton et al., 2017; Williams et al., 2018). The rate and magnitude of an increase in BP may be at least as important as the absolute level of BP in determining the magnitude of organ injury. Therefore, detailed history and previous BP readings, if available, are important. In addition, patients with chronic hypertension can often tolerate higher BP levels than previously normotensive individuals (Williams et al., 2018).

The most common hypertensive emergency symptoms will depend on the organs affected, but this may include headache, visual disturbances, chest pain, dyspnea, dizziness, and other neurological deficits. In patients with hypertensive encephalopathy, the presence of somnolence, lethargy, tonic clonic seizures, and cortical blindness may precede a loss of consciousness; however, focal neurological lesions are rare and should raise the suspicion of concomitant stroke (Whelton et al., 2017). Hypertensive emergencies demand immediate reduction of BP, but this does not necessarily mean that BP should be brought to normal level. The aim of BP reduction is to prevent any further target organ damage (Whelton et al., 2017). In general, use of oral therapy is discouraged for hypertensive emergencies. (Williams et al., 2018). **Table 2** provides the major intravenous antihypertensive medications indicated for hypertension emergency.

For most hypertensive emergencies, the mean arterial pressure should be reduced gradually by approximately 10%–20% in the first hour and by a further 5%–15% over the next 23 h. This often results in a target BP of $< 180/ < 120$ mmHg for the first hour and $< 160/ < 110$ mmHg for the next 23 h (Elliott, 2006). The major exceptions to gradual BP lowering over the first day are:

- The acute phase of an ischemic stroke: The BP is usually *not* lowered unless it is ≥185/110 mmHg in patients who are candidates for reperfusion therapy or ≥220/120 mmHg in patients who are not candidates for reperfusion (thrombolytic) therapy (Jauch et al., 2013).
- Acute aortic dissection: The SBP should be *rapidly* lowered to a target of 100–120 mmHg (to be attained in 20 min) to reduce aortic shearing forces (Li et al., 2013).

In contrast, hypertensive urgencies are situations associated with severe BP elevation in otherwise stable patients without acute or impending change in target organ damage or dysfunction. Many of these patients have withdrawn from or are noncompliant with antihypertensive therapy and do not have clinical or laboratory evidence of acute target organ damage. There is no indication for referral to the emergency department, immediate reduction in BP in the emergency department, or hospitalization for such patients (Whelton et al., 2017). It is generally discouraged to lower the BP quickly as ischemic damage can occur in vascular beds due to sudden drop in the BP (Whelton et al., 2017).

Antihypertensive Medication Selection Based on Patients' Characteristics and Compelling Indications

Patients with hypertension may present, in many cases, with some other CVDs and other medical conditions. As antihypertensive medications can have health beneficial effect beyond lowering the BP, patient's other medical conditions should be taken into account when selecting antihypertensive therapy. In addition to the medical conditions, genetics and race can play an important role in the choice of treatment for hypertension. For instance, African American patients, as a group, have a smaller BP reduction than white patients in response to ACE inhibitors, ARBs, and most beta-blockers when given as monotherapy (Materson et al., 1993; Wright et al., 2005). However, these drugs are effective when given in combination with thiazide diuretics or calcium channel blockers. **Table 3** summarizes the recommendations by guidelines regarding the first line antihypertensive medication based on patients' characteristics and comorbid conditions.

Many drugs are available for the treatment of hypertension and in most patients; BP can now be controlled effectively and with minimal adverse effects (Katzung et al., 2012). These drugs have a variety of mechanisms of action, and this allows combinations that target variable sources of BP elevation. **Table 4** summarizes commonly used antihypertensive medications and their major characteristics.

Table 3 Antihypertensive medication classes and their indications based on patients characteristics and comorbidities (James et al., 2014; Williams et al., 2018)

A. Patients without major medical conditions	*First-line drug*	*Add a second drug (to reach target BP)*	*Add a third drug (to reach target BP)*
African descent	CCB or thiazide diuretic	ARB or ACEI	Combination of CCB plus ACEI or ARB plus thiazide diuretic
White and other non-African descent (age < 60 years)	ARB or ACEI	CCB or thiazide diuretic	Combination of CCB plus ACEI or ARB plus thiazide diuretic
White and other non-African descent (age ≥60 years)	CCB or thiazide diuretic; ARB or ACEI also effective	ARB or ACEI; CCB or thiazide diuretic if ARB or ACEI used first	Combination of CCB plus ACEI or ARB plus thiazide diuretic
B. Patients with medical conditions	*First-line drug*	*Add a second drug (to reach target BP)*	*Add a third drug (to reach target BP)*
Diabetes (African descent)	CCB or thiazide diuretic	ARB or ACEI	Alternative 1st drug (CCB or thiazide diuretic)
Diabetes (white and other non-African descent)	ARB or ACEI	CCB or thiazide diuretic	Alternative 2nd drug (CCB or thiazide diuretic)
Coronary artery disease	Beta-blocker plus ARB or ACEI	CCB or thiazide diuretic	Alternative 2nd drug (CCB or thiazide diuretic)
Symptomatic heart failure	Beta-blocker plus ARB or ACEI	Add diuretic and spironolactone regardless of BP	CCB can be added if needed for BP control
Stroke	ACEI or ARB	CCB or thiazide diuretic	Alternative 2nd drug (CCB or thiazide diuretic)
Chronic kidney disease	ARB or ACEI	CCB or thiazide diuretic	Alternative 2nd drug (CCB or thiazide diuretic)

Table 4 Antihypertensive medications and their major characteristics (Katzung et al., 2012; DiPiro et al., 2016)

Class	*Subclass*	*Drug*	*Usual dose range (mg/day)*	*Frequency*	*Comments*
ACEIs		Captopril	12.5–150	BID or TID	• Hyperkalemia and acute kidney failure may occur.
		Enalapril	5–40	OD or BID	• Dry cough
		Fosinopril	10–40	OD	• Teratogenic
		Lisinopril	10–40	OD	• Starting dose should be reduced to 50% in patients who are on a thiazide diuretic or the elderly due to risks of hypotension
		Perindopril	4–16	OD	
		Ramipril	2.5–10	OD or BID	
ARBs		Candesartan	8–32	OD or BID	• May cause hyperkalemia and acute kidney failure
		Irbesartan	150–300	OD	• Does not cause dry cough
		Losartan	50–100	OD or BID	• Teratogenic
		Telmisartan	20–80	OD	• Starting dose should be reduced to 50% in patients who are on a thiazide diuretic or the elderly due to risks of hypotension
		Valsartan	80–320	OD	
Calcium channel blockers	Dihydropyridine	Amlodipine	2.5–10	OD	• Avoid short-acting dihydropyridines such as immediate-release nifedipine and nicardipine
		Felodipine	5–20	OD	
		Nicardipine SR	60–120	BID	• Beneficial to use in Raynaud's syndrome
		Nifedipine	30–90	OD	
	Non-dihydropyridine	Diltiazem	180–360	BID	• Extended-release products are used as anti-hypertensives
		Verapamil	80–120	OD	
Diuretics	Thiazide	Chlorthalidone	12.5–25	OD	• Usually taken in morning to avoid nocturnal diuresis
		Hydrochlorothiazide	12.5–50	OD	• Thiazides are more effective anti-hypertensives than loop diuretics
		Indapamide	1.25–2.5	OD	
		Metolazone	2.5–10	OD	• May exacerbate hyperglycemia and hyperlipidemia
					• Use with caution in patients with gout
	Loop	Bumetanide	0.5–4	BID	• Evening or night dose to be avoided
		Furosemide	20–80	BID	• High dose may be needed for patients with renal failure or heart failure
		Torsemide	5–10	OD	• Preferred over thiazides in patient with renal dysfunction and resistant hypertension

(*Continued*)

Table 4 Antihypertensive medications and their major characteristics (Katzung et al., 2012; DiPiro et al., 2016) (*cont.*)

Class	*Subclass*	*Drug*	*Usual dose range (mg/day)*	*Frequency*	*Comments*
	Potassium sparing	Amiloride Triamterene	5–10 50–100	OD or BID OD or BID	• Weak diuretic • May cause hyperkalemia • Used in combination with a thiazide to minimize hypokalemia • Does not significantly lower BP • Reserved for patients experiencing diuretic-induced hypokalemia; • Avoid in patients with CKD
	Aldosterone antagonist	Eplerenone Spironolactone	50–100 25–50	OD or BID OD or BID	• Dose in the morning and late afternoon (when twice daily) to avoid nocturnal diuresis • May cause hyperkalemia. • Eplerenone is contraindicated in patients with an estimated CrCl $<$50 mL/min, elevated serum creatinine and type 2 diabetes with microalbuminuria. • Spironolactone used as add-on therapy in resistant hypertension • Avoid spironolactone in patients with CKD (estimated CrCl $<$30 mL/min.
β-Blocker	Cardioselective	Atenolol Betaxolol Bisoprolol Metoprolol tartrate Metoprolol succinate extended release	25–100 5–20 2.5–10 100–400 50–200	OD OD OD BID OD	• Abrupt discontinuation may cause rebound hypertension • Non-selective at high doses • Exacerbate asthma • May be used in patients with atrial tachyarrhythmia or preoperative hypertension
	Nonselective	Nadolol Propranolol Timolol	40–120 160–480 10–40	OD BID OD	• Abrupt discontinuation may cause rebound hypertension • Inhibit β_1- and β_2-receptors • Exacerbate asthma • Offers benefits in patients with essential tremor, migraine, thyrotoxicosis and portal hypertension
	Intrinsic sympathomimetic activity	Acebutolol Carteolol Pindolol	200–800 2.5–10 10–60	BID OD BID	• Abrupt discontinuation may cause rebound hypertension • Partially stimulate β-receptors • Contraindicated in patients post-myocardial infarction
	Mixed α- and β-blockers	Carvedilol Labetalol	12.5–50 200–800	BID BID	• Abrupt discontinuation may cause rebound hypertension • α-blockade properties cause vasodilation and orthostatic hypotension
	Cardioselective and vasodilatory	Nebivolol	5–20	OD	• Abrupt discontinuation may cause rebound hypertension • Does not result in more orthostatic hypotension

The Role of Pharmacist in the Management of Hypertension

Pharmacist cares for patients with cardiovascular diseases (CVDs) in general (Dunn et al., 2015; Swieczkowski et al., 2016), and hypertension in particular has been widely reported in the literature (Carter et al., 2009a,b; Morgado et al., 2011; Di Palo and Kish, 2018). The pharmacist has an important role in the care and management of patients with CVDs through the provision of pharmaceutical care (Dunn et al., 2015; Swieczkowski et al., 2016). The pharmacist is also considered as an integral member of the multidisciplinary CVD healthcare teams (Brush et al., 2015; Dunn et al., 2015). Pharmacists providing care to patients with CVDs can be generalists or specialists in the cardiology pharmacy practice area. Specifically, cardiology pharmacy practice area focuses on the pharmaceutical care of patients with CVDs. Clinical pharmacists specializing in cardiology function and practice are an integral members of collaborative healthcare teams in a variety of settings, including, to coronary care units, cardiovascular intensive care units, telemetry units, medical wards, medical intensive care units, and other specialty outpatient clinics.

The role of the pharmacist in CVD settings has been widely reported in the literature and by relevant professional healthcare organizations (Dunn et al. 2015; Brush et al., 2015). In a perspective paper, Dunn et al. provide pertinent information on the clinical pharmacist's role in the care of patients with CVD, their training, certification, and contribution in a variety of practice models (Dunn et al., 2015). The paper indicated that pharmacist has a substantial role in both inpatient and ambulatory care settings, largely through medication therapy management, optimization of drug therapy, patient education and counseling, and transition of care activities focusing on medication reconciliation and patient education.

Evidence of Benefit of Pharmacist Interventions in Hypertension Management

The 2017 guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults issued by ACC and AHA has redefined hypertension, which places 46% of adult Americans as hypertensive (Whelton et al., 2018). Hypertension remains a modifiable risk factor of CVDs. Unfortunately, many patients do not achieve their therapeutic targets, owing to non-adherence to medications. Therefore, pharmacist has an opportunity to improve medication adherence and prevent clinical inertia in patients with uncontrolled high BP (Carter et al., 2009a,b; Di Palo and Kish, 2018). There are several approaches, services, and models of care provided by pharmacists to improve outcomes in patients with hypertension.

Evidence from clinical studies has clearly demonstrated the value of pharmacist intervention in significantly improving medication adherence and reducing BP (Di Palo and Kish, 2018). Since hypertension is a significant risk factor for CVD, stroke, and mortality, there is a considerable opportunity to improve outcomes by preventing the onset CVDs through optimal BP control. The risk of CVD morbidity, stroke, and mortality is particularly marked when there is insufficient control of BP.

Emerging Role of Pharmacist and Practice Models in Managing Hypertension

Recent hypertension clinical practice guidelines (Chobanian et al. 2003; Whelton et al., 2018) address the importance of improving adherence to antihypertensive medications, highlighting the role of healthcare professionals, including pharmacists. In this regard, pharmacists have been playing a key role in developing approaches and services to improve medication adherence and to prevent clinical inertia in hypertension management. The role of pharmacist in the management of hypertension is multifaceted and includes medication management, patient counseling and disease state education. Owing to their easy access to the public, pharmacists are highly placed to address the gap in the management of hypertension and should interact with patients to improve awareness of disease, identify CVD risk factors, and educate patients on anti-hypertensive medications adherence. Pharmacists can also work with other healthcare providers, especially physicians, to promote optimal treatment of hypertension. One key role is in the optimization of drug doses as an initial step, especially in patients receiving antihypertensive medications with documented benefits (e.g., ACEI in patients with concomitant CKD or post-MI). Pharmacists should also promote the use of combination therapy as a means to achieve target BP.

The focus of pharmacist's interventions in hypertension management have largely been on: (1) patient education and counseling on medications and disease state; (2) clinical recommendations to physicians about therapy management (identification and resolution of drug therapy problems); (3) direct medication therapy management with the patient (including monitoring and modification of therapy) (Tonna et al., 2007; Green et al., 2008; Carter et al., 2009a,b; Morgado et al., 2011; Carter et al., 2012; Santschi et al., 2015; Di Palo and Kish, 2018). Some of the activities which pharmacist can perform include the following:

- Assessment, screening, and counseling patients about cardiovascular risk and BP control.
- Recommendations to physicians about therapy management.
- Reviewing antihypertensive medications.
- Prescribing medications and modification of drug therapy.
- Educating patients on HBPM.
- Medication reconciliation in inpatient and outpatient settings.
- Ordering relevant laboratory tests.
- Referrals to physicians or general practitioners.
- Follow-up visits with the patients including BP monitoring.

Medication Therapy Management

Pharmacist-led medication therapy management service in patients with hypertension has demonstrated evidence of benefits in improving medication adherence, BP control, and cost-savings (Isetts et al., 2008; Di Palo and Kish, 2018). Medication therapy management is defined as a service or group of services that optimize therapeutic outcomes for individual patients (Bluml, 2005). In the USA, Canada, and other countries, clinical pharmacists in institutionalized and ambulatory care settings routinely provide medication therapy management to improve outcomes and minimize adverse drug events. Studies provide evidence that having pharmacist directly involved in drug therapy management improve therapy goals as well as improved economic outcomes (Isetts et al., 2008; Di Palo and Kish, 2018). A comprehensive medication management is provided through collaborative drug therapy management, which is an agreement between a physician and a pharmacist that allows the pharmacist to initiate, modify or discontinue drug therapy within a certain scope of practice (Di Palo and Kish, 2018). These collaborative practice agreements have demonstrated significant improvement in antihypertensive medication adherence, BP control, and utilization of evidence-based therapy.

Team-based Interventions

The management of hypertension using team-based approach involves the coordinated efforts of healthcare providers and inter-disciplinary clinicians including physicians, pharmacists, nurses, and others to deliver holistic and high quality care (Di Palo and Kish, 2018). Several studies have reported positive outcomes of pharmacist collaboration with other healthcare professionals. For

example, Carter et al. (2009a,b) in a cluster randomized controlled trial reported that a physician and pharmacist collaboration has resulted in better mean BP control compared to a control group. In addition, collaboration between pharmacist and nurse has also proven to be beneficial (Carter et al., 2012). Overall, team-based care involving pharmacist was associated with improved outcomes including medication adherence and BP control (Carter et al., 2009a,b; Morgado et al., 2011). A US Surgeon General's report documents the benefits of pharmacist delivered care in many settings and recommends optimizing the pharmacist's role in delivering patient centered care and disease prevention services in collaboration with physicians or as part of a healthcare team (Giberson et al., 2011).

Telehealth in Hypertension

The delivery of health services through various telecommunication pathways is increasing, especially with the advancement of mobile technology. With the advancement in information and communication technology, pharmacists are well positioned to provide telehealth and telemonitoring interventions that may potentially improve medication adherence and other clinical outcomes in patients with hypertension (Di Palo and Kish, 2018). Telehealth interventions may encompass short message service (SMS) reminders, telephone calls, digital pill counts, using mobile applications to track adherence, etc. The telemonitoring by pharmacists has also been demonstrated in hypertension. Green et al. (2008) had reported the effect of HBPM and web communication coordinated by a pharmacist on BP control. Overall, patients who received the home monitoring and web training plus pharmacist care have experienced greater reductions in BP compared with usual care (RR = 3.32; 95% CI, 1.86–5.94) (Green et al. 2008).

Conclusion

In conclusion, the care and interventions provided by pharmacists in patients with hypertension could make a substantial contribution to reducing clinical inertia and the CVD risks associated with the condition. Given their drug therapy expertise and patient counseling skills, pharmacists can play a significant role in the management of hypertension including monitoring BP, counseling and education, and managing patients' medications. Pharmacists with varying degrees of prescriptive authority can modify and optimize medication regimens to achieve better health outcomes. Furthermore, with their easy accessibility, pharmacists can also implement timely screening and prevention strategies among high-risk groups. Several models exist that allow pharmacists to provide patient-centered care to patients with high BP. However, practices differ from one country to another and caution should be exercised to practice within the context of the pharmacist's scope of practice and what is legally allowed in a particular country. Overall, pharmacist care and intervention in patients with hypertension could have meaningful results in terms of clinical and economic outcomes. The integration and recognition of pharmacists as key members of hypertension management can open the door of their involvement in other related chronic diseases.

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Acute Coronary Syndrome

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Learning Objectives

- Develop an understanding into signs and symptoms of ACS and the process involved in making a diagnosis
- Understand the various clinical investigations used to make a diagnosis in ACS
- Understand the different treatment regimens in the acute and long term management in patients with STEMI and NSTE-ACS
- Appreciate the role and where pharmacists can be involved in managing patients with ACS
- Recognize the importance of life-style modification as a preventative strategy for future episodes of ACS

Take-Home Messages

- Cardiac troponin levels (I and T) are the most sensitive biomarkers used to determine myocardial infarction
- ECG is an important tool which will enable the correct diagnosis: NSTE-ACS or STEMI
- All patients with suspected ACS will have a risk assessment conducted to guide optimal clinical management
- Acute management of ACS involves administering parenteral opioids and glyceryl trinitrate to provide pain relief caused by ischemia
- In confirmed STEMI diagnosis reperfusion therapy is recommended within 12 hours of symptoms and 2 hours from diagnosis of STEMI
- After acute management of STEMI the long term management will involve the prescribing of DAPT, beta-blockers, statins, ACE inhibitors
- In patients with NSTE-ACS aspirin, antithrombin therapy and beta-blockers are used in the acute management stage
- Long term management of NSTE-ACS is very similar to STEMI management
- Lifestyle modification such as smoking cessation or choosing a cardio-protective diet can significantly reduce future cardiovascular events
- Pharmacogenomics will become even greater in the future for managing patients with ACS

Introduction

Acute coronary syndromes (ACS) form a subgroup of coronary heart disease (CHD) that usually present with abrupt onset of symptoms, mainly at rest, caused by obstruction to cardiovascular blood flow. Reduction of oxygenated blood to cardiac tissue results in myocardial ischemia which if prolonged can lead to death of cardiac muscle cells. This chapter will focus on the key

presentations of ACS: unstable angina (UA) and Myocardial Infarction (MI), both of which are medical emergencies. MI can be further classified as either Non-ST-elevated MI (NSTEMI) or ST-elevated MI (STEMI), both of which are a major cause of premature death worldwide. UA and NSTEMI can have identical clinical presentation and have more recently been grouped together by the term Non-ST Elevation-ACS (NSTE-ACS) (Amsterdam et al., 2014).

Etiology

ACS is triggered by the erosion and rupture of an atheromatous plaque within the coronary artery wall. This encourages thrombosis formation and obstruction to blood flow resulting in myocardial ischemia. It is worth noting that "ischemia" is defined as a reduction of myocardial oxygen for less than 20 minutes, which causes damage that is reversible (Hashmi and Al-Salam, 2015). Infarction is characterized as oxygen deficiency for longer than two hours, resulting in irreversible damage. If there is complete blockage of the coronary artery this will result in a STEMI. NSTE-ACS is caused by partial coronary arterial blockage. The main management strategy is to restore coronary blood flow with either thrombolysis or angioplasty (see later in chapter; pharmacotherapy).

Plaques are formed by the process of coronary atherosclerosis beginning in the patient's late teens or early twenties. Initially a fatty streak appears in the coronary artery wall, progressing over time to form atherosclerotic lesions in the coronary arteries (Worrall and Fletcher, 2007). This, coupled with endothelial dysfunction facilitates plaque formation (Santos-Gallego et al., 2014). The dysfunction causes the adhesion of monocytes to the area. Platelets are activated and aggregate which, through various pathological processes, causes macrophages to be internalized into the developing plaque (Santos-Gallego et al., 2014). Finally, circulating lipids penetrate the plaque and are laid down as cholesterol. As the plaque increases in size, cell death occurs at the center, resulting in a lipid rich core coated by an external fibrous plaque. If this plaque becomes less stable due to physical stress or erosion, it will rupture exposing the lipid core (Scott, 2004). This promotes activation of thrombus formation causing partial or complete blockage.

Epidemiology

More people die worldwide from cardiovascular disease each year than from any other cause (The World Health Organisation, 2017). While mortality from CHD has gradually declined within Western countries since the 1970s, it remains a major cause of premature death and disability (Sanchis-Gomar et al., 2016; Scott, 2004). CHD itself is the largest single cause of death in the United Kingdom with 73,680 deaths recorded in 2012 (Townsend et al., 2014). The 2016 Heart Disease and Stroke Statistics update of the American Heart Association estimated that approximately every 42 seconds, an American person will suffer from an MI (Sanchis-Gomar et al., 2016). It is also thought that more than 780,000 persons will experience an ACS event each year in the USA (Amsterdam et al., 2014). In Australia, there were approximately 68,200 ACS events in 2012 (Chew et al., 2016). There is still disparity in overall mortality rates however, with differences between ethnic groups and socio-economic background. For example, deaths from ACS events occur on average at younger ages in low- and middle-income countries and frequently affect the poorer communities within these settings (Vedanthan et al., 2014). Approximately 80% of the global burden of CHD occurs within low- and middle-income countries (Yusuf et al., 2004).

Intrinsic patient factors that increase the risk of ACS include age, gender, and family history. In an American observational study, of all patients presenting with NSTE-ACS between 2001 and 2003 (n = 64,775), the average age of presentation with an ACS diagnosis was 68 years and the male:female ratio was 3:2 (Amsterdam et al., 2014; Peterson et al., 2006).

There are many modifiable risk factors that can reduce a patient's chance of developing CHD and experiencing an ACS event (see **Fig. 1**). A review of evidence by O'Flaherty et al. in 2013 concluded that the contribution of lifestyle modification was approximately equal to that of drug and interventional cardiovascular treatments in reducing coronary mortality (Flaherty et al., 2013; Timmis, 2015).

ICD-10 Classification

The World Health Organisation classifies ACS within the ICD codes I20 to I25 (Ischaemic Heart Diseases) (The World Health Organisation, 2014). Unstable angina is given code I20.0 (an additional code for hypertension can be added if required). MI specified as acute or with a stated duration of 4 weeks or less from onset is given code I21 with various subcodes available for defining location.

Universal Definition

The Third International Definition (Thygesen et al., 2012; Timmis, 2015) defines acute MI as presentation of chest pain associated with:

Non modifiable risk factors:

- Age—Over 83% of people who die from CHD are aged 65 or older.
- Gender–Men have a greater risk of developing CHD than women. Throughout the UK, prevalence of MI in men is almost three times greater than that found in women (Townsend et al., 2014).
- Early menopause–A meta analysis of 18 studies demonstrated a modest effect of early menopause on the risk of developing CHD (Atsma et al., 2006).
- Family history–Risk is doubled in those with a first degree relative who develops pre mature (age <60 years) CHD. Additional first and, to a lesser extent, second degree relatives will further increase this risk.
- Race–Certain populations are at increased risk. Some of this is due do the differences in prevalence of type II diabetes mellitus. For example, in Black Caribbean and Indian males the prevalence rates are 9.5% and 9.2% respectively, compared with 3.8% in the general UK population (Scarborough et al., 2010).

Modifiable risk factors:

- Smoking status–Tobacco smoke was one of the first risk factors identified by the Framingham Heart study in 1960 to increase the chance of developing CHD. It is estimated that up to 20,000 UK deaths each year from cardiovascular disease can be attributed to smoking.
- High blood cholesterol–An increased level of low-density lipoprotein (LDL) raises the risk, while high-density lipoprotein (HDL) may be protective.
- High blood pressure–Risk of cardiovascular disease is directly related to higher levels of blood pressure. Unhealthy diet is estimated to be responsible for half of hypertension with physical inactivity and obesity accounting for 20% each (Townsend et al., 2014).
- Exercise–Physical inactivity is a risk factor for CHD.
- Obesity–People who have excess body fat are more likely to develop CHD even if they have no other risk factors. This is especially true of those with a high hip-to-waist ratio (central abdominal obesity).
- Diabetes mellitus–Diabetes doubles the risk of developing CHD and is even greater if blood glucose is not well controlled. People with diabetes are about three times more likely to experience an MI.

Figure 1 Risk factors for developing CHD. *Adapted from: Worrell and Fletcher 2007—will need permission to use.*

Increase or decrease in troponin levels with at least one value >99th centile of upper reference limit, plus at least one of the following:

- Symptoms of ischemia
- New ST segment or T wave changes or new left bundle branch block on electrocardiography
- Development of pathological Q waves on electrocardiography
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or at postmortem examination

Diagnosis

Signs and Symptoms

Diagnosis of ACS is time critical and inappropriate identification is associated with increased mortality (Timmis, 2015). Almost all people with suspected ACS require hospital admission or referral to confirm the diagnosis. Patients typically present with "gripping" or "crushing" chest pain that radiates to the arms, neck, or jaw and is often associated with sweating, pallor, and shortness of breath (Douglas et al., 2013; Scott, 2004; Worrall and Fletcher, 2007). ACS should be suspected in patients where this pain occurs at rest or with minimal exertion lasting for longer than 15 minutes and there is hemodynamic instability. Pain symptoms can last anywhere between 10 and 20 minutes (Amsterdam et al., 2014; Chew et al., 2016; National Institute for Health and Care Excellence, 2010a; Roffi et al., 2016). It is estimated that pain is absent in up to 30% of presentations (Douglas et al., 2013) and therefore the history of the presenting complaint should be considered along with a physical examination, serial 12-lead electrocardiography (ECG), troponin level and a holistic assessment of the patient's risk of ACS (Chew et al., 2016; National Institute for Health and Care Excellence, 2010a). Patients may also present with atypical symptoms of ACS such as epigastric pain, indigestion, stabbing or pleuritic pain, and increasing shortness of breath which require further investigation. Older patients, women, and those with diabetes mellitus, impaired renal function, or dementia are more likely to present with these atypical symptoms (Amsterdam et al., 2014).

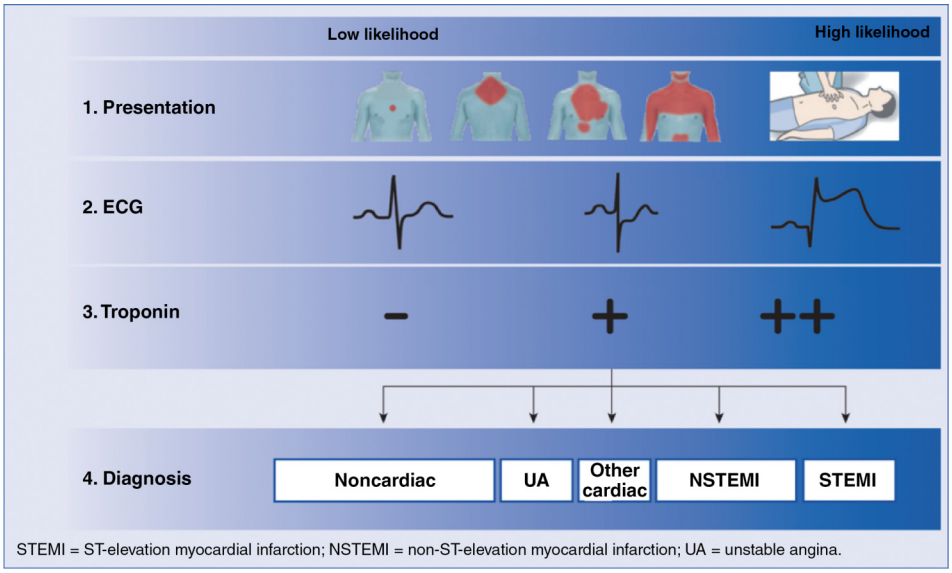

Figure 2 ECG changes and associated troponin levels which help in making a diagnosis in patients presenting with chest pain. *STEMI*, ST-elevated myocardial infarction; *NSTEMI*, non-ST elevated myocardial infarction; *UA*, unstable angina *From: 2015ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur. Heart J. 37(3) (2016) 267–315. https://doi.org/10.1093/eurheartj/ehv320. © The European Society of Cardiology 2015. All rights reserved.*

Clinical Investigations

A resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS and should be obtained within 10 minutes of presentation (Roffi et al., 2016). ECG changes indicative of NSTE-ACS include pathological Q waves, left bundle branch block, or ST-segment and T-wave abnormalities (ST depression, transient ST-elevation, or new T-wave inversion) (National Institute for Health and Care Excellence, 2010b; Roffi et al., 2016; Thygesen et al., 2012). Persistent ST-elevation or anterior ST depression is indicative of a STEMI. While the ECG can be useful in identifying ischemia, it is not definitive and these changes may not be seen for some patients (Scott, 2004). The only definitive ECG change is the development of a Q wave, which generally persists over time (giving no real indication as to time of ACS event) (Scott, 2004). Please refer to **Fig. 2** to see ECG changes and potential diagnosis.

Troponins I and T are specific and sensitive regulatory muscle proteins which demonstrate cardiac necrosis and are the recommended biomarker for MI (Chew et al., 2016; National Institute for Health and Care Excellence, 2010a; Thygesen et al., 2012). Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin (Roffi et al., 2016). Troponin should be measured at the time of presentation and repeated at clearly defined intervals in patients with suspected ACS (Chew et al., 2016). Levels tend to rise within four hours of infarction, peak at 12 hours and remain elevated for several days (Scott, 2004).

Unstable angina causes only small increases in troponin levels due to the reduced severity of injury to myocytes which can only be detected with high sensitivity assays (Timmis, 2015). Other conditions that directly or indirectly damage heart muscle (such as arrhythmias, pericarditis, pulmonary emboli, and myocarditis) can also cause an increase in serum troponin (Shah et al., 2013) so careful interpretation of the troponin level alongside the other presenting features is needed.

Additional clinical investigations can include the following tests:

- Echocardiography which helps in detecting heart wall abnormalities or alternative pathologies associated with chest pain (Roffi et al., 2016).
- Cardiac magnetic resonance (CMR) imaging can be useful for the assessment of function and perfusion and for the detection of scar tissue. CMR can also be useful to exclude or detect ACS, to assess myocardial viability, and to detect myocarditis (Roffi et al., 2016).
- A chest X-ray is recommended in some guidance for the assessment of cardiac enlargement and identification of other non-coronary causes of chest pain where the diagnosis is yet to be established, though the utility of this investigation may be limited (Chew et al., 2016).

Differential Diagnosis

Chest pain is a hugely common presentation within the emergency department setting. It can be challenging to recognize ACS from symptoms of other conditions such as musculoskeletal pain and gastro-esophageal reflux disease. Studies performed in Australian

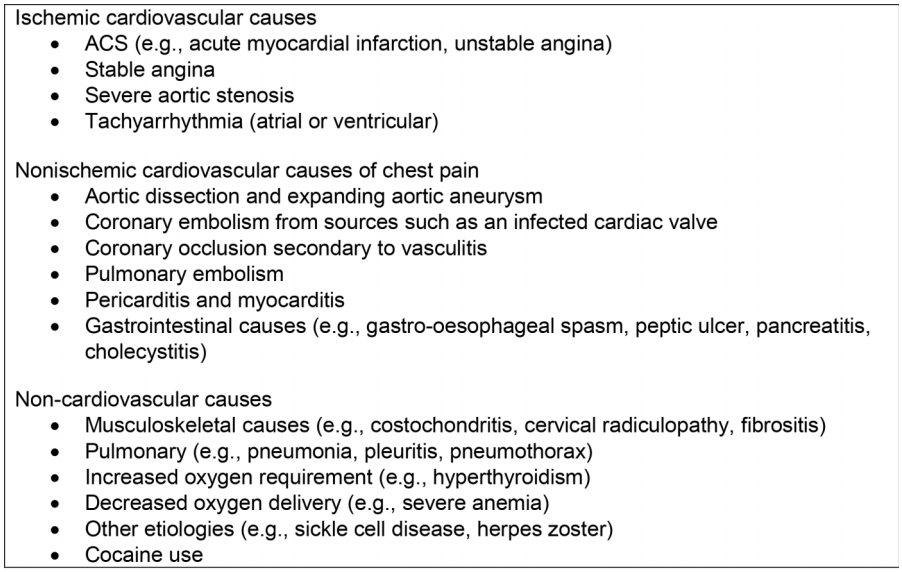

Figure 3 Differential diagnosis of causes of chest pain. *Taken from National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016 Permission needs to be sought.*

emergency departments demonstrated that the prevalence of different diagnostic groups in patients presenting with acute chest pain are: 2%–5% STEMI, 5%–10% NSTEMI, 5%–10% UA, 15%–20% other cardiac conditions, and 50%–70% noncardiac diseases, highlighting the importance of differential diagnosis (Chew et al., 2016). In fact, it is estimated that over 500,000 patients present with chest pain within Australia each year, but less than 20% of these patients will have a confirmed diagnosis of ACS (Chew et al., 2016; Kelly, 2012; Macdonald et al., 2011).

A systematic differential diagnosis must be made (Fig. 3) taking into consideration the patient's signs, symptoms, and investigations (Douglas et al., 2013). The European Society of Cardiology recommends that aortic dissection, pulmonary embolism, and tension pneumothorax should always be considered in the differential diagnosis of NSTE-ACS, because they are potentially life-threatening but also treatable (Roffi et al., 2016).

Prognosis

About 15% of people who have an acute MI in the US will die of it, half within the first hour of symptoms (Mozaffarian et al., 2016). Prognosis for patients with STEMI varies depending on time to presentation after onset of chest pain and time to treatment after presentation. Prognosis is improved by early reperfusion, adherence to appropriate medical therapy, and risk factor modification. Patients with elevated troponin levels have a worse prognosis than those with normal troponin levels (Setiadi et al., 2009). Adherence to evidence-based medicine has been shown to have better patient outcomes (Grech and Ramsdale, 2003). In-hospital death and reinfarction can affect 5%–10% of patients. Major bleeding as defined by the Bleeding Academic Research Consortium (BARC) or a raised Thrombolysis in Myocardial Infarction (TIMI) bleeding score is associated with worse 1-year mortality (Kikkert et al., 2014).

Patients who have experienced NSTE-ACS have a high risk of morbidity and death from a future event. The rate of sudden death in patients who have had an MI is 4–6 times the rate in the general population (Zaman and Kovoor, 2014). Life-threatening ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) occurring after 48 hours from the index ACS indicates a poor prognosis, and are most frequently associated with left ventricular dysfunction (Moss et al., 2002). The benefit of implantable cardioverter-defibrillators, for both primary and secondary prevention, in patients with significant left ventricular dysfunction has been well demonstrated. Implantation for primary prevention should be considered at a minimum of 40 days following hospital discharge based on current recommendations (Hohnloser et al., 2004).

Modern therapy for NSTE-ACS, particularly statins and revascularization, has decreased morbidity and mortality by reducing the likelihood of cardiogenic shock, recurrent MI, and death. However, these benefits are offset by the mortality associated with trends of older age in patients who present with ACS (Jeger et al., 2008).

Risk Assessment

Various validated risk stratification tools have been developed to help guide optimal clinical management of those patients with confirmed ACS and are commonly used in practice (Backus et al., 2011; Fhadil et al., 2015). These scoring tools formally assess

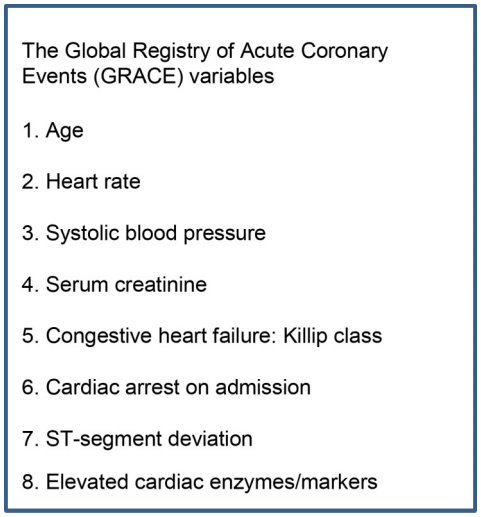

Figure 4 Variables used in the calculation of 6 month mortality specific for the GRACE tool. *Permission to use will be needed from: Fhadil, S., Wright, P., Antoniou, S., 2015. Non-ST elevation acute coronary syndrome: an update. Pharm. J. 295.*

Table 1 Risk stratification outcome scoring tool (Fhadil et al., 2015, permission needed)

Predicted 6-month mortality	*Risk of future adverse cardiovascular events*
1.5% or below	Lowest
>1.5%–3.0%	Low
>3.0%–6.0%	Intermediate
>6.0%–9.0%	High
Over 9.0%	Highest

individual risk of future adverse cardiovascular events and inform risk/benefit decisions regarding treatment using an established risk scoring system that predicts 6-month mortality (National Institute for Health and Care Excellence, 2010b). Examples that are validated in large populations and used internationally are the **T**hrombolysis **I**n **M**yocardial **I**nfarction (TIMI) risk score, the **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score and the **P**latelet glycoprotein IIb/IIIa in **U**nstable angina: **R**eceptor **S**uppression **U**sing **I**ntegrilin (eptifibatide) **T**herapy (PURSUIT) score. The National Institute for Clinical Excellence (2010) in England and the European Society of Cardiology (2016) both advocate the use of the GRACE tool, however American (2014) and Australian (2016) guidelines are less prescriptive.

In a study comparing the various risk stratification tools, Yan et al. (2007) found that they all demonstrated good discrimination for in-hospital death. Compared with TIMI, both PURSUIT and GRACE were found to better at discriminating in-hospital and 1-year mortality in patients presenting with a wide range of ACS (Yan et al., 2007).

GRACE: An Example of Risk Stratification in Practice

GRACE uses eight clinical variables to risk stratify patients (see Fig. 4). To calculate the GRACE score, the patient is assigned a series of points for each of the clinical variables, which is most commonly converted to determine the six month mortality. Patients scoring ≤88 points are deemed to be at low risk (<3%) of death postdischarge to six months, 89–118 is considered to be at intermediate risk (3–6%), and >118 is regarded high risk (>6%) (see Table 1). This risk stratification can be used by health care professionals to make informed decisions about the patient's management.

Pharmacological Management of Acute Coronary Syndromes

The pharmacotherapy of ACS will be described in the section below in two parts: management of ST-elevated myocardial infarction (STEMI) and management of non-ST-elevated acute coronary syndrome (NSTE-ACS). These conditions are managed similarly, and therefore will be discussed concurrently in one part.

The general pathway for the management of ACS is outlined in Fig. 5 and will be referred to throughout the next sections.

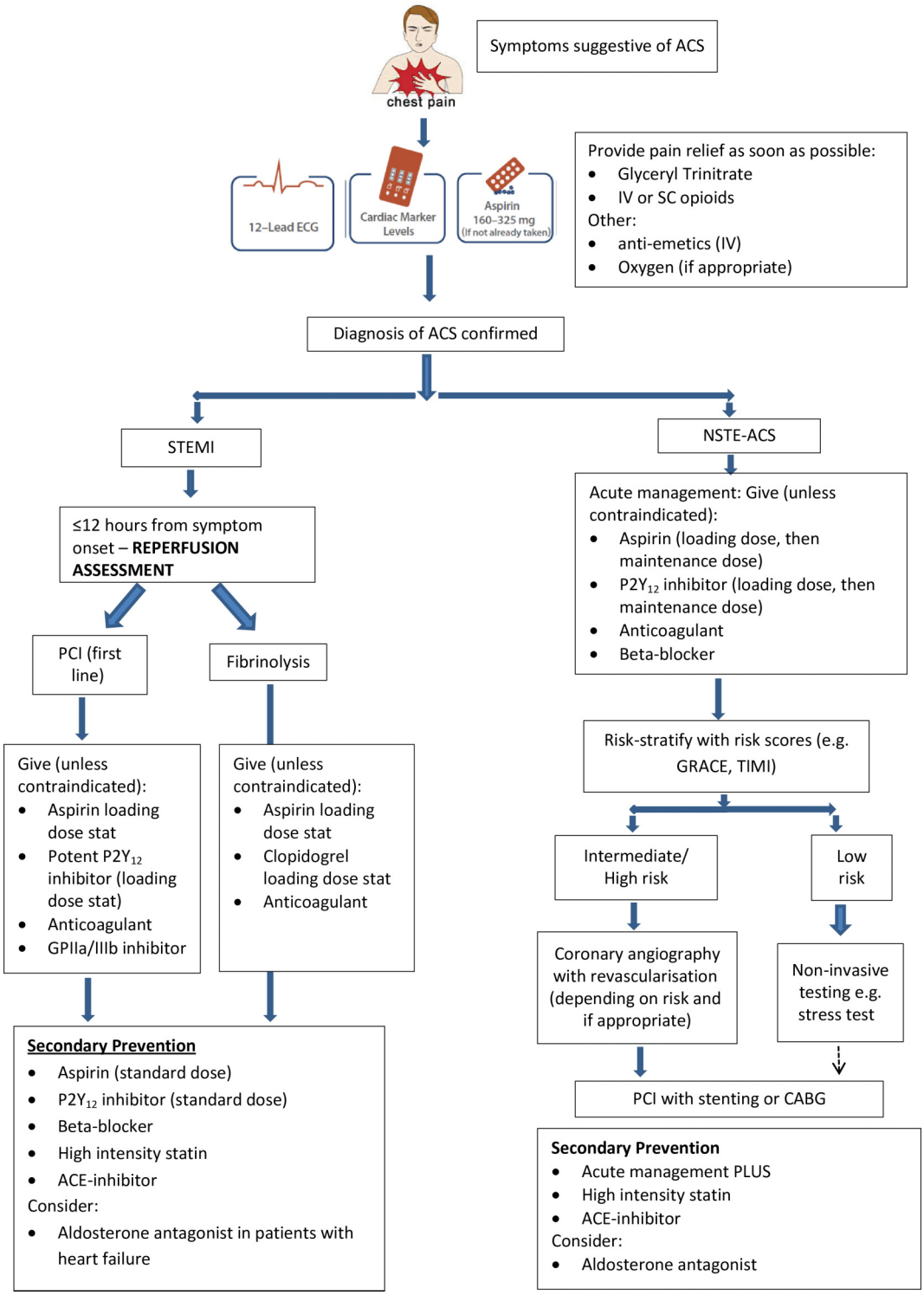

Figure 5 ACS pharmacotherapy management.

Pharmacotherapy Upon Presentation of Chest Pain Symptoms

All patients presenting with chest discomfort or other symptoms suggestive of ACS should be considered high priority medical cases. People who present with high-risk features such as ongoing chest pain, difficulty breathing, faintness, or palpitations should be admitted to hospital as soon as possible. Symptoms suggestive of ACS have been outlined in the "Signs and Symptoms" section earlier in the chapter.

The aim of initial treatment for all patients presenting with symptoms of ACS is provide pain relief caused by ischemia and to prevent further myocardial infarction (MI) and death. Aspirin is normally offered as soon as possible upon presentation of ACS, as a single loading dose (e.g., 300 mg at once in the UK). Immediate pain relief may be achieved with either glyceryl trinitrate (GTN), given sublingually or intravenously (IV); or parenteral opioids such as intravenous morphine (Chew et al., 2016; O'Gara et al., 2013).

GTN administered intravenously is more effective than sublingually with regard to symptom relief and regression of ST depression (Borzak et al., 1998). However, in certain cardiology units internationally, sublingual GTN is usually given first line, with IV GTN given if pain relief is not achieved after administration of sublingual GTN and IV morphine. Nitrates are contraindicated in patients who have recently taken phosphodiesterase type 5 inhibitors (either within 24 hours for sildenafil and vardenafil and 48 hours for tadalafil) due to the risk of severe hypotension (Schwartz et al., 2001).

Parenteral opioids such as diamorphine or morphine are commonly used to manage pain in ACS. An antiemetic (such as metoclopramide) can be given intravenously alongside parenteral opioid administration for the relief of opioid-induced nausea and vomiting. However, evidence suggests opioid use may slow the gastrointestinal absorption resulting in delayed onset of action of oral antiplatelet agents (e.g., clopidogrel, ticagrelor, and prasugrel) (Parodi et al., 2015).

Oxygen should be given to patients with evidence of hypoxemia ($SaO_2 < 90\%$), pulmonary edema or continuing MI.

Monitoring should be carried out during the initial phase of ACS for pain and symptom control, pulse, blood pressure, oxygen saturation, and heart rhythm. Clinical judgment should be used to determine how often monitoring should be done.

Confirmed ST-Elevated Myocardial Infarction Diagnosis

Many deaths occur very early after STEMI due to ventricular fibrillation (VF) (Larsen and Ravkilde, 2012). In patients following cardiac arrest and found to have ST-segment elevation on an ECG, an appropriate reperfusion strategy should be initiated as soon as possible.

Reperfusion

Reperfusion therapy, in this context, is a medical treatment to restore blood flow to blocked arteries after MI. There are two main types of reperfusion therapy: primary percutaneous coronary intervention (PCI) and fibrinolytic therapy.

Primary PCI is the preferred reperfusion therapy in patients with STEMI within 12 hours of symptom onset and within 120 minutes from the diagnosis of STEMI (Ibanez et al., 2017; O'Gara et al., 2013). PCI has been used over two decades and has evolved from balloon angioplasty to bare metal stent (BMS) implantation, drug eluting stents (DES), and more recently, biodegradable polymer stents (Serruys et al., 2009). The evolution of PCIs has been driven to help reduce the risk of stent thrombosis (ST). PCI has now become common practice where more than 300,000 patients undergo PCI procedures in the United States each year (Riley et al., 2011).

Fibrinolytic therapy or fibrinolysis is an alternative to primary PCI, particularly if PCI cannot be carried out within the timeframe as outlined above. Primary PCI is superior to fibrinolysis in reducing mortality, reinfarction, and stroke (Keeley et al., 2003). There is no current trial data which examine the extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis. The European (Ibanez et al., 2017) and UK guidelines (National Institute for Health and Care Excellence, 2013) recommend that the absolute time from STEMI diagnosis to PCI-mediated reperfusion should be up to 120 minutes. The American guideline (O'Gara et al., 2013) recommends 90–120 minutes depending on the capacity of the center in which the patient first presents. The Australian and New Zealand (ANZ) guideline (Chew et al., 2016) recommends within 90 minutes of first medical contact. The European guideline also recommends that for fibrinolysis, the bolus injection of fibrinolytics should be administered within 10 minutes from the STEMI diagnosis (Ibanez et al., 2017), while the American and ANZ guidelines (Chew et al., 2016; O'Gara et al., 2013) recommend administration within 30 minutes. The recommendation by Ibanez et al. (2017) for the European guidelines for fibrinolysis is based on the STREAM trial, where the median time from randomization to bolus administration was 9 minutes (Armstrong et al., 2013).

Fibrinolytic agents prevent 30 early deaths per 1000 patients treated within 6 hours after symptom onset (Fibrinolytic Therapy Trialists, 1994). The largest absolute benefit of fibrinolysis is when treatment is offered within two hours of symptom onset (Boersma et al., 1996). The later the patient presents (particularly after 3 hours), the more consideration should be given to transfer the patient for primary PCI because the efficacy and clinical benefit of fibrinolysis decreases as the time from symptom onset increases (Pinto et al., 2011). Fibrinolytic therapy is associated with a small but significant increase in strokes, largely due to cerebral

hemorrhage (Fibrinolytic Therapy Trialists, 1994). The use of fibrinolytic therapy is therefore contraindicated in patients with the following (Chew et al., 2016):

- uncontrolled systolic blood pressure (BP > 180/110 mmHg),
- previous stroke/transient ischemic attack (TIA)
- prior intracranial hemorrhage
- current anticoagulation use
- Recent trauma/surgery
- Gastrointestinal bleeding in the last 4 weeks

In this cohort of patients, the use of primary PCI may be preferred to fibrinolysis regardless of "time to reperfusion" (Chew et al., 2016).

Choice of Fibrinolytic

The fibrinolytics that are available on the market at the time of writing this chapter include: tenecteplase, reteplase, alteplase, and streptokinase. Tenecteplase, reteplase, and alteplase are fibrin-specific agents while streptokinase is nonfibrin-specific (O'Gara et al., 2013). Fibrin-specific agents are preferred to streptokinase (Chew et al., 2016; Ibanez et al., 2017). This is because fibrin-specific agents were found in a large scale trial to have a superior survival benefit over streptokinase (GUSTO Investigators, 1993).

Streptokinase and alteplase have short half-lives (18 minutes and 5 minutes respectively) and must be administered IV. Reteplase and tenecteplase (5.5 hours and 1–2 hours respectively) have longer half-lives and can be administered as bolus injections (Khatib and Wilson, 2018). Fibrinolysis therapy is usually coadministered with adjunct pharmacotherapies such as aspirin, clopidogrel, and anticoagulants. These are discussed later in this chapter under "Pharmacotherapy for Fibrinolysis."

Acute Management in ST-Elevated Myocardial Infarction

This section outlines the pharmacotherapy for different reperfusion pathways in the acute phase immediately after diagnosis of STEMI. This section will first outline the different pharmacotherapies and the evidence supporting their use. Individual drugs and corresponding doses used are outlined in **Table 2**. Dosages are based on those outlined in the guidelines from European, American, Australia and New Zealand, and UK, where appropriate.

Pharmacotherapy for Primary Percutaneous Coronary Intervention

Primary PCIs are performed as the initial approach to reperfusion for patients in the acute phase of STEMI, where its benefits are sensitive to the speed with which it is performed, as discussed earlier in this section. In contrast, some patients with STEMI may undergo a PCI during hospitalization that is not considered primary (Oberhauser et al., 2009). The pharmacotherapy discussed below is adjunct to primary PCI procedure in the acute phase of STEMI.

Patients undergoing primary PCI should receive dual antiplatelet therapy (DAPT) and a parenteral anticoagulant. DAPT is a combination of aspirin and a $P2Y_{12}$ inhibitor. The choice of $P2Y_{12}$ inhibitor and duration of DAPT has an effect on the net benefit of PCI.

Aspirin

Aspirin can be given orally, or IV before primary PCI to ensure complete inhibition of thromboxane A2 (Dai and Ge, 2012; Khatib and Wilson, 2018). The oral dose of plain aspirin (non-enteric-coated formulation) should be 150–300 mg. It is unclear what the optimal dose for IV aspirin is to achieve complete inhibition of platelet aggregation. A recent randomized study showed that a single dose of 250 or 500 mg acetylsalicylic acid administered IV was associated with faster and more complete inhibition of thromboxane-related platelet aggregation compared to aspirin 300 mg orally (Zeymer et al., 2017).

$P2Y_{12}$ Inhibitors

There is limited evidence with respect to the timing of $P2Y_{12}$ inhibitor initiation in patients with STEMI. However, early initiation of a $P2Y_{12}$ inhibitor while the patient is being transported to a primary PCI center is common practice in Europe. Otherwise, patients should be initiated on $P2Y_{12}$ inhibitor at the time of primary PCI. Most guidelines (European, UK, Australia, and New Zealand) state that the preferred $P2Y_{12}$ inhibitors are prasugrel (60 mg loading dose) or ticagrelor (180 mg loading dose). The American guideline (O'Gara et al., 2013) is less explicit in its preference.

Prasugrel and ticagrelor are superior to clopidogrel in onset of action, potency, and clinical outcomes such as reduction in the rate of death from vascular causes, MI, or stroke (Wallentin et al., 2009). Prasugrel or ticagrelor should not be used in patients with a previous hemorrhagic stroke, patients on regular oral anticoagulants, or in patients with moderate-to-severe liver disease. In the event that prasugrel and ticagrelor cannot be used, the ESC (Ibanez et al., 2017), ACC (O'Gara et al., 2013), and National Institute for

Table 2 Doses of antiplatelet and parenteral anticoagulant therapies in primary PCI

Antiplatelet therapies	
Aspirin	Loading dose: 150–300 mg orally or 75–250 mg intravenously[a] 162–325 mg orally[b] 300 mg orally[c,d] Maintenance dose: 75–100 mg/day[a] 75 mg/day[c] 100–150 mg/day[d] 81–325 mg/day[b]
Clopidogrel	Loading dose: 300–600 mg orally Maintenance dose: 75 mg daily
Prasugrel	Loading dose: 60 mg orally Maintenance dose: 10 mg daily Dose adjustment to 5 mg/day maintenance dose is recommended in patients with body weight ≤60 kg.
Ticagrelor	Loading dose: 180 mg orally Maintenance dose: 90 mg twice a day
Parenteral anticoagulants	
UFH	70–100 units/kg intravenous bolus when no GPIIb/IIIa inhibitor is planned 50–70 units/kg intravenous bolus with GPIIb/IIIa inhibitors
Enoxaparin	0.5 mg/kg intravenous bolus[a]
Bivalirudin	0.75 mg/kg i.v. bolus followed by intravenous infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure
Glycoprotein IIb/ IIIa inhibitors	
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 mcg/kg/min infusion (maximum 10 mcg/min) for 12 hours[a,b,c]
Eptifibatide	Double bolus of 180 mcg/kg i.v. (given at a 10-minute interval) followed by an infusion of 2 mcg/kg/min for up to 18 hours[a,b,c]
Tirofiban	25 mcg/kg over 3 minutes intravenously, followed by a maintenance infusion of 0.15 mcg/kg/min for up to 18 hours[a,b,c]

Doses are standard across ANZ, ESC, ACC, and the British National Formulary unless otherwise stated.
The abovementioned doses do not take into consideration drug interactions and renal impairment.
[a]ESC guideline.
[b]ACC guideline.
[c]British National Formulary.
[d]ANZ guideline.

Health and Care Excellence (2015) guidelines recommend the use of higher clopidogrel loading dose (600 mg stat). Clopidogrel has not been evaluated against placebo in any large outcomes studies in primary PCI, but 600 mg/150 mg (loading dose/ maintenance dose) in the first week of STEMI was superior to the 300/75 mg regimen in the subset of patients undergoing PCI in the CURRENT-OASIS-7 trial (Mehta et al., 2010b).

The other $P2Y_{12}$ inhibitor, cangrelor, has limited use in current practice. A meta-analysis of three RCTs which compared cangrelor against clopidogrel in patients undergoing PCI. Steg et al. (2013) found that it was effective in reducing PCI complications. However, only about 18% of the patients in the trials presented with STEMI, and patients with ACS were not treated with potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel), limiting the applicability of results to current practice. Cangrelor is an IV preparation, which provides rapid onset of action (within a few minutes) and potent inhibition of $P2Y_{12}$ receptors. It has a half-life of 3–6 minutes, and has a fast offset of action. ESC and National Institute for Health and Care Excellence (2015) recommend that cangrelor may be an alternative option for some people undergoing PCI and for whom oral $P2Y_{12}$ inhibitors are not feasible or desirable. For example:

- Patients who are unable to absorb oral agents;
- Patients with an unclear coronary anatomy where early administration of long-acting $P2Y_{12}$ inhibitors may increase clinical risk such as aortic dissection, pericarditis, or esophageal tear; and
- Patients in an unconscious state undergoing emergency PCI in whom bleeding risk is deemed to be low (Ibanez et al., 2017; National Institute for Health and Care Excellence, 2015).

Anticoagulant

Anticoagulant options for primary PCI include unfractionated heparin (UFH), enoxaparin, and bivalirudin. The choice of anticoagulant in PCI differs between different international guidelines. In Australia and New Zealand, the first line of anticoagulant is either UFH or enoxaparin (Chew et al., 2016). In the USA and Europe, the ACC and the ESC recommend UFH (with or without GPIIb/IIIa inhibitors) and bivalirudin as first line treatments. NICE guidance in the UK has included all three agents in their recommendation (National Institute for Health and Care Excellence, 2013).

The dosing of UFH is weight adjusted and its anticoagulation effect monitored closely using either activated clotting time (ACT) or activated partial thromboplastic time (aPTT). There has been no placebo-controlled trial evaluating UFH in primary PCI, but there is a large body of experience with this agent (Ibanez et al., 2017). The recommended dosing of UFH depends on the concurrent use of fibrinolytics and GPIIb/IIIa inhibitors.

Enoxaparin is a low molecular weight heparin (LMWH) with a more predictable dose effect relationship than UFH and is associated less frequently with heparin-induced thrombocytopenia (HIT) (Junqueira et al., 2009). HIT is an adverse drug reaction of heparin, involving production of antibodies which activate platelets, leading to thromboembolic complications such as deep vein thrombosis, pulmonary embolism, MI, and stroke (Linkins, 2015). In a meta-analysis which included 23 trials, enoxaparin was superior to UFH in reducing death, MI complications and major bleeds in patients undergoing primary PCI (Silvain et al., 2012).

Bivalirudin acts by binding directly to thrombin and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin. It has a more predictable anticoagulant effect compared to UFH. A meta-analysis of five trials which compared bivalirudin with UFH, with or without GPIIb/IIIa inhibitors, showed that bivalirudin was noninferior to UFH in reducing mortality, superior in reducing risk of major bleeding and inferior in risk of acute stent thrombosis (Capodanno et al., 2016). The use of bivalirudin has been recommended by some guidelines for patients with high bleeding risk (Chew et al., 2016; Ibanez et al., 2017).

It is important to note here that the use of fondaparinux in the context of primary PCI was associated with potential risk of stent thrombosis in the OASIS 6 trial (Yusuf et al., 2006) and is not recommended to be used in primary PCI. The use of fondaparinux in other context is discussed elsewhere in this chapter.

Glycoprotein IIb/IIIa Inhibitors

Intravenous GPIIb/IIIa inhibitors block platelet aggregation by inhibiting fibrinogen binding to the GPIIb/IIIa receptor on two adjacent platelets (Patrono et al., 2011). The GPIIb/IIIa inhibitors currently available on the market are: eptifibatide, tirofiban, and abciximab. Studies of IV glycoprotein IIb/IIIa inhibition in combination with heparin among ACS patients were conducted in an era prior to the routine use of $P2Y_{12}$ inhibitors therefore limiting the applicability of the results of these studies (Chew et al., 2016; O'Gara et al., 2013). A meta-analysis of glycoprotein IIb/IIIa inhibition in ACS demonstrated a relative reduction in death or MI among patients undergoing PCI, but was associated with an increased risk of major bleeding (Bosch et al., 2010). A study by Stone et al. (2008) found that procedural use of abciximab plus UFH showed no benefit compared to bivalirudin. Therefore, both the European and American guidelines recommend the adjunctive use of GPIIb/IIIa agents at the time of PCI can be considered when there is evidence of large thrombus burden, no-reflow, or other thrombotic complications (Ibanez et al., 2017; O'Gara et al., 2013). The routine adjunctive use of GPIIb/IIIa inhibitors for patients receiving bivalirudin as the primary anticoagulant is not recommended (Stone et al., 2008).

Pharmacotherapy for Fibrinolysis

Antiplatelets

Aspirin (loading dose) and clopidogrel (loading dose) should be administered to patients with STEMI who receive fibrinolytic therapy. Clopidogrel added to aspirin reduces the risk of cardiovascular events and overall mortality in patients treated with fibrinolysis (Chen, 2005). Aspirin should be continued indefinitely and clopidogrel should be continued for at least 14 days and up to a year (Chen, 2005; Sabatine et al., 2005). The doses of aspirin and clopidogrel used for this indication are outlined in **Table 3**. The use of clopidogrel alongside aspirin and fibrinolytic therapy in the trials was for a duration of hospital stay (a mean of approximately 14 days) (Chen, 2005; Sabatine et al., 2005). The recommendation for the use of clopidogrel up to a year was extrapolated from experience with DAPT in patients with NSTE-ACS. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis.

Anticoagulant

Parenteral anticoagulation should preferably be given until the revascularization procedure (if performed). Otherwise, it should be given for at least 48 hours or for the duration of hospital stay, and up to 8 days (Ibanez et al., 2017; O'Gara et al., 2013). The doses of individual anticoagulants discussed below are outlined in **Table 3**. The ESC guideline recommends the use of enoxaparin over UFH owing to the net clinical benefit of enoxaparin (e.g., absence of death, nonfatal infarction, and intracranial hemorrhage) (Giraldez et al., 2007). The ACC guideline recommends the use of enoxaparin over UFH if anticoagulation is needed for more than 48 hours (O'Gara et al., 2013).

Fondaparinux was shown in the large OASIS-6 trial to be superior to placebo or UFH in preventing death and reinfarction especially in patients who received streptokinase as fibrinolytic agent (Yusuf et al., 2006). The ESC guideline recommends fondaparinux in patients treated with streptokinase (Ibanez et al., 2017). At the time of writing, fondaparinux was not yet approved for use in Australia (Chew et al., 2016).

Bivalirudin is not recommended as an adjunct to fibrinolysis. The use of bivalirudin with streptokinase was found to be associated with reduction in reinfarctions but had an increased risk of bleeding (White, 2001). The use of bivalirudin has not been studied with fibrin-specific agents so the evidence to support this combination use is limited.

Table 3 Doses of antiplatelet and anticoagulant therapies adjunct to fibrinolysis

Aspirin	Loading dose: 150–300 mg orally or 75–250 mg intravenously[a] 162–325 mg orally[b] 300 mg orally[c,d] Maintenance dose: 75–100 mg/day[a] 75 mg/day[c] 100–150 mg day[d] 81–325 mg/day[b]
Clopidogrel	Loading dose: 300 mg orally for patients ≤75 years of age[a,b] 75 mg orally for patients >75 years of age[a,b] Maintenance: 75 mg daily for at least 14 days and up to 1 year[a,b]
Enoxaparin	If age <75 years: 30 mg i.v. bolus, followed 15 min later by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first two doses) If age ≥75 years: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first two doses) Duration: for the index hospitalization, up to 8 d or until revascularization
Unfractionated Heparin	IV bolus of 60 U/kg (maximum 4000 Units) followed by an infusion of 12 U/kg/h (maximum 1000 Units) initially, adjusted to maintain aPTT at 1.5–2.0 times control (approximately 50–70 s) for 48 hours or until revascularization[a,b]
Fondaparinux (only for use with streptokinase)	Initial dose 2.5 mg i.v., then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 days or until revascularization[a,b,c]

Doses are standard across ANZ, ESC, ACC, and the British National Formulary unless otherwise stated.
The abovementioned doses do not take into consideration drug interactions and renal impairment.
[a]ESC guideline
[b]ACC guideline
[c]British National Formulary
[d]ANZ guideline

Secondary Prevention in ST-Elevated Myocardial Infarction

This section outlines the pharmacotherapy for the long-term maintenance treatment after the acute phase of STEMI. The section will first outline the different pharmacotherapies used and the evidence supporting their use. Individual drugs and corresponding doses used are outlined in Table 4. Dosages are based on those outlined in the guidelines from European, American, Australia and New Zealand, and UK, where appropriate.

The main goal of long-term maintenance pharmacotherapy is to prolong survival through risk factor modification and ultimately, prevent further acute coronary episodes also known as secondary prevention. Optimal medical therapy, lifestyle changes such as diet, exercise, and smoking cessation, is important in the prevention of recurrent ischemic events (Chow et al., 2010).

Aspirin

Aspirin is recommended indefinitely in all patients with STEMI (Mehta et al., 2010a). For long-term prevention, low dose aspirin (75–100 mg) is indicated. However, indefinite antiplatelet therapy with clopidogrel is recommended in patients who have had prior stroke (not related to atrial fibrillation) or if the patient has peripheral vascular disease, or cannot tolerate aspirin long-term.

$P2Y_{12}$ Inhibitors

In patients with confirmed STEMI at intermediate or high risk of recurrent ischemic events, the use of a $P2Y_{12}$ inhibitors at maintenance dose is recommended in addition to aspirin 75–100 mg daily (refer to Table 4 for doses). The ANZ and ESC guidelines recommend the use of ticagrelor or prasugrel over clopidogrel (Chew et al., 2016; Ibanez et al., 2017). This is due to the superiority of prasugrel (Wiviott et al., 2007) and ticagrelor (Wallentin et al., 2009) over clopidogrel in reducing mortality, recurrent MI, and stroke in patients with intermediate or very high risk ACS. However, in patients over 75 years of age or of low body weight (<60 kg) or previous cerebrovascular disease, prasugrel was associated with more harm than benefit when compared with clopidogrel.

Table 4 Maintenance treatment and doses post-STEMI

Aspirin	75–100 mg/day[a]
	75 mg/day[b]
	100–150 mg/day[c]
	81–325 mg/day[d]
Ticagrelor	90 mg BD for 12 months
	Duration could be shortened or lengthened depending on bleeding/thrombotic risk—see duration of DAPT section
Prasugrel	10 mg daily for 12 months
	Duration could be shortened or lengthened depending on bleeding/thrombotic risk—see duration of DAPT section
Clopidogrel	75 mg daily for 12 months
Beta-blockers:	
Metoprolol	Maintenance 200 mg daily in divided doses
Atenolol	Maintenance 100 mg daily
Carvedilol	Initially 3.125 mg twice daily, dose increased gradually at intervals of at least 2 weeks up to the highest tolerated dose. Maximum 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg; maximum 50 mg twice daily in patients over 85 kg
Nebivolol	Initially 1.25 mg once daily, dose increased at intervals of 1–2 weeks, to the maximum tolerated dose. Maximum 10 mg once daily
Bisoprolol	Initially 1.25 mg once daily, dose increased at weekly intervals, to the maximum tolerated dose. Doses at 5 mg or above will require longer titration interval of 4 weeks or more. Maximum 10 mg per day
Lipid-modifying therapy:	
Atorvastatin	80 mg daily
Other high intensity statins less preferable	An LDL-C goal of $<$1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70–135 mg/dL) is recommended
Ezetimibe	For patients unable to tolerate any dose of statin
	10 mg daily
ACE-inhibitors:	
Ramipril	Initially 2.5 mg twice daily for 3 days, then increased to 5 mg twice daily. (Lower starting dose may be required if patient is unable to tolerate 2.5 BD starting dose)
Perindopril (Arginine)	Initially 5 mg once daily for 2 weeks, then increased if tolerated to 10 mg once daily. (Lower dose may be required in elderly patients)
Perindopril (Erbumine)	Initially 4 mg once daily for 2 weeks, then increased if tolerated to 8 mg once daily. (Lower dose may be required in elderly patients)
ARB	
Valsartan	Initially 20 mg twice daily, increased if necessary up to 160 mg twice daily, doses to be increased over several weeks if tolerated
Eplerenone	Initially 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment
	Maximum dose of 25 mg daily with concurrent use of amiodarone or moderate inhibitors of CYP3A4

Individual drugs are largely derived from clinical trials conducted, and doses are standard across ANZ, ESC, ACC, and the British National Formulary unless otherwise stated. The abovementioned doses do not take into consideration drug interactions and renal impairment.

[a]ESC guideline.

[b]British National Formulary.

[c]ANZ guideline.

[d]ACC guideline.

Duration of Dual Antiplatelet Therapy

Dual Antiplatelet Therapy , combining aspirin and a $P2Y_{12}$ inhibitor, is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months) (Wallentin et al., 2009; Wiviott et al., 2007). Clopidogrel is recommended for 1 month in patients treated with fibrinolysis without subsequent PCI (Chen, 2005). However, extension of DAPT duration to 12 months should be considered in these patients (Ibanez et al., 2017). For patients undergoing fibrinolysis and subsequent PCI, DAPT is recommended for 12 months. Clopidogrel is the $P2Y_{12}$ inhibitor of choice as coadjuvant and after fibrinolysis. Potent $P2Y_{12}$ inhibitors have not been investigated in patients undergoing fibrinolysis, and safety (e.g., bleeding complications) is not well established. The evidence of $P2Y_{12}$ inhibitors in this cohort of patients is referred to under "Pharmacotherapy for Fibrinolysis" section.

In patients with high bleeding risk, studies have shown that shortening DAPT duration to 6 months, compared with 12 months or longer, reduces the risk of major bleeding complications, with no apparent trade-off in ischemic events (Costa et al., 2015).

On the contrary, two major studies have shown the benefit toward reduction of nonfatal ischemic events in patients receiving longer than 12 months of DAPT (Bonaca et al., 2015; Mauri et al., 2014). However, the DAPT study only included approximately 10% of STEMI patients and no information has so far been provided with respect to the benefit of prolonging clopidogrel or prasugrel from 12 to 30 months in this patient subset. Hence, no formal recommendations are possible for the use of clopidogrel or prasugrel beyond 1 year (Ibanez et al., 2017). Data available from the PEGASUS-TIMI 54 trial showed that extension of DAPT beyond 1 year (up to 3 years) in the form of aspirin plus ticagrelor 60 mg twice a day may be considered in patients who have tolerated DAPT without a bleeding complication and having one additional risk factor for ischemic events such as a previous stroke (Bonaca et al., 2015).

The use of DAPT may sometimes be indicated in addition to long-term oral anticoagulation, in patients with conditions such as atrial fibrillation (AF) (Kirchhof et al., 2017). The ESC guideline estimated that approximately 6%–8% of patients undergoing PCI have an indication for long-term oral anticoagulation (Roffi et al., 2016). This is referred to as "triple therapy," e.g., DAPT and oral anticoagulation. Triple therapy increases bleeding risk and therefore, the duration of triple therapy should be kept to the minimum required for maximum benefit/risks ratio. The recommended duration of triple therapy is highly dependent on the individual bleeding risk versus clotting risk factors of the patient. In the absence of safety and efficacy data, the use of prasugrel or ticagrelor as part of triple therapy should be avoided (Roffi et al., 2016). Coprescription with a proton pump inhibitor (PPI) is recommended for gastroprotection to help reduce the risk of gastrointestinal bleed.

Beta-Blockers

Beta-blockers should be started within the first 24 hours of the presentation of chest pain in patients who are hemodynamically stable (Ibanez et al., 2017). Beta-blockers reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and myocardial contractility.

After early IV beta-blocker treatment such as metoprolol, patients should be continued on oral vasodilatory beta-blocker therapy long-term, unless contraindicated. Vasodilatory beta-blockers include carvedilol, bisoprolol, nebivolol, and metoprolol. These beta-blockers reduce peripheral vascular resistance while maintaining or improving cardiac output, stroke volume, and left ventricular function; and may limit infarct size (Dargie, 2001).

The benefit of long-term treatment with oral beta-blockers after STEMI is well established, although most of the supporting data come from trials performed in the pre-reperfusion era (Freemantle et al., 1999). However, the evidence supporting use of beta-blockers is stronger among patients with reduced Left Ventricular (LV) function following ACS. Therefore, in patients with MI without underlying heart failure, the ACC guideline recommends that beta-blocker use be limited to a three-year course (Smith et al., 2011). The National Institute for Health and Care Excellence (2013) recommends that beta-blocker use in this cohort of patients (without underlying heart failure) should be reviewed after 12 months with a view to stopping treatment, taking into account the extent of coronary disease or evidence of ischemia, concurrent conditions, and any adverse effects.

Lipid Modification Therapy

All the guidelines recommend that high-intensity statin (e.g. statin regimens that reduce low-density lipoprotein cholesterol (LDL-C) by approximately 50%) should be initiated as soon as the patient is stabilized and has no contraindications, and continued long term (Chew et al., 2016; Ibanez et al., 2017; National Institute for Health and Care Excellence, 2013; O'Gara et al., 2013). Treatment with statins in patients stabilized after an ACS, including STEMI, lowers the risk of CHD death, recurrent MI, stroke, and the need for coronary revascularization (Sacks et al., 1996). A metaanalysis of trials comparing more versus less intensive LDL-C lowering with statins indicated that more intensive statin therapy produced greater reductions in the risks of cardiovascular death, nonfatal MI, ischemic stroke, and coronary revascularization (Baigent et al., 2010).

Among currently available statins, only high-dose atorvastatin (80 mg daily) has been shown to reduce death and ischemic events among patients with ACS (Cannon et al., 2004; Schwartz et al., 2001). Treatment with statins is irrespective of cholesterol concentration at presentation.

In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered. Ezetimibe is recommended for patients with intolerance of statin by the ESC (Ibanez et al., 2017) and the ANZ guidelines (Chew et al., 2016). This recommendation was largely based on the In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), where 18,144 patients with a recent ACS (29% with STEMI) were randomized to either ezetimibe plus simvastatin or simvastatin alone, which found that ezetimibe plus simvastatin produced statistically significant reduction in the composite outcome of cardiovascular death, MI, hospital admission for unstable angina, coronary revascularization, or stroke (Cannon et al., 2015).

Renin-Angiotensin System (RAS) Inhibitors

Oral angiotensin converting enzyme (ACE) inhibitors reduce fatal and nonfatal major cardiovascular events in patients with STEMI (Pfeffer et al., 1992). Their protective effects have been demonstrated independent of the use of other pharmacotherapies (e.g., fibrinolytics, aspirin, and beta-blockers). The magnitude of clinical benefit is greatest in high-risk patient subgroups (e.g. anterior MI, ejection fraction ≤40%, heart failure, prior MI, and tachycardia) (Dickstein et al., 2002). The role of routine long-term ACE inhibitor therapy in low-risk patients after STEMI is less clear (Braunwald et al., 2004). The benefit of early initiation of these agents in patients with MI is evident and thus recommended by the ACC, ESC, NICE, and ANZ guidelines for patients without existing contraindications. The guidelines recommend that all patients with evidence of heart failure, LV systolic dysfunction, or any other risk factors should be initiated on ACE inhibitors within 24 hours of STEMI. ACE inhibitors may be considered for patients with low-risk in the absence of contraindications.

In patients who cannot tolerate ACE inhibitors, angiotensin receptor blockers (ARBs) are indicated. Valsartan is the preferred ARB, owing to the VALIANT (Valsartan in Acute Myocardial Infarction) trial, where it was found to be noninferior to captopril (Pfeffer et al., 2003). Individual doses of ACE inhibitors and ARBs are outlined in **Table 4**.

Aldosterone Antagonist

Aldosterone antagonist is recommended in patients with Left Ventricular Ejection Fraction dysfunction (LVEF ≤40%) and heart failure after STEMI (Girerd et al., 2015). Eplerenone is the only aldosterone antagonist with evidence for use in this cohort of patients at the time of writing. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) study established the benefit of eplerenone, added to optimal medical therapy in patients 3–14 days after STEMI with Ejection Fraction ≤40% and either symptomatic heart failure or diabetes mellitus (Pitt et al., 2003). A secondary analysis of the EPHESUS trial data suggested that initiation of eplerenone within 7 days of MI significantly reduced the rates of all-cause mortality, sudden cardiac death (SCD), and cardiovascular mortality/hospitalization, whereas initiation after 7 days had no significant effect on the above mentioned outcomes (Adamopoulos et al., 2009).

When using eplerenone, care should be taken in patients with reduced renal function and routine monitoring of serum potassium is warranted.

Confirmed Non-ST-Elevated Acute Coronary Syndrome Diagnosis

As soon as the diagnosis of UA or NSTEMI is made, and aspirin and antithrombin therapy has been offered, patients should be formally assessed to establish their risk of future adverse cardiovascular events and bleeding events using a risk scoring systems. The American College of Cardiology (ACC) does not recommend any one predictor model, while NICE and ANZ guidelines recommend the Global Registry of Acute Coronary Events (GRACE) scoring system. More information on risk scores are described earlier on in the chapter.

The risk of future adverse cardiovascular events would also determine if coronary angiography would be needed, and the urgency of the procedure. Patients deemed to be at high risk (refer to earlier section on risk stratification) require coronary angiography within 72–96 hours (with follow-on PCI if indicated). Coronary angiography is a procedure where a long, thin tube called a catheter is inserted into a blood vessel, usually through the groin or arm, which allows X-ray images (angiograms) to be taken. Coronary angiography is an important procedure to detect and determine the extent of any clots in the blood vessels, which helps to plan further interventions such as PCI (balloon and stent insertion to widen blocked arteries), or coronary artery bypass graft (CABG) (surgical procedure to divert blood around blocked arteries). Low risk patients require rapid angiography if they experience refractory or recurrent ischemic symptoms despite optimally treated with medicines, or if they are hemodynamically unstable, or if deemed clinically beneficial by consultant cardiologists and interventionists.

Pharmacotherapy in Non-ST-Elevated Acute Coronary Syndrome

This section outlines the pharmacotherapy for both the acute and maintenance phases of NSTE-ACS. Similar to the layout of the STEMI section, this section will first outline the different pharmacotherapies used and the evidence supporting their use. Individual drugs and corresponding doses are outlined in **Table 5**. Dosages are based on those outlined in the guidelines from European, American, Australia and New Zealand, and UK, where appropriate.

Acute Management in Non-ST-Elevated Acute Coronary Syndrome

This section outlines the pharmacotherapy in the acute phase of NSTE-ACS, immediately after diagnosis. Doses for individual drugs are outlined in **Table 5**.

Aspirin

Aspirin is normally offered as soon as possible upon presentation of UA or NSTEMI, as a single loading dose. For patients with aspirin hypersensitivity, clopidogrel should be given as an alternative (loading dose: 300–600 mg). Following this, a maintenance dose (75–100 mg) of aspirin should be continued indefinitely. The benefit of aspirin has been demonstrated in four RCTs in the pre-PCI era where aspirin has shown to be effective in patients with unstable angina by reducing the incidence of MI or death (Theroux et al., 1988).

$P2Y_{12}$ Inhibitors

As soon as the risk of adverse cardiovascular events has been assessed, patients should be offered a loading dose of 300 mg clopidogrel in addition to aspirin with a predicted 6-month mortality of more than 1.5% (GRACE criteria low risk or higher) and no contraindications (e.g., an excessive bleeding risk). Patients who may undergo PCI within 24 hours of hospital admission should also be treated with a 300 mg loading dose of clopidogrel.

Table 5 Doses of pharmacotherapy used in acute phase of NSTE-ACS

Aspirin	Loading dose: 150–300 mg orally or 75–250 mg intravenously[a] 162–325 mg orally[b] 300 mg orally[c,d]
Clopidogrel	Single loading dose: 300–600 mg Maintenance dose: 75 mg
Ticagrelor	Loading dose: 180 mg Maintenance dose: 90 mg BD
Prasugrel	Loading dose: 60 mg Maintenance dose: 10 mg daily
Anticoagulants	
Fondaparinux	2.5 mg s.c. once a day Not recommended if eGFR $<$20 mL/min/1.73 m^2
Unfractionated heparin (UFH)	60–70 units/kg i.v. (max 5000 units) and infusion (12–15 units/kg/h) (max 1000 units/h), target aPTT 1.5–2.5x control[a] 60 units/kg i.v. (max 4000 units) with initial infusion 12 units/kg/h (max 1000 units/h)[b]
Enoxaparin	1 mg/kg s.c. twice a day for the duration of hospitalization or until PCI is performed
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h
Beta-blockers	
Carvedilol	Initially 3.125 mg twice daily, increased gradually at intervals of at least 2 weeks up to the highest tolerated dose
Bisoprolol	Initially 1.25 mg once daily, increased gradually at weekly interval up to 5 mg daily, then increased at 4-weekly intervals (if tolerated) to a maximum 10 mg per day

Individual drugs are largely derived from clinical trials conducted, and doses are standard across ANZ, ESC, ACC, and the British National Formulary unless otherwise stated. The abovementioned doses do not take into consideration drug interactions and renal impairment.
[a]ESC guideline.
[b]ACC guideline.
[c]British National Formulary.
[d]ANZ guideline.

Thereafter, a $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds. $P2Y_{12}$ inhibitors available at the time of writing include: clopidogrel, prasugrel, ticagrelor, and cangrelor. Their mode of action was described earlier in the chapter under "Pharmacotherapy for Primary PCI" section.

The choice of $P2Y_{12}$ inhibitor in patients with NSTE-ACS depends on the reperfusion strategy chosen. For example, prasugrel is only indicated for NSTE-ACS patients undergoing PCI, while ticagrelor and clopidogrel are indicated for all reperfusion strategies,e.g., PCI or angiography guided revascularization.

Ticagrelor is the preferred $P2Y_{12}$ inhibitor in all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins) without contraindications (Amsterdam et al., 2014; Chew et al., 2016; Roffi et al., 2002). The loading dose of ticagrelor is 180 mg orally, followed by 90 mg twice a day. Ticagrelor is a $P2Y_{12}$ inhibitor with a fast and more consistent onset of action compared with clopidogrel in addition to more rapid recovery of platelet function (Gurbel et al., 2009). A major trial which compared clopidogrel with ticagrelor in patients with moderate to high risk NSTE-ACS was the PLATelet inhibition and patient Outcomes (PLATO) trial, which found that (Wallentin et al., 2009):

- Ticagrelor was more effective than clopidogrel at reducing primary end points including death from CV causes, MI or stroke, and all-cause mortality (Lindholm et al., 2014).
- Ticagrelor increased risk of major bleeds, but no statistically significant difference on fatal bleed compared to clopidogrel.
- Ticagrelor was superior at reducing stent thrombosis compared to clopidogrel (Lindholm et al., 2014).

In patients who are proceeding to PCI, prasugrel (60 mg loading dose, followed by 10 mg daily maintenance dose) is recommended (National Institute for Health and Care Excellence, 2013; Roffi et al., 2002). Prasugrel, a prodrug that blocks platelet $P2Y_{12}$ receptors, has a faster onset and a more potent antiplatelet effect than clopidogrel (Wiviott et al., 2007). The landmark trial was the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) which showed that prasugrel patients had less recurrent CV events and stent thrombosis, but more bleeding complications compared with clopidogrel (De Servi et al., 2014). Therefore, prasugrel should be considered in patients who present with stent thrombosis despite compliance with clopidogrel therapy (Wiviott et al., 2008).

Patients with NSTE-ACS should be treated with DAPT. Clopidogrel is also used in combination with aspirin at a maintenance dose of 75 mg daily in patients with NSTE-ACS although its place in therapy depends on individual guidelines. Clopidogrel is an inactive prodrug that requires oxidation by hepatic enzyme CYP450 to generate an active metabolite. Approximately 85% of the prodrug is hydrolyzed by esterase enzymes into an inactive form, leaving only 15% of clopidogrel available for transformation to the active metabolite, which inactivates platelet $P2Y_{12}$ receptors and thus inhibits platelet aggregation (Savi et al., 2001). For this reason,

pharmacodynamic and pharmacokinetic studies have shown substantial interindividual variability in the antiplatelet response to clopidogrel, resulting in an increased risk of ischemic and bleeding events in clopidogrel hypo- and hyper-responders, respectively (Matetzky et al., 2004; Simon et al., 2009) (please see "Pharmacogenomics" section for further details). DAPT comprising aspirin and clopidogrel has been shown to reduce recurrent ischemic events in the NSTE-ACS patients compared with aspirin alone (Yusuf et al., 2001).

Patients identified as having a higher risk of bleeding (e.g., those with previous bleeding complications, low platelet count, concurrent use of anticoagulation) should be assessed and considered for a shorter duration of dual antiplatelet therapy (e.g., less than 12 months) (National Institute for Health and Care Excellence, 2010b). DAPT duration may be shortened (e.g., 3–6 months) or extended (e.g., up to 30 months) if required based on individual patient ischemic and bleeding risk profiles (Navarese et al., 2015). A PPI is recommended to be taken in combination with DAPT in patients with higher risk of gastrointestinal bleeds. It is important to note the interaction between certain PPI which undergo CYP450 metabolism and hence reduce plasma levels of clopidogrel (Yasuda et al., 2009). For further information, see "Interactions" section.

Anticoagulant

Anticoagulation therapy should then be offered in the initial management of NSTE-ACS. Anticoagulants are used to inhibit thrombin generation, thereby reducing thrombin-related events.

There is evidence that anticoagulation is effective in reducing ischemic events in NSTE-ACS and that the combination with antiplatelets is more effective than either treatment alone (Eikelboom et al., 2000). Several anticoagulants, acting at different levels of the coagulation cascade, have been approved or are under investigation for this indication, which are discussed below.

During the acute phase of NSTE-ACS, parenteral anticoagulant should be administered, depending on the bleeding and ischemic risk profiles (clotting risk) of the patient. Parenteral anticoagulant options include: fondaparinux, bivalirudin, unfractionated heparin (UFH), or enoxaparin. These individual drugs and their mode of action are described in detail earlier in the chapter under "Pharmacotherapy for Primary PCI" section. The doses of anticoagulants used in the acute phase of NSTE-ACS differ from those used in acute phase of MI. The dosing regimen of all pharmacotherapy used in the acute management of NSTE-ACS can be found in **Table 3**.

Fondaparinux

Fondaparinux is the preferred parenteral anticoagulant by ESC due to its favorable safety and efficacy profile as found by the landmark trial OASIS-5 discussed below (Roffi et al., 2002). The recommended dose in NSTE-ACS is 2.5 mg a day. Fondaparinux has shown to be superior to enoxaparin in reducing in-hospital major bleeding and mortality and showed noninferiority to enoxaparin with respect to ischemic events in the Organisation to Assess Strategies in Acute Ischaemic Syndromes (OASIS-5) study (Yusuf et al., 2006).

Unfractionated Heparin

UFH remains a widely used anticoagulant in NSTE-ACS in the context of short delays to coronary angiography despite consistent evidence for greater bleeding risk compared with other strategies (Silvain et al., 2012). UFH is given in the PCI setting in combination with GPIIb/IIIa inhibitor. UFH should be stopped after PCI unless there is a clinically valid reason for it to be continued. One of the major adverse effects of UFH is HIT. HIT is covered earlier in the chapter under "Pharmacotherapy for Primary PCI Anticoagulant" section.

Low Molecular Weight Heparin

The most widely used anticoagulant in the acute phase of NSTE-ACS is enoxaparin (1 mg/kg administered subcutaneously twice daily, with appropriate dosage adjustment in patients with renal impairment). LMWH has the advantage over UFH for not requiring routine monitoring except for patients with renal impairment and with bodyweight of >100 kg.

A meta-analysis of all trials testing enoxaparin versus UFH in ACS showed a marginally significant reduction in the combined endpoint of death or MI at 30 days in favor of enoxaparin but no statistically significant differences in major bleeds at 7 days (Murphy et al., 2007).

Bivalirudin

Bivalirudin is recommended to be used as an alternative (to UFH plus GPIIb/IIIa inhibitors) in patients presenting in the acute phase of NSTE-ACS who have to undergo PCI (Roffi et al., 2002). In the ACUITY trial, which compared bivalirudin with UFH or LMWH, no significant differences were found between bivalirudin and UFH/LMWH for the composite ischemia endpoint at 30 days or for major bleeds (Stone et al., 2006). For this reason, the use of bivalirudin is now limited to being an alternative to UFH plus GPIIb/IIIa inhibitors during PCI (Roffi et al., 2016).

Beta-Blockers

Patients without contraindications should receive beta-blockers as soon as possible after diagnosis. The duration of treatment with beta-blockers in patients without heart failure is 1 year by National Institute for Health and Care Excellence (2013) and 3 years by ACC (Smith et al., 2011). In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem hydrochloride or verapamil hydrochloride can be given.

The evidence for the beneficial effects of beta-blockers in NSTE-ACS are derived from a meta-analysis of 27 studies showing that beta-blocker treatment was associated with a significant 13% relative risk reduction (RRR) of mortality in the first week following MI (Yusuf et al., 1988). However, in more recent trials, beta-blockers have been associated with a significant reduction in recurrent MI and angina, but a significant increase in heart failure and cardiogenic shock (Kontos et al., 2011). Caution in using beta-blockers should be exercised when LV function is known to be low or there is evidence of hemodynamic compromise, conduction abnormalities, or inferior infarction (Amsterdam et al., 2014; Chew et al., 2016).

For patients with contraindications or severe side effects to beta-blockers, such as shortness of breath on initiation and those with severe peripheral vascular disease, a non-dihydropyridine calcium channel blocker (diltiazem or verapamil) can be given instead. Diltiazem is initiated at 60 mg three times daily and titrated to response, up to a usual maximum dose of 360 mg daily, which can be given in divided doses or as a long acting preparation. Similarly, verapamil can be started at 40–80 mg three times a day and increased according to response, up to a daily dose of 360–480 mg, depending on the preparation used. **Table 5** outlines the drugs and doses used in the acute management of NSTE-ACS.

Secondary Prevention in Non-ST-Elevated Acute Coronary Syndrome

This section outlines the pharmacotherapy for the long-term maintenance treatment after the acute phase of NSTE-ACS. The section will briefly outline the different pharmacotherapies used and the evidence supporting their use. The pharmacotherapy for secondary prevention in both STEMI and NSTE-ACS are similar, and most of the points discussed below can be cross-referenced to the earlier section of "Secondary Prevention in STEMI."

Lipid Modification Therapy

It is recommended to initiate high-intensity statin therapy as early as possible after admission in all NSTE-ACS patients (in the absence of contraindications) (Baigent et al., 2010). At the time of writing, the preferred statin in this case is atorvastatin 80 mg daily, unless patient preference, interacting drugs or high risk of adverse effects warrant a dose reduction. If the control of LDL-C is not sufficient after NSTE-ACS despite taking the maximum tolerated dose of statin, further cholesterol lowering with a nonstatin agent (, e.g., ezetimibe) may be considered (Cannon et al., 2015). There is only one trial, the IMPROVE-IT, at the time of writing, that was sufficiently powered for clinical outcomes to show a modest benefit with ezetimibe added to a statin (Cannon et al., 2015).

Antiplatelets

The duration of DAPT and choice of $P2Y_{12}$ inhibitor is discussed in the earlier section "Pharmacotherapy in NSTE-ACS."

Beta-Blockers

The evidence for the beta-blockers as maintenance secondary prevention therapy in patients after NSTE-ACS is unclear. In a large-scale observational propensity matched study in patients with known previous MI, beta-blocker use was not associated with a lower risk of CV events or mortality. The current recommendation from ESC and ACC guidelines is that beta-blockers should be used, in the absence of contraindications, in patients with reduced systolic LV function (LVEF $\leq$40%).

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are recommended in patients with systolic LV dysfunction or heart failure, hypertension or diabetes. Agents and doses with proven efficacy should be used such as captopril and enalapril. ACE inhibitors should be started while in hospital and continued long-term in all patients with NSTE-ACS or those with left ventricular systolic dysfunction to prevent cardiac remodeling (Amsterdam et al., 2014). Cardiac remodeling refers to changes in size, shape, structure, and function of the heart, often occurring after injury to the heart muscles (Pfeffer and Braunwald, 1990).

In patients who cannot tolerate ACE inhibitors, an ARB should be used: preferably candesartan or valsartan.

Aldosterone Antagonist

Aldosterone antagonist therapy with eplerenone is recommended in patients with LV dysfunction (LVEF $\leq$40%), heart failure, or diabetes after NSTE-ACS (Zannad et al., 2011).

Anticoagulant

Some anticoagulants such as the nonvitamin K antagonist oral anticoagulants (NOACs) have been trialed recently for their use in patients with recent ACS treated with clopidogrel and aspirin with no history of atrial fibrillation. The only NOAC currently approved for use in Europe is rivaroxaban 2.5 mg BD for this indication. This is following the ATLAS ACS-2 TIMI 51 trial, which compared rivaroxaban 2.5 mg and 5 mg twice daily with placebo in patients following ACS (Mega et al., 2012). At a mean follow-up of 13 months, both strengths of rivaroxaban resulted in a reduction in CV death, MI or stroke and stent thrombosis rate. Rates of CV death were significantly lower with rivaroxaban 2.5 mg compared with placebo but not with rivaroxaban 5 mg. Non-CABG major bleeds and intracranial hemorrhage were higher in rivaroxaban 5 mg cohort.

The use of rivaroxaban 2.5 mg twice daily, while not recommended in patients treated with ticagrelor or prasugrel, might be considered in combination with aspirin and clopidogrel if ticagrelor and prasugrel are not available for NSTE-ACS patients who have high ischemic and low bleeding risks. This combination should be continued for approximately 1 year.

This section outlines current recommendations for use of anticoagulants in combination with DAPT for patients with ACS alone, and does not cover treatment recommendations for patients needing oral anticoagulants long-term in combination with DAPT for other indications, e.g., atrial fibrillation, mechanical heart valves, or venous thromboembolism.

Interactions

Nitrates

Drugs with antimuscarinic effects may cause dry mouth, this can reduce the effectiveness of nitrate tablets. Caution should be exercised when administering nitrates and antihypertensives due to additive risk of hypotension. Phosphodiesterase type 5 inhibitors have a pharmacodynamic interaction with nitrates and they can exacerbate the vasodilatory action of nitrates (Schwartz and Kloner, 2010). Due to this interaction, which may cause severe life threatening hypotension their concurrent use, is contraindicated.

Fibrinolytics

Although combination of fibrinolytics with antiplatelets or antithrombins have known therapeutic benefits, caution must be taken due to the increased risk of bleeding. Nonsteroidal antiinflammatory drugs (NSAIDs) and other drugs which increase the risk of bleeding, should be avoided or used with caution (Joint Formulary Committee, 2017).

$P2Y_{12}$ Inhibitors

Clopidogrel is mainly metabolized by esterases and CYP2C19; therefore, concomitant use of drugs that inhibit the activity of CYP2C19, such as omeprazole, cimetidine, erythromycin, and carbamazepine results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition (Bates et al., 2011). Prasugrel is not known to have clinically significant interactions with inducers or inhibitors of cytochrome P450 enzymes. There is an increased risk of bleeding when prasugrel is given concurrently with other drugs that cause a similar effect (Joint Formulary Committee, 2017).

ACE Inhibitors and ARBs

Most interactions of ACE inhibitors and ARBs relate to additive risk of hypotension, hyperkalemia, or renal impairment when used concomitantly with other medications that share such actions. Furthermore, combination of ACE inhibitors and ARBs increases risk of hyperkalemia, hypotension, renal impairment, and angioedema. Close monitoring is required if ACE inhibitors or ARBs are used with mineralocorticoid receptor antagonists, potassium sparing diuretics, ciclosporin, and antihypertensives. ACE inhibitors and ARBs can increase plasma concentrations of lithium and digoxin, therefore close therapeutic dose monitoring is required in concurrent use (Joint Formulary Committee, 2017).

Beta-Blockers

Pharmacodynamic interactions can occur if beta-blockers are given with other drugs that share similar therapeutic effects, such as antihypertensives and drugs with negative inotropic effects, for example, digoxin, amiodarone, and rate-limiting calcium channel blockers (Joint Formulary Committee, 2017).

PCSK9 Inhibitors

This class of drugs are not thought to interact with other medications or cytochrome P450 enzymes.

Statins

Most statins are metabolized by cytochrome P450 enzymes. Therefore, the risk of side effects, particularly muscle-related, increases when they are concomitantly used with drugs that inhibit these enzymes. Examples to remember include azole antifungals, antiretrovirals, macrolides, calcium channel blockers, amiodarone, and grapefruit (Joint Formulary Committee, 2017). It may be necessary to avoid concurrent use.

Side Effects

Nitrates

Dizziness, postural hypotension, tachycardia, and throbbing headache are common side effects (Joint Formulary Committee, 2017). Due to risk of hemodynamic compromise in patients with ischemic heart disease, nitrates should be avoided in those with systolic blood pressure lower than 90 mmHg, or with marked brady- or tachycardia (Kushner et al., 2009). Prolonged intravenous infusion of nitrates has been associated with methemoglobinemia (Joint Formulary Committee, 2017).

Fibrinolytics

Hemorrhage is the most common side effect associated with this class of drugs, this can range from minor bleeding to major gastrointestinal bleed and hemorrhagic stroke. Therefore, fibrinolytics are contraindicated in active bleeding and in patients at high risk of bleeding (e.g., recent hemorrhage, trauma or surgery, coagulation defects, endocarditis). Another side effect is hypotension, this can usually be controlled by elevating the patients' leg, or by reducing the infusion rate or temporarily stopping it. Other side effects include allergic reactions, fever, nausea, and vomiting (Joint Formulary Committee, 2017).

$P2Y_{12}$ Inhibitors

Thienopyridines increase the risk of bleeding, however prasugrel has a greater bleeding risk than clopidogrel (Wiviott et al., 2007). Common side effects of clopidogrel include abdominal pain, bleeding disorders, diarrhea, and dyspepsia (Joint Formulary Committee, 2017).

ACE Inhibitors and ARBs

Adverse effects include dizziness, fatigue, headache, and nausea (Joint Formulary Committee, 2017). A profound first-dose hypotension can occur, especially in salt-depleted patients due to coadministration with diuretics (Wang et al., 2011). Therefore, for hypertension the first dose should preferably be given at bedtime. Some patients treated with ACE inhibitors may experience a persistent cough (Joint Formulary Committee, 2017). This can develop as early as one week after initiation or can be delayed by months; cessation of therapy will resolve symptoms (Wang et al., 2011). ACE inhibitors may rarely cause angioedema, with higher incidence reported in Afro-Caribbean patients. It can occur within hours to weeks of initiating treatment and can affect the GI tract, brain, tongue, and larynx. The ACE inhibitor must be stopped immediately and treatment with adrenaline may be required if there is potential airway obstruction and the ACE inhibitor should not be restarted (Joint Formulary Committee, 2017). ACE inhibitors should be discontinued if marked elevation of hepatic enzymes or jaundice occurs, due to reports of cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure (Joint Formulary Committee, 2017). ARBs have a similar side effect profile to ACE inhibitors, however they are much less likely to cause cough or angioedema.

Beta-Blockers

Common side effects include fatigue, malaise, low mood, sexual dysfunction, and sedation. As a result of their therapeutic effect, beta-blockers can cause hypotension, bradycardia, and cardiac conduction disturbances. Beta-blockers may also mask signs of hyperthyroidism and hypoglycemia (Joint Formulary Committee, 2017).

Statins

Common side effects of statins include, GI disturbances, rash, insomnia, myalgia, and altered liver function tests (Joint Formulary Committee, 2017).

Pharmacogenomics in Acute Coronary Syndrome

In the last 10 years there has been considerable advancements in understanding genetic factors influencing response to a variety of drugs including those used for cardiovascular diseases. There is sufficiently strong evidence and genetic information available

relating to *CYP2C19* for clopidogrel, *VKORC1*, *CYP2C9;* and *CYP4F2* for warfarin; and *SLCO1B1* for statins to guide treatment and some clinicians are already using this genetic information to determine treatment appropriateness for their patients (Johnson and Cavallari, 2013).

There is strong evidence where genetic polymorphism on CYP2C19 has been associated with substantial reduction in the efficacy of clopidogrel, which is the mainstay pharmacological treatment for ACS resulting in diminished platelet inhibition and a significantly higher rate of major cardiovascular events (Lala et al., 2013). In response to the evidence regarding clopidogrel the US FDA announced a black box warning in March 2010 to alert clinicians to the reduced effectiveness of clopidogrel in subjects who are poor clopidogrel metabolizers. Despite the FDA warning and the risk that clopidogrel nonresponders face when on clopidogrel, it is still widely used (Antoniades et al., 2009). Moreover, interindividual, ethnic, and racial variability in drug metabolism of clopidogrel through genetic polymorphism of CYP2C19 enzymes in the Asian population has been attributed to adverse cardiovascular outcomes (Zhong et al., 2018).

Pharmacogenomics in CVD is not yet established clinical practice and some studies published on genetic polymorphisms have produced inconsistent results due to the complex systems underlying CVD. Large scale pharmacogenomic trials are needed to provide more convincing evidence to guide choosing drug treatment with the greatest potential of efficacy and smallest risk of adverse drug reactions (Johnson and Cavallari, 2013).

Nonpharmacological Management

Lifestyle Modification

Relevant lifestyle modification can reduce the risk of having further cardiovascular events. These include:

- Smoking cessation
- Adopting a cardio-protective diet (a diet similar to Mediterranean diet):
  - Total fat intake should be 30% or less of total energy intake, and saturated fat (which is mainly from animal sources) should be 7% or less.
  - Using olive oil or rapeseed oil for spreads, salad dressings, cooking, baking, and other food preparation rather than animal-based fats such as butter.
  - Eating at least 200 g of fruits and 200 g of vegetables per day.
  - Eating fish at least once a week, including a portion of oily fish.
  - Eating at least 4–5 portions per week of a mixture of unsalted nuts and seeds. (One portion is about a handful or about 30 g.)
  - Choosing wholegrain varieties of cereals, breads, and other starchy foods.
  - Keeping salt intake low (less than 6 g per day).
  - Minimizing intake of foods containing refined sugars, including fructose.
  - Dietary supplements including omega-3 capsules or supplemented foods are not recommended as there is no good evidence that they reduce CVD risk.
- Maintain an active lifestyle
  - In general, the minimum aim is 150 minutes per week of moderate-intensity aerobic activity (to the point of slight breathlessness).
  - Activity in bouts of 10 minutes or more is as effective as longer bouts so long as the total per week is as above. Moderate intensity activities include those that can be incorporated into everyday life such as brisk walking, using stairs, and cycling.
  - For people not active to this level, start at a level that is comfortable, and increase the duration and intensity of activity as fitness improves.
- Maintain a healthy weight (ideally Body Mass Index <25 kg/m^2)
- Limit alcohol consumption
  - In UK males and females should not consume no more than 14 units of alcohol per week.
  - Avoid binge drinking and intoxication.

Pharmacist Role in the Management of Acute Coronary Syndromes

Pharmacists are one of the most accessible health care professionals in the community and are experts in the safe and effective use of medicines. Pharmacists play an essential role in the care of ACS patients, starting from their admission to hospital, throughout their hospitalization, their transition to primary care settings and thereon (Coombes et al., 2002; Walker et al., 2009).

The expanding role of pharmacists has allowed pharmacists to become a valuable resource in assisting other members of the health care team with pharmacotherapeutic decision making, reducing medication errors, pharmacovigilance, and improving medication safety systems to optimize patient outcomes in addition to improving cost effectiveness.

Pharmacists also have a role to play in promoting secondary prevention strategies for patients with CHD. Patients with ACS choosing healthy lifestyles, managing risk factors and being on optimized drug treatment for ACS can reduce the risk of recurrent and fatal future episodes (Garcia et al., 2014).

The appropriate transition of patients from secondary to primary care can help reduce morbidity and mortality, therefore reducing readmission rates and associated health care costs. It is important that pharmacists ensure the correct continuation of prescribed medications when patients are transitioning between settings. This will help avoid discrepancies and confusion in the planned medication regimen. It is therefore paramount for pharmacists to recognize the importance of patients receiving and adhering to the prescribed drug therapy for successful ACS treatment outcomes and their quality of life.

Patient education is essential, while in hospital and on discharge, in addition to each patient interaction. Pharmacists are best placed in educating patients regarding the reasons for prescribing of specific medication and dosages and the importance of taking their medication as prescribed. Adherence to recommended therapies is vital to secondary prevention of events in ACS patients. It is also important to remember that this can be troublesome for some patients who are prescribed four or more medications on discharge. Such patients would benefit from regular monitoring and interactions with pharmacists and pharmacy teams to ensure adherence and compliance. Poor adherence may result in recurrent episodes of ACS, morbidity, and mortality in addition to rehospitalization and the need for further diagnostics tests, dosage adjustments, and changes to treatment plans (Sokol et al., 2005).

An example of services provided by community pharmacists in the UK is the New Medicines Service (NMS). The service provides support for patients with long term conditions such as ACS who have been newly prescribed medications. This process increases patient engagement with their condition and medicines, while supporting them in making decisions about their treatment and self-management. This will aid in reducing hospital admissions due to adverse events from medicines in addition to a reduction in medicines wastage. The Medicines Use Review (MUR) and Prescription Intervention Service in the UK are examples of other services provided by community pharmacies which focus on improving adherence to treatment.

A study by Nunes et al. (2009b) estimated the level of nonadherence to medicines in patients with long-term conditions to be between 33% and 50%. Several studies show that there is a significant level of non-adherence to secondary prevention medicines by CHD patients. This was associated with a 10%–40% relative increase in risk of cardiac hospitalizations and a 50%–80% relative increase in mortality (Nunes et al., 2009a).

You are presented with two case studies on optimizing ACS management from a primary and secondary care perspective within the UK.

Medication Review in General Practice (Primary Care)

Clinical pharmacist in UK general practice often perform medication reviews for patients on long-term medicines. The aim of these reviews is to ensure patients are getting the best outcomes from their medicines by optimizing the prescribing, minimizing risks, and improving cost effectiveness. In this example a patient with a history of cardiac disease is reviewed.

Age 65 male; White-British; smoker; BMI 27

Previous Medical History

- STEMI 15 months ago
- Mild Left Ventricular Failure
- Hypertension
- Nonulcer dyspepsia
- Latest blood pressure 155/90 mmHg
- No recorded pulse rate
- Urea and electrolytes last done 12 months ago
- No recorded cholesterol since the STEMI
- Kidney function Class G3a 45–59 ml/min/1.73 m^2 (e.g., mild/moderate reduction)

Prescribed Medicines

- Bisoprolol 2.5 mg daily
- Ramipril 2.5 mg daily
- Aspirin 75 mg daily
- Ticagrelor 90 mg twice daily
- Atorvastatin 20 mg daily
- Lansoprazole 15 mg

Treatment Goals

1. To maximize secondary prevention of MI treatments/life style
2. To maximize LVF treatments

Specifically, to:

- Check if the patient is managing with his medicines; is adherent with medicines and if having any problems such as adverse effects
- Manage blood pressure to less than 140/90 mmHg or lower if possible
- Titrate ACE-I and beta-blocker to evidence-based dose or maximum tolerated dose
- Cholesterol aim for a 40% reduction in non-HDl cholesterol
- Stop smoking if possible

Interventions

The medication review firstly involves looking at the patient's clinical record to identify questions and to generate queries that might be answered from the record or might only be answered when the patient is seen.

In this example the following are identified from the record

1. The ticagrelor 90 mg twice can now stop as it is more than 12 months post-STEMI. Ticagrelor at this dose will provide no extra benefit but continued prescribing will increase the bleed risk. The dose should be reduced to 60 mg twice daily or it may be possible to stop all together depending on what advice the cardiologists have given.
2. Can the atorvastatin be increased to 80 mg? If it is increased, then liver function tests (especially ALT) and non-HDL cholesterol will need to be checked once on higher dose.
3. Can the ramipril dose be up-titrated? Is there any evidence in the record that this has been tried before but caused hypotension or worsening kidney function for example?
4. If the ramipril is up-titrated, then a check on Blood Pressure and U&Es will be needed after each dose increase to the evidence-based dose or maximum tolerated dose.
5. Once the ramipril has been managed can the beta-blocker dose be increased to an evidence-based dose or tolerated dose? Again is there evidence in the record that this has been tried before but caused problems such as bradycardia or other unacceptable side effects?
6. If the bisoprolol is up-titrated a check on blood pressure and pulse should be made after the dose increase

The patient is then invited in for a face-to-face review.

At this review any patient ideas, concerns, or expectations about the condition and the treatments should be explored before moving onto the pharmacist's agenda. The pharmacists will explain to the patient:

1. The treatment plan for the ACE-I and beta-blocker and check if the patient has had a failed dose titration before; the benefits of dose titration what adverse effects to expect.
2. Why you are recommending a change in ticagrelor dose and what side effects to expect, especially the bleed risk and what to do if a bleed occurs.
3. The benefits of smoking cessation advice and what support the practice can offer support.

The pharmacists should explore whether the patient has any adverse effects such as cough from ACE-I; muscle pains from atorvastatin; bleeds from antiplatelets. If any of these are present then appropriate action should be taken, e.g., change ACE-I to an ARB, recommend to GP a review of the antiplatelets.

Depending on the pharmacist's level of clinical examination expertise an assessment may also need to be made of whether loop diuretic are required for the LVF. If the pharmacists is less experienced and the patient is complaining of ankle swelling, symptoms of pulmonary edema than the pharmacist could refer onto a GP colleague or nurse practitioner within the surgery.

The lansoprazole should be left at 15 mg daily to provide gastro-protection against dual antiplatelet treatment.

Case Study of a Consultant Cardiologist Pharmacist Working in Secondary Care

CHD is the leading cause of death both in the UK and worldwide. Every year the Leeds Teaching Hospitals NHS Trust cardiology department treats over 2500 patients with myocardial infarction. Our audits showed that post-MI patients are waiting too long to be seen in outpatient cardiology for a review postdischarge. Many did not have all their cardiovascular risk factors and medicines optimized. We developed and delivered a new Consultant Pharmacist Led Post for Myocardial Infarction Medicines Optimization service to tackle these issues and improve patient experience and outcomes.

The multidisciplinary (MDT) medicines optimization outpatient clinics include both a Consultant Cardiology Pharmacist and a Consultant Cardiologist/interventionist. In the clinic, patients are triaged to see either a consultant pharmacist, a consultant cardiologist or both.

The consultation offered is based on the principles of medicines optimization as defined by NICE. Patients' needs and issues they wanted addressing are tackled and given priority. Patients receive full advice and provided with a clear plan which is shared with their GP and the cardiac rehabilitation team.

This new innovative service greatly improved medicines optimization post-MI, reduced patient's waiting time to be seen in outpatient cardiology postdischarge, and was associated with reduction in readmissions. The feedback from patients was tremendously positive. Patients expressed their extreme satisfaction with the service and indicated that their medicines needs were met and their concerns were alleviated.

The plans are to widen the service. Currently we are expanding the service by training advanced cardiovascular pharmacists to support these clinics.

Monitoring

Close monitoring of patients with ACS diagnosis and treatment is required which warrants a review by the cardiologist within 1–2 weeks of postdischarge. Lipid levels should be monitored at least every 6 months until a target LDL <1.8 mmol/L (<70 mg/dL) is reached. It may also be necessary to request cardiac ultrasounds to evaluate and monitor ventricular function (Amsterdam et al., 2014).

In addition to promoting healthy lifestyles patients should be encouraged to quit smoking when appropriate, increase physical activity and where available signpost patients to cardiac rehabilitation which has been proven to be extremely helpful in ACS patients.

Cardiac rehabilitation, a long-term multifaceted program including exercise, dietary and lifestyle interventions, patient education, and counseling is associated with improved clinical outcomes and should be promoted to all patients. Psychosocial risk factors such as anxiety and depression should be addressed in all ACS patients and pharmacists are best placed to screen and refer patients presenting with symptoms indicative of these conditions and this should be managed through pharmacological treatment where appropriate. Depression in particular has been associated with a poor prognosis (Lichtman et al., 2014).

Furthermore, ejection fraction should be assessed by echocardiography 3 months after the acute episode and then periodically thereafter, depending on LV function and symptoms. Patients with ejection fraction <35% at 3 months' follow-up should be referred to an electrophysiologist for consideration of an Implantable Cardioverter, as there is a high risk for arrhythmias in this population. Patients who develop diminished LV function and congestive heart failure should be followed up and managed appropriately (Sallam et al., 2015). Patients should also be encouraged to maintain their blood pressure <140/90 mmHg in the absence of known coronary artery disease conditions, diabetes, renal disease, or heart failure. Patients should also be encouraged to tightly control their blood glucose levels and should strive to keep their HbA1C <0.07 (<7% of total hemoglobin) especially in patients with diabetes (Roffi et al., 2016).

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Management of Coronary Artery Disease & Dyslipidemia and Pharmacist's Role

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Learning Objectives

Upon completion of reading the chapter, the reader will be able to:

1. Describe the epidemiology and the pathophysiology of coronary artery (heart) disease.
2. Assess cardiovascular risk in patients at risk of atherosclerotic cardiovascular diseases.
3. Discuss the current evidence and recent advances in the primary prevention of coronary artery (heart) disease.
4. Evaluate the current evidence and recent advances in the therapeutics of acute coronary syndromes and dyslipidemia.
5. Recommend secondary prevention (long-term management) of coronary artery (heart) disease.
6. Describe the role of pharmacist in the care of patients with coronary heart artery (heart) disease.

Take Home Messages

- Coronary artery disease (CAD), also called coronary heart disease (CHD) or ischemic heart disease (IHD), comprises of the following common clinical manifestations: (1) chronic stable angina and (2) acute coronary syndromes (ACS) of ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina.
- CAD is as a result of an imbalance between myocardial oxygen demand and oxygen supply that is most often caused by coronary atherosclerosis.
- The clinical management of the wide spectrum of CAD is highly variable and is based on the manifestations a patient is experiencing.
- Early detection and modification of modifiable risk factors is a key strategy for delaying the progression of CAD and preventing CAD-related complications including mortality.
- Patients with angina-type chest pain (i.e., chest pressure that is typically provoked by activity and relieved with rest) should be assessed for CAD, whether or not the pain is associated with discomfort in the neck, shoulder, or arm.
- The goals of therapy for CAD depends on the clinical manifestation, but generally clinicians aim to control risk factors, alleviate acute symptoms of myocardial ischemia, prevent acute coronary syndromes, and prevent recurrent symptoms of myocardial ischemia or adverse cardiac events.
- The role of pharmacist in the management of CAD has become increasingly important as the primary focus of management shifts to optimizing drugs and targeting cardiovascular risk factor goals.
- Evidence has shown that HMG-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitors (ACEIs), antiplatelets, and β-blockers provide vasculoprotective effects and reduce the risk of acute coronary events as well as mortality in patients with CAD.
- In all patients with a history of myocardial infarction without contraindications, antiplatelet therapy with aspirin should be considered, but dual antiplatelet therapy with P2Y12 inhibitors (e.g., clopidogrel, prasugrel, ticagrelor) may be considered in some patients.
- Other agents such as calcium channel blockers, nitrates, and anticoagulants are also used on as needed basis in the setting of CHD, depending on the specific diagnosis as well as patient's comorbidities.
- It is recommended that patients with a history of angina should have sublingual nitroglycerin tablets to relieve acute ischemic symptoms and should be educated on its use and when to call emergency medical service.
- Patients with CHD should be regularly monitored for drugs effectiveness, safety, and adherence.

Epidemiology and Pathophysiology of Coronary Artery (Heart) Disease

Definition of Coronary Artery Disease

Coronary artery disease (CAD), also termed coronary heart disease (CHD) or ischemic heart disease (IHD), is a global term referring to a wide spectrum of diseases comprising of stable angina, progressive angina, unstable angina (UA), non-ST-segment elevation

myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (Agarwal et al., 2010). CHD occurs most commonly due to CAD, which is characterized by atherosclerotic narrowing of the coronary arteries. This results in myocardial ischemia and therefore is also known as IHD. These terms are used interchangeably among health-care professionals, although they may not sometimes refer to the same. CHD can present in a chronic form known as chronic stable angina also simply known as "stable angina" or in an acute form known as "acute coronary syndrome (ACS)." ACS comprises of STEMI, NSTEMI, and UA.

Epidemiology and Global Burden of Coronary Artery Disease

Cardiovascular diseases (CVD) are one of the leading causes of morbidity and mortality worldwide. The global incidence and prevalence of CVD is 54 million and 469 million, respectively (Disease et al., 2017). Importantly, the global incidence and prevalence of IHD is 20 million and 153 million, respectively. Globally, death due to CVD is estimated to be 17.6 million (Collaborators, 2017). This represents an increase of 14.5% between 2006 and 2016. IHD is responsible for 53.7% of all deaths due to CVD and accounts for 9.48 million deaths worldwide. This represents an increase of 19% between 2006 and 2016. Globally, IHD is the leading cause of total years of life lost (YLL). Total YLL due to IHD is less in high-income regions such as North America and Western Europe, whereas it is high in other regions such as Central Europe, Central Asia, and Eastern Europe.

Etiology and Pathogenesis of Coronary Artery Disease

CHD occurs when narrowing of the coronary arteries due to a process known as atherosclerosis reduces blood and oxygen supply to the heart. Therefore, oftentimes, the term IHD is used to refer to this group of conditions. This results in an imbalance between myocardial oxygen demand and supply. Consequently, during times of increased physical activity, oxygen supply to the heart is unable to meet the requirements of the functioning heart resulting in ischemia. In some forms of CHD, the atherosclerotic plaque ruptures resulting in further reduction in lumen of the coronary arteries due to thrombus formation and even occlusion leading to total lack of oxygen supply to the heart resulting in necrosis of the myocardium known as infarction (Antman and Loscalzo, 2018a, 2018b). Furthermore, inadequate perfusion of the myocardium results in decreased myocardial oxygen tension. This could affect the biochemical, electrical, and contractile functions of the heart. Since atherosclerosis tends to be focal, ischemic episodes affect certain regions of the myocardium, resulting in regional disturbances in contractile function. Initial periods of ischemia affect the endothelial function, reduce subendocardial perfusion, and alter cardiac energy metabolism. Prolonged periods of ischemia affect the relaxation and contractile functions of the heart (Antman and Loscalzo, 2018a, 2018b; Shaw et al., 2009).

Risk Factors of Coronary Artery Disease

The Framingham study was the first to identify several risk factors that could potentially increase the risk of CVD. Among these, the major risk factors are high blood pressure, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, smoking, and diabetes (Vasan et al., 2005). Age, gender, and psychosocial issues also constitute risk of developing heart diseases. Risk factors are classified depending on whether they are amenable to modification or not. The five leading modifiable risk factors are hypertension, high blood cholesterol levels, smoking, diabetes, and obesity. Others include lack of physical activity, diet, and stress. Conversely, nonmodifiable risk factors include age, gender, family history, and race. In about 90% of individuals experiencing CHD, at least one risk factor is present. Male gender tends to have a higher risk of CHD compared to female. The incidence of CHD in men is about threefold higher than women, and mortality is fivefold higher.

Chronic Stable Angina

Chronic stable angina occurs primarily as a result of inadequate myocardial perfusion resulting in imbalance between oxygen demand and supply. This inadequate perfusion is due to reduction in lumen of the epicardial coronary arteries, which most often occurs due to a process known as atherosclerosis.

Pathophysiology of Chronic Stable Angina

Atherosclerosis is a process that leads to accumulation of lipids in arterial wall of coronary arteries (Ross, 1986, 1999). Atherosclerotic plaque in arterial wall causes fixed partial obstruction of the coronary artery lumen resulting in reduced or inadequate oxygen supply to the myocardium under conditions of increased oxygen demand such as exercise (Antman and Loscalzo, 2018a, 2018b). One of the initial events that leads to atherosclerosis is endothelial dysfunction. Normally, the endothelium functions to maintain vascular tone and prevents platelet aggregation. Nitric oxide is one important factor that mediates normal functions of the endothelium. Endothelial dysfunction results in decreased nitric oxide generation resulting in endothelial activation and inflammation. Atherosclerosis begins with the formation of a fatty streak, which includes accumulation of lipids within the arterial wall. Endothelial activation recruits monocytes that transform into macrophages and uptake oxidized LDL. Oxidative stress within the fatty streak results in the development of atherosclerotic plaque. Smooth muscle cell migration and proliferation into the plaque result in the growth of plaque. This atherosclerotic plaque further reduces blood flow through the arterial lumen and is often observed in chronic stable angina. However, in ACS that is detailed below, inflammation leads to plaque rupture, adhesion and aggregation of platelets as well as activation of the coagulation cascade resulting in thrombus formation.

Clinical Presentation of Chronic Stable Angina

The condition is characterized by angina pectoris that presents as mild chest discomfort generally described as heaviness, pressure, or squeezing in character over the sternum (Antman and Loscalzo, 2018a, 2018b; Wright and Antoniou, 2012). Patients rarely experience frank pain. The discomfort may radiate to the shoulder, arms (ulnar surface), jaw, interscapular region (back), neck, and the epigastric region. This typically occurs in individuals during exertion (exercise) or emotion (anger or frustration). Importantly, patients with stable angina describe the discomfort as recurring after a certain fixed level of activity such as after walking for a certain distance or taking a certain number of flight of stairs, which is due to fixed coronary obstruction. This discomfort usually lasts for a few minutes and is relieved by rest or nitrates. However, stable angina may present with atypical symptoms in women and patients with diabetes in terms of location and may not be provoked by the factors mentioned above. The occurrence of such discomfort may be seasonal, being more common in the winter. In patients with diabetes and the elderly, other symptoms known as anginal equivalents such as dyspnea, nausea, fatigue accompanied by episodes of fainting may be observed.

Diagnosis of Chronic Stable Angina

Diagnosis of stable angina in patients with history of CAD can usually be made based on a known or typical history of angina, classic symptoms and whether additional cardiovascular risk factors are present (Antman and Loscalzo, 2018a, 2018b; Wright and Antoniou, 2012). However, investigations are necessary to confirm or rule out a diagnosis and to determine the extent of the disease. The initial choice of diagnosis is an exercise stress test with electrocardiogram (ECG), or imaging. In patients who are unable to perform exercise, pharmacological stress testing may be utilized. Exercise ECG changes such as ST depression of >0.2 mV suggest ischemia. In addition, investigations for evaluation of risk factors such as diabetes, renal disease, hyperlipidemia, and highly sensitive C-reactive protein (hsCRP) may be useful.

Acute Coronary Syndromes

ACS refers to a spectrum of clinical conditions ranging from UA to NSTEMI to STEMI due to acute myocardial ischemia (Kumar and Cannon, 2009). However, based on the need for evaluation of patients presenting with symptoms suggestive of ACS and the management strategy, ACS can be broadly classified as (1) acute myocardial infarction STEMI on ECG and (2) non-ST-segment elevation ACS (NSTE-ACS). The latter is further classified as those without myocardial necrosis known as UA or those with evidence of myocardial necrosis known as NSTEMI (Antman and Loscalzo, 2018a, 2018b; Giugliano et al., 2018).

Pathophysiology of Acute Coronary Syndromes

Once atherosclerotic plaque is formed, its progression and stability plays a role in the pathogenesis of ACS (Fuster et al., 1992; Kumar and Cannon, 2009; Libby, 2001). In some individuals, the characteristic of the atherosclerotic plaque may be described as being high risk or vulnerable plaque based on their tendency to rupture (Moreno et al., 1994). Even within the same individual, plaques at different locations may have different characteristics. Vulnerable plaques have a large lipid core surrounded by a thin fibrous cap, increased expression of matrix metalloproteinases that degrade collagen, outward remodeling of the atherosclerotic plaque all of which increase the risk of rupture of the plaque. These vulnerable plaques are abundant in macrophages and T lymphocytes and have very little smooth muscle cells. Macrophages promote inflammation, which determine the vulnerability of the plaques.

An important event that determines the occurrence of an acute coronary event is plaque disruption and subsequent thrombus formation. In most cases of fatal myocardial infarction, plaque rupture is the cause, while 25% of cases occur due to endothelial erosion (Moreno et al., 1994; van der Wal et al., 1994). In both cases, an overlying thrombus formation partially or totally occludes coronary lumen resulting in an acute coronary event. After plaque rupture or endothelial erosion, thrombus formation is initiated by the exposure of subendothelial matrix to circulating blood. Platelet adhesion to the arterial wall is mediated by the platelet Gp1b-IX receptor and von Willebrand factor (VWF) on endothelial cells. Upon subsequent platelet activation by agonists such as adenosine diphosphate (ADP), platelet aggregation is mediated by the platelet receptor GpIIb–IIIa and fibrinogen. Thrombin of the coagulation cascade activates factor XIII to XIIIa and also converts fibringen to soluble fibrin which is made into insoluble fibrin by factor XIIIa, resulting in a firm thrombus (clot) which traps platelets. These processes together result in formation and enlargement of the thrombus. STEMI is associated with rapid formation of thrombus that totally occludes the coronary artery lumen, while in UA/NSTEMI, thrombus formation is slow and partially occludes the artery.

Clinical Presentation of Acute Coronary Syndromes

UA and NSTEMI have certain similarities in terms of pathophysiologic mechanisms, clinical presentation, and management and will therefore be considered together. Chest pain is the most common presenting symptom in patients with both NSTEMI/UA and STEMI. It is described as severe heavy crushing chest pain, substernal in location that radiates to arms, lower jaw, neck, and occasionally to the abdomen, and lasts more than 10–20 min. The pain is very similar to that observed in angina, except that it is severe and lasts longer. This pain may occur at rest and is most common in the morning. Chest pain may also be accompanied by sweating (diaphoresis), nausea, vomiting, anxiety, and fear of impending doom. In addition, anginal equivalents such as breathlessness, loss of consciousness, or hypotension may suggest ACS (Antman and Loscalzo, 2018a, 2018b; Kumar and Cannon, 2009).

Diagnosis of Acute Coronary Syndromes

Diagnosis of NSTEMI/UA is based on ECG and cardiac biomarkers. A diagnosis of NSTEMI is made in such patients by the presence of cardiac biomarkers such as cardiac troponins and CK-MB, which are absent in UA (Kumar and Cannon, 2009). This may or may not be accompanied by ischemic ECG changes such as ST-segment depression, transient ST-segment elevation, or T-wave inversion. Similarly, both ECG and cardiac biomarkers are important in the diagnosis of STEMI. ECG criteria for the diagnosis of STEMI include: (1) New ST segment elevation at the J point in two contiguous leads of >0.1 mV in all leads except V2-V3. For leads V2-V3, ≥0.2 mV in men ≥40 years, ≥0.25 mV in men < 40 years, or ≥0.15 mV in women or (2) New left bundle branch block (LBBB) (Thygesen et al., 2012). Cardiac biomarkers are useful in establishing a diagnosis of STEMI. Cardiac-specific Troponin T and I are highly accurate and sensitive for the determination of myocardial injury (Alpert et al., 2000; Thygesen et al., 2007). However, these biomarkers may not be elevated up to 6 h after myocardial necrosis and therefore may need to be measured at presentation and after 3–6 h in patients with high suspicion for STEMI. Therefore, management decisions should be made largely based on clinical presentations and ECG findings.

Management of Acute Coronary Syndromes

Detailed information about the management of ACS is available in another chapter within the Encyclopedia. Therefore, our intention is to summarize the major evidence-based recommendations as provided in most recent clinical practice guidelines.

Acute Pharmacological Management—Onset of Stabilization

The initial management plan on presentation for patients with ACS is summarized in Table 1.

Table 1 Interventions on presentation and for onset of stabilization for any ACS (American College of Clinical Pharmacy (ACCP), 2016a; Amsterdam et al., 2014; Ibanez et al., 2018; O'Gara et al., 2013; Roffi et al., 2017)

Intervention	*Comments*
Oxygen	• Reduces the ischemic burden secondary to tissue hypoxia. • Supplemental oxygen should be considered if SaO_2 is less than 90%, respiratory distress, or other high-risk features of hypoxemia. • Oxygen is administrated at a rate of 2–4 L/min via nasal cannula. • It should be administered with caution in patients with chronic obstructive pulmonary disease (COPD) and carbon dioxide retention.
Nitrates	• Ameliorates signs and symptoms of MI by reducing left ventricular preload and increasing coronary blood flow. • Administer one sublingual nitroglycerin (NTG) tablet or one aerosol spray under tongue every 5 min up to three doses, then assess the need for IV NTG. • IV NTG is indicated if patient has persistent ischemia, HTN, or signs of heart failure (HF), provided there are no sign of hemodynamic compromise and no contraindication for its use. IV NTG can also be helpful in patients with pulmonary edema.
Aspirin	• Inhibits platelet aggregation. • Irrespective of the need for thrombolytic therapy, non-enteric-coated aspirin (162–325 mg) should be chewed and swallowed immediately, unless there is a compelling contraindication (e.g., history of anaphylactic reaction). • Patients with severe nausea and vomiting or known upper gastrointestinal disorders may use a rectal suppository dose of 600 mg.
Morphine	• Provides potent analgesic and anxiolytic effects and attenuates pain-induced sympathetic hyperactivity that increases myocardial oxygen demand and predisposes patients to tachyarrhythmias. It may also induce vasodilation. • IV morphine may be reasonable for continued ischemic chest pain despite maximally tolerated antiischemic medications. • Administer a dose of 2–4 mg IV over 1–2 min and repeat at 5–15 min intervals until ischemic pain is relieved or side effects occur (i.e., hypotension, respiratory depression, or vomiting) that preclude further administration.
β-Blocker	• Reduces myocardial oxygen consumption by reducing heart rate, contractility, and blood pressure and increases diastolic filling time of ventricles, thus produce favorable redistribution of coronary blood flow. • Oral β-blocker (without increased sympathomimetic activity) should be administered within the first 24 h of acute MI unless contraindicated. • May initiate IV β-blocker in patients with refractory hypertension or ongoing ischemia.
Statin	• In addition to LDL lowering, statin my lead to plaque stabilization, reversal of endothelial dysfunction, decreased thrombogenicity, and reduced inflammation. • High-intensity statin therapy (80 mg of atorvastatin or 20–40 mg of rosuvastatin daily) should be started as soon as possible after the diagnosis of ACS is established.

Revascularizations: Nonsurgical and Surgical

Nonsurgical Interventions

Details of interventional cardiology procedures are too broad to be discussed in this chapter and will be found elsewhere within the textbook. However, the following are some recommendations for preprocedural considerations and interventions in patients undergoing cardiac catheterization and percutaneous coronary intervention (PCI): (Ibanez, 2018; Levine et al., 2011, Levine, 2016; O'Gara et al., 2013).

1. Contrast-induced acute kidney injury (AKI)
    a. Patients should be assessed for the risk of contrast-induced AKI before PCI.
    b. Patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration:

    Isotonic crystalloid (1.0–1.5 mL/kg/h) for 3–12 h before the procedure and continuing for 6–24 h after the procedure.
    N-acetyl-L-cysteine does not prevent contrast-induced AKI in patients undergoing angiographic procedures.

2. Patients with evidence of an anaphylactic reaction to contrast media should receive appropriate prophylaxis before repeat contrast administration.
3. Administration of a high-dose statin is reasonable before PCI to reduce the risk of periprocedural MI (Class IIaA for statin-naïve patients and IIaB for those on chronic statin therapy).
4. The glomerular filtration rate should be estimated and the dosage of renally cleared medications should be adjusted (e.g., eptifibatide, tirofiban, bivalirudin).
5. Bleeding risk—All patients should be evaluated for risk of bleeding before PCI and measures to minimize the risks of bleeding complications instituted.
6. Aspirin—Patients already on daily aspirin therapy should take 81–325 mg before PCI, while patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI.

Common nonsurgical interventions (ACCP, 2016a, 2016b; Byrne et al., 2015; Helms et al., 2006; Ibanez et al., 2018; O'Gara et al., 2013; Roffi et al., 2016).

1. Plain old balloon angioplasty: Balloon inflation and at least temporary displacement of occlusion at site of lesion
    a. It is reasonable to perform balloon angioplasty without stenting in patients with high bleeding risk, inability to comply with 12 months of dual antiplatelet therapy (DAPT), or anticipated invasive or surgical procedures within the next 12 months, during which time DAPT may be interrupted.
    b. Risk of early abrupt vessel closure, coronary dissection, and relatively high rate of restenosis at the site of the treated lesion.
2. Stent placement
    a. It is important to take into consideration patient characteristics (e.g., medication adherence, risk of bleeding, financial status), types of stents, number of stents placed, and locations of stent placement.
    b. Bare metal stent (BMS)

    Requires aspirin for life and $P2Y_{12}$ antagonist (clopidogrel, ticagrelor, prasugrel) for at least 1 month (12 months preferred) to allow adequate time for endothelization of the stent(s)
    Preferred over drug-eluting stent in patients with high bleeding risk, inability to comply with 12 months of DAPT, or anticipated invasive or surgical procedures within the next 12 months, during which time DAPT may be interrupted
    Higher risk of in-stent restenosis over time as reendothelialization occurs

    c. Drug-eluting stent (DES)

    Reduce the rate of restenosis and, accordingly, target lesion revascularization compared to BMS
    Requires aspirin for life and $P2Y_{12}$ antagonist for at least 12 months. Longer duration may be considered, depending on the number and/or location(s) of the stent(s)
    Associated with lower rate of in-stent restenosis compared to BMS
    Higher risk of stent thrombosis; the rate of endothelialization over the stent is slowed by the drug coating on the stent, thus leaving metal exposed that can potentiate thrombus formation

Surgical Interventions

Again, details of PCI and coronary artery bypass grafting (CABG) procedures are too broad to be discussed in this section. According to the Society of Thoracic Surgeons/American College of Cardiology/American Heart Association (STS/ACC/AHA) CABG guidelines (2013), there are some recommendations for preprocedural considerations and interventions in patients undergoing urgent CABG

1. Aspirin (100–325 mg daily) should be administered to CABG patients preoperatively.
2. Clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications.

3. Short-acting IV glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2–4 h before surgery and abciximab for at least 12 h beforehand to limit blood loss and transfusions.
4. β-Blockers should be administered for at least 24 h before CABG to all patients without contraindications to reduce the incidence or clinical sequelae of postoperative atrial fibrillation (AF).
5. Preoperative administration of amiodarone to reduce the incidence of postoperative AF is reasonable for patients at high risk for postoperative AF who have contraindications to β-blockers.
6. Digoxin and nondihydropyridine calcium channel blockers can be useful to control the ventricular rate in the setting of AF, but are not indicated for prophylaxis.

Parenteral Antithrombotic Therapy in Acute Management of Acute Coronary Syndromes

Table 2 provides a summary of guidelines recommended parenteral antithrombotic agents used in acute management of ACS. The optimal use of these agents depends on the treatment strategy used and the diagnosis of STEMI compared with NSTEMI/UA.

The choice of an agent may depend on the diagnosis, management plan (i.e., invasive or ischemia-guided), timing/dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of the procedure.

Primary Prevention of Coronary Artery Disease

A group of risk factors contributes to CHD. These are not equally contributing to CHD, but they are affected by the presence of each other. Studies have demonstrated that primary prevention results in a decrease in the burden of CVD in patients who are at risk (Ebrahim, 2005; Puska, 2010). The focus of this section will be mainly on the modifiable and nonmodifiable risk factors of CHD, early identification of risk groups and their assessments, and the strategies that can be applied in primary care to modify the risk factors and prevent the development of new-onset CVD.

Risk Factors of CHD

Nonmodifiable Risk Factors

Advanced age, gender, family history of premature CHD are nonmodifiable risk factors for CHD that cannot be avoided or controlled (Lloyd-Jones, 2010). Guidelines indicated that, in both women and men, absolute risk of CHD increases with age due to atherosclerosis (Grundy et al., 1998). The development of CVD in women is 10 years later than in men (Epstein and Wei, 1992). However, the overall prevalence of CVD is more common in men than in women. In addition, the transition of menopause is associated with a worsening CHD risk profile (Maas and Appelman, 2010). Another strong indicator of CHD risk is family history of premature CHD, which is defined as having a definite MI or sudden cardiac death before age 55 years in first-degree male relatives, or before age 65 years in first-degree female relatives (Jellinger et al., 2017a, 2017b). Genetic factors are also considered as nonmodifiable risk factors for CHD (Steinberg and Cannon, 2016). Odonnell and Nabel (2011) have highlighted that many loci, which were identified by genome-wide association studies, contained genes that are crucial in the pathways that contribute to CVD development.

Modifiable Risk Factors

Dyslipidemia, diabetes mellitus, hypertension (HTN), and smoking are established atherosclerotic cardiovascular disease (ASCVD) risk factors that can be controlled if identified early.

Low-density lipoprotein cholesterol (LDL-C) has a great role in the process of CHD. It is reported that relative risk of CHD increases by 30% for every 30 mg/dL rise in LDL-C above 40 mg/dL and by reducing LDL-C by 1.0 mmol/L, the risk reduction in CVD mortality and nonfatal MI is estimated to be 20%–25% (Piepoli et al., 2016). The increase in high-density lipoprotein cholesterol (HDL-C) is associated with a reduction in CHD mortality. Thus, HDL-C is considered a negative cardiac risk factor, unlike high triglycerides levels, which increase CVD risk (Steinberg and Cannon, 2016). It is reported that type 2 diabetes mellitus (T2DM) is associated with a twofold increase in CHD mortality in men and threefold in women (Steinberg and Cannon, 2016). It should be noted also that this factor is always linked to obesity and physical inactivity, which are lifestyle risk factors for CHD. Furthermore, individuals who are diagnosed with HTN have ASCVD five years earlier than individuals with no HTN. The risk of death from stroke, heart disease, or other vascular disease is doubled with each systolic blood pressure rise of 20 mmHg and each diastolic blood pressure rise of 10 mmHg. Also, meta-analyses have demonstrated that prehypertension is associated with an increased risk for CVD and mortality (Benjamin et al., 2017). Finally, *to*bacco smokers are at an increased risk of developing CHD. This predictor is the most significant preventable contributing factor. Smoking in a short term leads to platelet aggregation and oxygen supply reduction. In the long-term, smoking causes an increase in triglycerides (TG), a decrease in HDL-C, endothelial damage, elevation of inflammatory markers, and rise in cortisol secretion (Wakabayashi and Groschner, 2013).

Other CHD Predictors

Guidelines discuss other risk factors that should be considered when evaluating an individual at risk of ASCVD. High level of high-sensitivity C-reactive protein (hs-CRP), which is a biomarker of vascular inflammation, has been associated with increased risk of

Table 2 Parenteral antithrombotic agents used in acute coronary syndromes (ACCP, 2016a; Bradley and Hass, 2017; Garcia et al., 2012; Helms et al., 2006; Zeind and Carvalho, 2018)

Medication	*Heparin (UFH)*	*Enoxaparin*	*Fondaparinux*	*Cangrelor*
	Indirect thrombin inhibition—mediates decreased propagation of clot			*$P2Y_{12}$ antagonist*
Mechanisms of action	*Inhibits factor IIa and Xa*	*Inhibits factor Xa> IIa*	*Inhibits factor Xa> IIa*	
Dosing	**Fibrinolysis[a], NSTEMI/UA, or ischemia-guided therapy[b]:** • 60 unit/kg bolus (max 4000 units) + 12 units/kg/hr infusion (initial max 1000 units/hr), titrated to therapeutic aPTT for 48 h or until revascularization **PCI with planned GPI:** • 50–70 units/kg IV bolus to achieve therapeutic ACT **PCI without planned GPI:** • 70–100 units/kg IV bolus to achieve therapeutic ACT	**Fibrinolysis:** • ≤75 yr: 30 mg IV bolus then 15 min later 1 mg/kg SC q12hr (max 100 mg for first two doses, give first dose with initial IV dose) • >75 yr:No bolus, 0.75 mg/kg SC q12hr (max 75 mg for first two doses) • Duration is for index hospitalization up to 8 days, or until revascularization **NSTEMI/UA/ischemia-guided therapy:** • 1 mg/kg SC q12hr for duration of hospitalization or until revascularization Primary **PCI:** • 0.5–0.75 mg/kg IV bolus if no anticoagulation previously 0.3 mg/kg IV if last SC dose was > 8 hr before PCI, or only one SC dose given	**Fibrinolysis:** • 2.5 mgIV × 1,then 2.5 mg SC daily starting the next day for index hospitalization up to 8 days or until revascularization **NSTEMI/UA /ischemia- guided therapy:** • 2.5 mg SC daily for duration of hospitalization or until revascularization **PCI:** • Not recommended without additional anticoagulant with anti-II activity	**PCI:** • 30 μg/kg IV bolus, 4 μg/kg/min infusion for at least 2 hr
Recovery of platelet function	N/A	N/A	N/A	Within 1 hr of discontinuation
Elimination	Hepatic and reticuloendothelial system	Renal	Renal	58% renal and 35% in feces inactive metabolite
Monitoring	aPTT, anti-Xa, and/or ACT (200–250 s during PCI with GPI or 250–300 s without GPI), Hgb, Hct, Plt, bleeding	Renal function, Hgb, Hct, Plt, anti-Xa (as indicated)	Renal function, Hgb, Hct, Plt, SrCr	Bleeding
Clinical pearls	• Cannot be used in patients with a history/suspicion of HIT	• Cannot be used in patients with history of HIT • If CrCl < 30 mL/ minute/1.73 m^2, 1 mg/kg SC daily	• Avoid if CrCl < 30 mL/minute/1.73 m^2 • Should not be used as a sole anticoagulant for PCI	• Must be loaded with oral $P2Y_{12}$ antagonist on transition off the infusion

Medication	*Bivalirudin*	*Abciximab*	*Eptifibatide*	*Tirofiban*
Mechanisms of Action	Direct thrombin (II) inhibitor	GP IIb/IIIa inhibitor		
Dosing	• ACS: 0.15–2 mg/kg/hr infusion, titrated to aPTT goal • PCI: 0.75 mg/kgIV bolus + 1.75 mg/ kg/hr infusion	• PCI: 0.25 mg/kg IV/IC bolus, followed by 0.125 μg/ kg/min (max 10 μg/min) for 12 hr	• ACS: of uncertain benefit in patients adequately pretreated with a P2Y12 antagonist; single bolus used as in PCI • PCI: 180 μg/kg IV bolus (max 22.6 mg) × 2 (10 min apart) for PCI, followed by 2 μg/kg/min (max 15 mg/hr) infusion for 18–24 hr	• ACS: 0.4 μg/kg/minute for 30 min, then 0.1 μg/kg/ minute for 18–72 h • PCI: 25 μg/kg IV bolus followed by 0.15 μg/kg/min for 18–24 h
Recovery of platelet function	N/A	Within 24–48 h of discontinuation	Within 6–8 h of discontinuation	Within 4–8 h of discontinuation
Elimination	80% plasma proteolysis, 20% renal	Proteolytic cleavage	Renal	Renal
Monitoring	PTT and/or ACT as indicated (200–250 s during procedure), renal function, Hgb, Hct	Bleeding, Hgb, Hct, Plt, aPTT, PTT	Renal function, bleeding, PT/aPTT (maintain aPTT between 50 and 70 s unless PCI is to be performed), ACT with PCI (200–300 s during PCI)	Bleeding, Hgb, Hct, Plt,
Clinical pearls	• If CrCl $<$ 30 mL/ minute/1.73 m^2, reduce infusion to 1 mg/kg/h • If on hemodialysis, reduce infusion to 0.25 mg/kg/h • Can be used in patients with/without history of HIT	• Not recommended in ACS without PCI • Murine monoclonal antibody—may produce antigenicity	• If CrCl $<$50 mL/min Reduce infusion to 1 μg/kg/min • Contraindicated in ESRD	• If CrCl $<$ 60 mL/min/1.73 m^2, reduce infusion to 0.075 μg/kg/min

NSTEMI, non-ST-segment elevation acute coronary syndrome; UA, unstable angina; PCI, percutaneous coronary intervention; GPI, glycoprotein IIb/IIIa inhibitors; ACT, activated clotting times; S, second; Hgb, hemoglobin; Hct, hematocrit; Plt, platelet; HIT, heparin-induced thrombocytopenia; SrCr, serum creatinine; CrCl, creatinine clearance, PPT, prothrombin time; ACT, activated clotting times; S, second; Hgb, hemoglobin; Hct, hematocrit; Plt, platelet; HIT, heparin-induced thrombocytopenia; SrCr, serum creatinine; CrCl, creatinine clearance.

[a]Fibrinolytics preferred when PCI cannot be performed within 120 minutes of first medical contact (class I). Door-to-needle time less than 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 h with IV UFH or IV/ SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[b]Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. Recommended for patients with a low-risk score (TIMI 0 or 1, GRACE less than 109).

CHD, and it is a strong predictor for first CV events (Steinberg and Cannon, 2016). The threshold for hs-CRP to be considered as risk discriminator is when it is more than or equal to 2.0 mg/L (Stone et al., 2014). Another risk factor is coronary artery calcium (CAC) score. Stone et al. (2013) concluded that measuring CAC was a useful approach for individuals at intermediate risk of CHD. Moreover, ankle-brachial index and albuminuria may help in screening patients at risk of ASCVD. However, they are weakly suggested as alternative risk stratifications.

Early Identification of At-risk Individuals and their Assessments

There are several risk calculators that are used to estimate ASCVD in adults including Framingham Risk Calculator, Reynolds Risk Score, ACC/AHA Pooled Cohort Equation Risk Calculator, Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk with Coronary Artery Calcification Calculator, and the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine. Each calculator focuses on a specific outcome. For example, the 10-year and lifetime ASCVD risk can be estimated when using ACC/AHA 2013 Pooled Cohort Calculator. In 2017, the American Association of Clinical Endocrinologists (AACE) published a table for key cardiovascular risk scoring tools, which summarizes the Framingham, MESA, Reynolds, and UKPDS ASCVD risk calculators (refer to AACE 2017 guidelines Page 7-8, for further information). These are useful tools that can be used in primary care for risk assessment and management.

Primary Prevention Strategies for CHD: What can be Done in Primary Care?

Health-care providers (HCPs) at primary care settings should assume their role in primary prevention of CHD and other CVD. They shall discuss with their patients the importance of managing existing risk factors after stratifying their risk. Screened individuals may be eligible for statin, aspirin, and other medical therapies and/or lifestyle modifications.

Statins

Statins have been proposed as the primary pharmacologic agents to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials (AACE, 2017). A systematic review that included 19 RCTs showed that patients who received statins compared to those who did not, experienced fewer MI (RR 5 0.64, 95% CI: 0.57–0.71), ischemic stroke (RR 5 0.71, 95% CI: 0.62–0.82), and cardiovascular mortality (RR 5 0.69, 95% CI: 0.54–0.88). Regarding its safety with lifelong use, statins are remarkably safe when used for primary prevention. Despite the fact that statins do increase the risk of T2DM, a meta-analysis that focused on primary prevention trials did not find a statistically significant increase in the risk of diabetes (Kazi et al., 2017). AACE guidelines (2017) recommended that for very high-risk individual (based on risk estimators) with diabetes who also has at least one risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL and for extreme-risk individuals, statins is recommended to target an even lower LDL-C treatment goal of <55 mg/dL.

Aspirin

Aspirin use has been encouraged by the American Diabetes Association (2016) for all patients with diabetes who have Framingham score of 10% 10-year risk of CVD. The 2016 European Society of Cardiology (ESC) guidelines and the European Association for the Study of Diabetes (EASD) are against the use of aspirin for primary prevention in patients with diabetes who have no overt CVD (Piepoli et al., 2016; Ryden et al., 2013). Generally, aspirin benefit contributed to a 23% proportional reduction in nonfatal MI in primary prevention. HCPs need to weigh the ischemic and bleeding risk before starting patients on aspirin. When starting aspirin for primary CVD prevention, a low dose (75–100 mg) is recommended (Leggio et al., 2018).

Lifestyle Interventions

Physical inactivity is an important contributor to CHD. When regular physical activity is practiced, blood pressure will decrease and the likelihood of obesity will diminish. Guidelines recommend a steady activity of 30 min for 5 days or more per week. Such activities can include walking, swimming, cycling, and dancing. Also, patients with body mass index (BMI) more than 25 kg/m^2 should be advised to enroll in weight management program and follow a healthy diet so that a target of 5–10 kg weight loss over 3 months is achieved (Blenkinsopp et al., 2014).

Blood Pressure Control

In patients with overt or latent CHD, there are no clinical studies that concluded about the most appropriate target for blood pressure (Vlodaver et al., 2014). Guidelines recommend aggressive blood pressure-lowering approach for patients with HTN. A blood pressure target of <130/80 mmHg is recommended in individuals with diabetes mellitus, chronic kidney disease, CAD risk equivalents, peripheral arterial disease, or abdominal aortic aneurysm (Rosendorff et al., 2007).

Smoking Cessation

Smoking cessation reduces the risk of CVD. HCPs should determine the readiness of patients to quit smoking. Based on their willingness, education, counseling, social support referral, and initiation of the pharmacotherapy shall be determined. Nicotine replacement therapy, bupropion, and varenicline are examples of drugs that can be used (Vlodaver et al., 2014).

Long-term Management of Coronary Artery Disease

After the diagnosis of CAD and the treatment of the acute phase, the next level of treatments is directed toward prevention of future cardiovascular events and death (secondary prevention). The treatment strategy for secondary prevention of CAD targets the multiple modifiable risk factors using multiple approaches. These treatment approaches include medications (pharmacological) and lifestyle changes (nonpharmacological) (Smith et al., 2011). The pharmacological management involves the use of multiple medications from different pharmacological classes, which also target some of the risk factors associated with the CAD process such as HTN and dyslipidemia. The core classes of medications with proven benefit for secondary prevention of CAD include antiplatelet agents (e.g., aspirin and clopidogrel), statins (e.g., atorvastatin), β-blockers (e.g., carvedilol), and angiotensin-converting enzyme inhibitors (ACEIs) (e.g., lisinopril), or angiotensin receptor blockers (ARBs) (e.g., losartan). Other medications include aldosterone receptor blockers (e.g., spironolactone) and vaccinations (e.g., influenza vaccine) (Smith et al., 2011). Lifestyle changes improve the modifiable risk factors associated with CAD and it includes smoking cessation, engaging in physical activity, eating healthy diets, and maintaining healthy weight.

Pharmacologic Agents for Secondary Prevention of Coronary Artery Disease

Antiplatelet Agents

Low-dose aspirin (75–100 mg) is an antiplatelet agent that is recommended to be taken for long-term after CAD for secondary prevention of future CV events (Baigent et al., 2009). Evidence has not shown the benefit of high dose of aspirin (162–325 mg) over the low dose in preventing a future CAD. However, the low-dose aspirin is relatively safer as it is associated with lower incidence of gastrointestinal (GI) bleeding. For patients who are unable to tolerate low-dose aspirin, clopidogrel 75 mg/day is recommended as the long-term antiplatelet agent (Ibanez et al., 2017).

For patients who undergo PCI with stent placement, up to 12 months (6–12 months) of a second antiplatelet agent ($P2Y_{12}$ inhibitor such as clopidogrel, prasugrel, or ticagrelor) is recommended to be administered concomitantly with aspirin (Ibanez et al., 2017). The shorter duration (1–6 months) of DAPT of aspirin and $P2Y_{12}$ inhibitor in earlier guidelines was based on the type of stent (BMS vs. DES) implanted. The use of longer duration of $P2Y_{12}$ inhibitor beyond 12 months (i.e., 18–48 months) for outcomes such as secondary prevention of cardiac events, mortality reduction, and prevention of stent thrombosis have been studied, leading to the approval for the use of $P2Y_{12}$ inhibitor beyond 12 months for prevention of myocardial infarction and late stent thrombosis, but with a trade-off of significant GI bleeding (Bittl et al., 2016; Bonaca et al., 2015; Ibanez et al., 2017; Mauri et al., 2014).

In terms of the mortality benefits of the longer duration of DAPT, the "2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease" suggests that prolonged DAPT does not offer significant all-cause mortality benefit (Levine et al., 2016a, 2016b). For patients with history of CAD, this guideline has a Class I recommendation for the 6–12 months DAPT and a Class II recommendation for DAPT administered beyond 12 months (Levine et al., 2016a, 2016b). It also recommends lower daily doses of aspirin (75–100 mg/day) when DAPT is used (Levine et al., 2016a, 2016b).

The key to reducing the bleeding risk associated with the use of DAPT is to identify patients who are at increased risk of bleeding from DAPT. The factors associated with increased risk of bleeding include history of previous bleeding, oral anticoagulation, female gender, advanced age, CKD, diabetes mellitus, anemia, chronic steroid therapy, and nonsteroidal anti-inflammatory drug (NSAID) therapy (Levine et al., 2016a, 2016b). A risk score called DAPT score has been derived from a large DAPT study in patients who had received DAPT after stent implantation (Mauri et al., 2014). In this study by Mauri et al., 30 months of DAPT (longer duration DAPT) was compared to 12 months of DAPT (shorter duration) (Mauri et al., 2014). The DAPT score, which is based on ischemic and bleeding risk factors, can help in decision making regarding which patients would benefit from a longer duration of DAPT vs. short DAPT duration. A DAPT score ≥ 2 is associated with a favorable benefit/risk ratio for prolonged DAPT. However, DAPT score of <2 is associated with an unfavorable benefit/risk ratio (Yeh et al., 2016). The factors used to calculate the DAPT score and the respective points allocated to each factor are presented in **Table 3**.

Per the "2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease," the addition of a proton pump inhibitors (PPI) to DAPT should be avoided in patients with low risk of GI bleeding. However, in those with a history of GI bleeding, PPI should be added to DAPT. Also, patients at high risk of bleeding (e.g., concomitant use of anticoagulants, NSAIDs or oral steroids) will benefit from the use of PPIs (Levine et al., 2016a, 2016b).

Statins

Statins are initiated in all patients with established CAD who are 75 years or younger irrespective of their baseline LDL-C levels for secondary prevention (Stone et al., 2014). For those who can tolerate high-intensity statin therapy (e.g., atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) is the standard (Stone et al., 2014). If the high-intensity statin therapy cannot be tolerated, then the alternative option is the use of moderate-intensity statin (e.g., simvastatin 20–40 mg/day, pitavastatin 2–4 mg/day, pravastatin 40–80 mg/day, lovastatin 40 mg/day, atorvastatin 10–20 mg/day, or rosuvastatin 5–10 mg/day) (Stone et al., 2014). For patients with established CAD, there is evidence that the intensive statin therapy may be more effective in preventing CAD and death than the moderate-intensity statin therapy (Cannon et al., 2004; LaRosa et al., 2005; Pedersen et al., 2005).

Table 3 Factors used to calculate the score used to stratify patients to shorter vs. longer duration of DAPT

Variable	*Points*
Age ≥75 years	−2
Age 65 to <75 years	−1
Age <65 years	0
Current cigarette smoker	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter <3 mm	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Vein graft PCI	2

CHF, Congestive heart failure; *DAPT*, dual antiplatelet therapy; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention.

Note: A total score of ≥2 is associated with a favorable benefit/risk ratio for prolonged DAPT; a total score of <2 is associated with an unfavorable benefit/risk ratio for prolonged DAPT.

Table adapted from Yeh et al. (2016)

β-Blockers

The use of β-blockers after CAD has two benefits. First, it is associated with prevention of future CAD (secondary prevention) and reduction of cardiovascular mortality (Freemantle et al., 1999; Hall and Lorenc, 2010). Second, it helps to manage BP, which is an established risk factor for CAD. The goal BP in patients with established CAD is less than 140/90 mmHg (James et al., 2014a, 2014b). β-Blockers are recommended for all patients with CAD unless contraindicated (Smith et al., 2011). In patients with CAD and normal LV function, β-blockers started after diagnosis is recommended to be continued for three years (Smith et al., 2011).

However, in CAD patients with LV dysfunction (i.e., ejection fraction (EF) ≤40%), specific β-blockers have been shown to reduce mortality. The β-blockers shown to reduce mortality in CAD patients with LV dysfunction are bisoprolol, carvedilol, and metoprolol succinate (Domanski et al., 2003; Packer et al., 1996; Poole-Wilson et al., 2003).

Angiotensin-converting Enzyme Inhibitors/Angiotensin Receptor Blockers

ACEIs are recommended to be given indefinitely to all CAD patients with LVEF ≤40% as it improves cardiovascular outcomes (Smith et al., 2011). They are also the recommended first-line therapy for CAD patients with HTN who require BP reduction (goal <140/90 mmHg), diabetes, or CKD (Smith et al., 2011). In CAD patients who are unable to tolerate ACEIs, ARBs are used. A meta-analysis of randomized trials published in 2017 showed that in CAD patients without HF, the benefit of ACEIs in reducing all-cause mortality, reducing cardiovascular mortality, and reducing MI was significant when compared to placebo, but not active controls (Bangalore et al., 2017). Based on Bangalore et al., it may be therefore beneficial to give ACEIs to only CAD patients with LV dysfunction if they do not have comorbid HTN, diabetes, or CKD, even though there is evidence that ACEI blockade with ramipril reduces death and cardiovascular events in patients with history of CAD who may not have these comorbidities (Yusuf et al., 2000).

Others

Aldosterone receptor antagonists

Per the "AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update," aldosterone receptor blockers (e.g., spironolactone, eplerenone) are recommended for patients with established CAD who are on therapeutic doses of ACEIs and β-blockers, have LVEF ≤40%, and have either diabetes or HF (Smith et al., 2011). The use of aldosterone receptor blockers (eplerenone 50 mg/day) in those patients on optimal therapy after acute MI significantly reduces morbidity and mortality (Pitt et al., 2003; Zannad et al., 2011).

Vaccines

Annual influenza vaccine is recommended for all Individuals with established CAD irrespective of their age (Smith et al., 2011). Even in younger individuals less than 65 years old with high-risk medical conditions, it has been shown, that influenza vaccination significantly reduces hospitalization from acute respiratory diseases and CVD (CDC, 2017; Hak et al., 2005). Some randomized clinical studies have shown significant mortality benefit (all-cause mortality and cardiovascular mortality) at 12 months in individuals with CAD when they are vaccinated with the seasonal influenza vaccine (Ciszewski et al., 2008; Gurfinkel et al., 2004). However, there is a randomized trial in individuals with established CAD, which did not show significant mortality benefit even though the results showed significant reduction in cardiovascular events (Phrommintikul et al., 2011).

Nonpharmacologic Management for Secondary Prevention of Coronary Artery Disease

Smoking Cessation

Smoking cessation is probably the most important lifestyle modification when managing established CAD. There is a mortality benefit (up to 36% reduction in all-cause mortality) of stopping smoking, hence the need to enrol patients with CAD in smoking cessation programs to aid them to quit smoking (Critchley and Capewell, 2003). Also in patients with established CAD who continue to smoke, there is evidence of increased risk of recurrent coronary events (Rea et al., 2002). However, upon quitting smoking, this risk is reduced to the level of nonsmokers within 3 years (Rea et al., 2002). It is therefore recommended that at each clinic visit of a patient with CAD, smoking status is assessed using the "5 A's" approach to smoking intervention (Siu, 2015; Smith et al., 2011).

Physical Activity

Inadequate physical activity is a risk factor for CAD. But, there are multiple benefits of physical activity which include improving the other CAD risk factors such as LDL-C, HDL-C, weight, and BP. Physical activity include various activities such as walking, running, swimming, gardening, cleaning, and resistance exercises. Most organizations have guidelines that recommend 30 min of physical activity most days of the week. For patients with established CAD, physical activity should be recommended as tolerated after a thorough assessment due to potential limitation of physical activity as a result of CAD (Smith et al., 2011).

Healthy Diet

Healthy diet encompasses the consumption of diet from various food groups such as fruits, vegetables, legumes, whole grains and nuts, and fish and lean meat. In addition, the intake of foods such as red meat, non-vegetable oils/saturated fats, processed foods, sugary drinks, and high-calorie foods should be limited (Eckel et al., 2014). Different diet plans such as the Dietary Approaches to Stopping Hypertension (DASH) diet include foods from the various healthy food groups.

Weight Management

An added advantage of the lifestyle changes (i.e., diet and physical activity) is weight management. Being overweight with a BMI of 25.0–29.9 kg/m^2 or obese (BMI ≥30 kg/m^2) are risk factors for CVD. The 2011 AHA/ACCF guideline on secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommends a healthy weight of BMI 18.5–24.9 kg/m^2. The initial goal of weight loss for patients with high BMI is to lose 5%–10% of body weight over 3–6 months (Smith et al., 2011). The loss of 5%–10% of body weight provides cardiovascular protection.

Blood Pressure Management

The nonpharmacologic management of BP in established CAD include the use of low sodium diet (2400 mg/day or less), DASH diet, adequate physical activity, limiting alcohol consumption (2 drinks per day for adult males and 1 drink per day for adult females), and regular BP monitoring (Piepoli et al., 2016). The goal BP in patients with CAD is 140/90 mmHg (James et al., 2014a, 2014b).

Cholesterol Management

High levels of LDL-C and TG, as well as low levels of HDL-C, are risk factors for CAD collectively referred to as dyslipidemia (Jellinger et al., 2017a, 2017b). After a CAD diagnosis, dyslipidemia is managed with both medications and lifestyle changes. Lifestyle changes with diet and exercise reduce LDL-C and TG and increase HDL-C.

Dyslipidemia Management—New Updates

In 2013, a new guideline on the treatment of dyslipidemia by the ACC/AHA was published (Stone et al., 2013). That report changed the old standard of treating lipid disorders. The focus of treatment was not on the specific level of cholesterol as usual. It was mainly based on ASCVD risks. Thus, treating individuals at specific LDL-C level was no longer recommended. The guidelines have listed four statin benefit groups as follows: individuals with clinical ASCVD, individuals with primary elevations of LDL-C >190 mg/dL, individuals 40–75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD, and individuals without clinical ASCVD or diabetes who are 40–75 years of age and have LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of more than or equal to 7.5%. These individuals can be identified using the risk estimators discussed in "Primary Prevention of Coronary Heart Diseases" section of the chapter. Later on, American Association of Clinical Endocrinologists (AACE) 2017 Guidelines were published and the treatment goals for dyslipidemia were suggested to be personalized according to risk levels. **Table 4** indicates the risk category and the treatment goals for each group (Jellinger et al., 2017a, 2017b).

Patients with familial hypercholesterolemia should receive treatment for reducing LDL-C levels by 50% from baseline. For other lipid parameters, total cholesterol is recommended to be less than 200 mg/dL, HDL-C should be greater than 40 mg/dL. A non–HDL-C goal to be 30 mg/dL higher than the individual's specific LDL-C goal is recommended and for 25 mg/dL higher for those at extreme risk and needs to be less than 150 mg/dL. In order to achieve these targets, it is recommended to have a comprehensive strategy that includes modifying risk factors, treating metabolic abnormalities, and use of pharmacotherapy. Statins are recommended as the primary pharmacologic agent among all lipid-lowering agents. Fibrates are recommended for

Table 4 AACE 2017 Guidelines' ASCVD risk categories and LDL-C treatment goals

		Treatment goals		
Risk category	*Risk factors/10-year risk*	*LDL-C (mg/dL)*	*Non-HDL-C (mg/dL)*	*Apo B (mg/dL)*
Extreme risk	• Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL • Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular disease, 10-year risk >20% • DM or stage 3 or 4 CKD with 1 or more risk factor(s) • HeFH	<70	<100	<80
High risk	• ≥2 risk factors and 10-year risk 10%–20% • DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HeFH, heterozygous familial hypercholesterolemia; ACS, acute coronary syndrome.

severe hypertriglyceridemia. The use of combination therapy can be considered when monotherapy does not achieve specific therapeutic goal.

Pharmacological Management of Dyslipidemia

Statins

Statins work by inhibiting cholesterol synthesis by reducing the conversion of HMG-CoA to mevalonate and increasing the number of hepatic LDL receptors to enhance the uptake and catabolism of LDL. They are considered the most potent LDL-lowering agents. However, they have a less pronounced effect on TG and HDL-C (Urteaga, 2013). Common side effects of statins are myalgia, myositis, and GI upset. Myopathy/rhabdomyolysis occurs in rare cases. Hepatotoxicity occurs in less than 0.3%, thus liver function test prior to therapy is indicated (Martin and Talbert, 2013). A drug–drug interaction may occur potentially between some statins and CYP450 3A4 inhibitors, protease inhibitors, cyclosporine, and warfarin (Jellinger et al., 2017a, 2017b).

Fibrates

Fibric acid derivatives (fibrates), which include gemfibrozil, fenofibrate, and fenofibric acid, act by the activation of peroxisome proliferator-activated receptor (PPAR-α) that increase lipoprotein lipase activity and reduces secretion of very low-density lipoprotein (VLDL) from the liver (Urteaga, 2013). Primarily, fibrates decrease TG by 20%–35% and increase HDL-C by 6%–18%. However, fenofibrate may reduce TC and LDL-C by 20%–25% (Jellinger et al., 2017a, 2017b). Common adverse effects of fibrates include abdominal pain, indigestion, and acute appendicitis. Rarely, they may cause a potential reduction in renal function, hepatotoxicity, myopathy, rhabdomyolysis, and cholelithiasis (Martin and Talbert, 2013).

Bile Acid Sequestrates

Cholestyramine, colestipol, colesevelam are bile acid sequestrants that act by binding to bile acids resulting in resin–bile acid complex excretion in feces. This results in a compensatory conversion of hepatic cholesterol to bile, thus depleting hepatic stores and resulting in upregulation of LDL receptors (Urteaga, 2013). They, primarily, reduce LDL-C by 15%–25%. Side effects of this class include constipation, abdominal pain, flatulence, and nausea. Rarely, they cause steatorrhea. Serious but rare side effects such as fecal impaction, intestinal obstruction, fat-soluble vitamin deficiency (vitamins A, D, and K), and osteoporosis on long-term use may occur (Martin and Talbert, 2013).

Niacin

Niacin or nicotinic acid acts by decreasing hepatic synthesis of LDL-C and VLDL-C. Niacin reduces LDL-C by 10%–25%, reduces TG by 20%–30%, and increases HDL-C 10%–35%. Side effects of niacin include skin flushing, pruritus, abdominal discomfort, hepatotoxicity nausea, peptic ulcer, atrial fibrillation, and uric acid elevation (Jellinger et al., 2017a, 2017b).

Omega-3 Fatty Acid

Omega-3-acid ethyl esters and icosapent ethyl reduce TG by 27%–45%, TC by 7%–10%, VLDL-C by 20%–42%, apo B by 4%, and non-HDL-C by 8%–14% in individuals with severe hypertriglyceridemia. Icosapent ethyl reduces LDL-C by 5%, and omega-3-acid ethyl esters increase LDL-C by 45% (Jellinger et al., 2017a, 2017b). Omega-3 fatty acids work by reducing VLDL production.

They cause a reduction in all-cause and CV mortality post-MI. Dyspepsia, fishy taste, and burping are common side effects of Omega-3 fatty acid (Urteaga, 2013). Omega-3 fish oil may prolong bleeding time thus monitoring for coagulation status is advised.

Cholesterol Absorption Inhibitors

Ezetimibe inhibits intestinal absorption of exogenous cholesterol and biliary free cholesterol leading to LDL receptor upregulation. It reduces LDL-C by 10%–18%. When combined with statins, an additional reduction of LDL by 25% is achieved (Jellinger et al., 2017a, 2017b). However, there is no definitive evidence that it reduces coronary events in clinical trials (Kopin and Lowenstein, 2010). Diarrhea, arthralgia, and upper respiratory infection symptoms are common side effects of ezetimibe. Rare but serious adverse effects include myalgia, anaphylaxis, angioedema, pancreatitis, hepatitis, and cholelithiasis (Martin and Talbert, 2013).

New Therapies for Dyslipidemia

PCSK9 inhibitors (subcutaneous alirocumab and evolocumab, which is given every 2 weeks), cholesterol ester transfer protein inhibitors (torcetrapib, dalcetrapib), the antisense inhibitor of apoB synthesis (Mipomersen), and microsomal transfer protein inhibitors (Lomitapide) are new emerging therapies for treating dyslipidemia. As they are newly approved, ongoing trials to explore their definite outcomes are needed for better understanding of their roles in the management of dyslipidemia.

Nonpharmacological Management of Dyslipidemia

Lipid-lowering medications should be used adjunct with lifestyle modifications including healthy diet, regular exercises/physical activity (at least 30 min for 5 days per week), smoking cessation, and weight loss as needed. Details of these were previously discussed in the Long-Term Management of Coronary Artery Disease section.

The Role of Pharmacist in the Care and Management of Patients with Coronary Artery Disease

Pharmacist has an important role in the care and management of patients with CVDs in general and CAD in particular (Dunn et al., 2015; Swieczkowski et al., 2016; White, 2006). In general, the cardiology pharmacy practice area, which is considered a speciality in some countries such as North America, focuses on the delivery of pharmaceutical care (PC) for patients with CVDs (Dunn et al., 2015; White, 2006). Even in countries where the delivery of PC in cardiology setting is available but not considered as a specialization, the role of pharmacists is highly recognized and becoming increasingly important. This section highlights the role of pharmacist as an integral member of multidisciplinary CVD and CAD health-care teams and summarizes the evidence supporting the benefits of pharmacists' services in this setting.

Typically, pharmacists specialize in cardiology practice as part of interprofessional health-care teams in a variety of settings, including, but not limited to, coronary care units, cardiovascular intensive care units, medical wards, telemetry units, cardiac rehabilitation units, and other outpatient (ambulatory) clinics (White, 2006). Cardiology specialty ambulatory clinics focus on HTN, dyslipidemia, CHD, HF, anticoagulation, arrhythmias, and others. Some of the activities of cardiology pharmacists reported in the literature include disease state and medication therapy management; patient education and counseling on cardiovascular medications, adverse effects, and self-care skills; therapeutic drug monitoring; modification of medications based upon evidence-based guidelines and potential for adverse effects; medication reconciliation; dosage adjustments based on renal function, hepatic function, and potential drug interactions; pharmacokinetic monitoring; education and training of pharmacy students, medical students, and residents; and involvement in clinical, health services, basic, and translational research. A perspective paper by the American College of cardiology (ACC) (Dunn et al., 2015) has outlined that the clinical pharmacist may operate on a patient-specific, facility-specific, or global level to achieve optimal medication outcomes. Patient-specific services include, but are not limited to, patient education, drug interaction screening, drug therapy monitoring, drug and disease management, pharmacogenetics, drug information, pharmacokinetic–pharmacodynamic dosing, and collaborative practice agreements. On the other hand, facility-specific services include protocol, guideline, and policy development and review, research, core measure and quality improvement initiatives, formulary management and financial stewardship, and medication safety. Finally, global services include governmental and societal committees and agencies, societal guideline and policy development, legal consultations, and public health initiatives (Dunn et al., 2015).

Pharmacist role in various CVD settings has been highlighted in the literature and by professional health-care organizations such as the American College of Clinical Pharmacy (ACCP) and the ACC (Brush et al., 2015; Dunn et al., 2015; White, 2006; Wiggins, 2013). Collaborative (team-based) cardiovascular care, including the involvement of clinical pharmacists, can result in the delivery of high-quality care (Dunn et al., 2015). In 2015, the ACC issued a health policy statement on team-based care and the role of advanced practice providers in cardiovascular care (Brush et al., 2015). Furthermore, a perspectives paper from the Cardiovascular Team and Prevention Councils of the ACC provides pertinent information on the pharmacist's role, training, credentialing, and potential contribution in a variety of practice models (Dunn et al., 2015). The paper succinctly summarized several systematic reviews, highlighting the benefit of clinical pharmacy services in CVD settings. The report highlighted that clinical pharmacist has substantial roles in inpatient and ambulatory settings, mainly through optimization of drug therapy,

avoidance of adverse drug events, and transitional care activities focusing on medication reconciliation and patient education. However, barriers to implementation of such services identified include policy, legislation, and compensation barriers. Professional organizations and health-care institutions should support efforts to overcome these barriers, allowing pharmacists to deliver high-quality patient care to the full extent of their education and training.

It is worthwhile to note that pharmacists providing care to patients with CVDs can be generalists or specialists in the cardiology pharmacy practice area. The specialists possess unique knowledge, skills, and experience in the care of cardiovascular patients. As a prerequisite, pharmacists specializing in cardiology typically complete formal postgraduate residency training in cardiology practice settings (Dunn et al., 2015; Wiggins et al., 2013). They should have sound knowledge of the epidemiology and pathophysiology of CVDs; interpretation of laboratory and diagnostic procedures used in cardiology; pharmacotherapy of CVDs; advanced cardiac life support; application of pharmacokinetics, pharmacodynamics, and pharmacogenetics in cardiovascular care; evaluation of biomedical literature in cardiovascular pharmacotherapy; as well as systems and procedures designed to ensure medication safety. Pharmacist who do not have the opportunity to specialize in cardiology pharmacy practice can still provide care to patients with CVDs, but they must be competent in the knowledge areas listed above. Countries should develop formal and structured training programs to train competent pharmacists in the area of cardiology.

Evidence supports the role of the pharmacist as part of a multidisciplinary team caring for CVD patients (Peterson et al., 2008; White, 2006). Pharmacist care in cardiovascular ICU has been associated with economic benefits (White and Chow, 1998).The literature has reported the effect of pharmacist care on the management of major CVD risk factors and on secondary prevention of CAD with varying results. Here we summarized available systematic reviews and meta-analyses, which highlight the benefit of pharmacist care in CVD and CAD setting. A systematic review by Santschi et al. (2011) among adult outpatients with CVD risk factors documented significant reductions in blood pressure, cholesterol, and tobacco smoking. Equally, a systematic review by Altowaijri et al. (2013), involving 59 studies (45 RCTs), reported the clinical and economic effectiveness of pharmacist intervention in secondary prevention of CVDs. However, another systematic review in patients with CAD by Cai et al. (2013) concluded that pharmacist has a beneficial role in the care of patients with CAD, but the evidence supporting positive impacts on mortality and morbidity remains uncertain.

Furthermore, the impact of multidisciplinary health care on the outcomes of patients with ACS is well-established in the literature. There is evidence of benefits of interventions provided by pharmacists and other health-care providers in improving outcomes such as medication adherence, rehospitalization, and mortality, among patients post-ACS. Pharmaceutical care activities, including discharge counseling and education, medication reconciliation, and post-discharge follow-up and monitoring, have been shown to decrease adverse cardiovascular outcomes postdischarge (Ho et al., 2014; Peterson et al., 2012; Xavier et al., 2016). Varying models of care have been used in this setting. Particularly, pharmacists have been involved in the care of patients with ACS after hospital discharge either as part of multidisciplinary teams or as sole providers. In addition to traditional dispensing of medications, other activities performed by pharmacist in ACS setting include discharge patient education and counseling on medications, medication reconciliation, promoting self-care, and other PC interventions (Dunn et al., 2015; Wiggins et al., 2013). Nevertheless, there is paucity of evidence on the role of pharmacist care in this setting. Kang et al. (2016) conducted a systematic review with quantitative and qualitative meta-analysis to determine the impact of a pharmacist-involved care for patients with ACS and HF. Although all-cause hospitalization and performance measures such as prescription rates demonstrated improvement in the PC group, the strength of evidence for most of the outcomes was insufficient. This review concluded that the evidence of benefit of pharmacist care on patient-related outcomes was not conclusive. Similarly, a recent systematic review by El Hajj et al. (2018) has evaluated the impact of pharmacist care on readmission, mortality, emergency visits, and medication adherence among patients with ACS at or post-discharge. The authors concluded that there was a lack of adequate evidence regarding the effect of pharmacist care on emergency visits, hospitalization, readmission, and mortality in ACS patients. However, the reviewers pointed that the reviewed studies had several limitations that might have hindered the effectiveness of pharmacist care. Further research is warranted to determine the contribution of pharmacist care on tangible endpoints of CAD.

Furthermore, pharmacists have an important role in interdisciplinary cardiac rehabilitation teams. Although, a previous review by White and Anderson (2005) has reported that there is insufficient evidence about the effectiveness of the involvement of pharmacists in cardiac rehabilitation, but recent studies have found that pharmacists can play a vital role as part of an interdisciplinary cardiac rehabilitation team to ensure proper adherence to cardiac medications and patient safety through patient education and interventions (Packard et al., 2012). Pharmacists in cardiac rehabilitation provide medicines information and education to patients, and optimize drug therapy. Some studies have also reported economic benefits and improvement in quality of life as a result of the involvement of a pharmacist in cardiac rehabilitation (Anchah et al., 2017; Kammer, 2004).

Pharmacists providing care and/or specializing in cardiology pharmacy practice area have demonstrated tremendous benefits and value in improving health-care outcomes. Because of their expertise in pharmacotherapy, pharmacists have unique opportunity to function as part of interdisciplinary health-care teams to ensure medication safety and to improve health outcomes in patients with CVDs. Therefore, we recommend the inclusion of pharmacists as part of the interdisciplinary team caring for patients with CAD to improve quality of care and overall health outcomes. Professional health organizations, accreditation agencies, and academic institution should jointly design formal training programs to produce competent pharmacists in the area of cardiology pharmacy practice. We also recommend that more robust clinical studies should be designed to determine the effect of pharmacist care on the outcomes of patients with CAD in general.

Online Cardiovascular Risk Assessment Tools

https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score
https://www.mdcalc.com/ascvd-atherosclerotic-cardiovascular-disease-2013-risk-calculator-aha-acc
https://www.mdcalc.com/reynolds-risk-score-cardiovascular-risk-women

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Management of Cardiovascular Disorders and the Pharmacist's Role: Heart Failure

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Objectives

- To optimize pharmacist's skills and knowledge in the implementation of evidence-based pharmacotherapy in HF sufferers and strategies to overcome common barriers to optimal HF management.
- To improve pharmacist's knowledge and contribution in the nonpharmacological management of HF.
- To expand knowledge of pharmacists' roles and settings in which they may practice to improve HF patient's goals of therapy.

Take Home Messages

1. Despite identification of the means to significantly improve HF outcomes, the burden of HF is increasing with sufferers experiencing poor quality of life, frequent hospitalizations, and reduced survival.
2. HF with reduced ejection fraction has a good evidence base that guides pharmacological management and improves sufferers' outcomes.
3. There is good evidence that a structured multidisciplinary team approach improves a HF sufferer's outcomes.
4. HF patients commonly have comorbidities and experience polypharmacy, both of which require frequent review by multidisciplinary teams across the continuum of care.
5. Pharmacists have an important role to play in ensuring safe and effective dosing of HF medications, monitoring medication adherence, and reducing inappropriate polypharmacy.
6. As readily accessible health-care professionals, community pharmacists can assist HF sufferers' understanding and adherence to medicines and self-care management strategies.

Introduction to the Condition

Heart failure (HF) occurs when the heart is unable to pump sufficient blood to meet the body's requirements (or can only do so at an elevated intracardiac filling pressure). It is a complex clinical syndrome resulting from structural or functional cardiac disorders that impair the ability of the ventricle(s) to fill with and/or eject blood. HF is a multifactorial disease involving a number of organs and activation of a number of neurohormonal systems. No one drug can counteract all the adverse pathophysiological pathways.

Epidemiology

The prevalence of HF is approximately 1%–2% of the adult population in developed countries and is increasing (Ponikowski et al., 2016). Up to 2 in 1000 adults are diagnosed with HF each year. Its incidence increases with increasing age and at least 10% of over 70 years old have HF.

The burden of HF is increasing with sufferers experiencing poor quality of life, frequent hospitalizations, and reduced survival. Annual mortality rates vary between approximately 7% for stable HF patients to 17% for hospitalized HF patients (Fonarow et al., 2011).

HF is a common cause of hospitalization and death in older adults. Approximately 1% of all hospital admissions are due to HF, and it is the most common condition for which patients aged 65 or over are admitted to hospital. In addition, approximately 50% of HF patients will be readmitted to hospital within 6 months of their last admission. Up to two-thirds of hospitalizations are reported to be preventable. Most deaths in HF patients are cardiovascular either due to sudden death from arrhythmia or worsening HF. However the cause of hospitalizations is often for noncardiovascular reasons, and optimal management of comorbid conditions is an essential strategy to improve outcomes in HF patients.

Although heart transplant could be considered a cure, it provides no solution due to the scarcity of donor hearts and mechanical hearts, their expense, and the complexity of management accompanying such interventions.

Etiology

There are a number of conditions due to diseased myocardium, abnormal loading conditions, or arrhythmias that can lead to HF (Atherton et al., 2018; Ezekowitz et al., 2017; Ponikowski et al., 2016). The most common are ischemic heart disease, hypertension, and diabetes. Less common causes are nonischemic idiopathic dilated cardiomyopathy, valvular disease such as aortic stenosis, viral cardiomyopathy, and alcoholic cardiomyopathy. Illicit drugs such as cocaine and metamphetamine (Ecstasy'), anticancer therapies such as anthracyclines, antineoplastic antibodies (e.g., trastuzumab, pertuzumab), tyrosine kinase inhibitors (e.g., sunitinib, sorafenib), clozapine, and thiazolinediones may cause cardiomyopathies resulting in HF (Ezekowitz et al., 2017; Maxwell and Jenkins, 2011; Reed et al., 2014).

Types of HF: HF sufferers are generally classified into two groups: those with left ventricular systolic dysfunction, identified with a finding of an ejection fraction of less than 50% and those with preserved systolic function (i.e., having an ejection fraction of greater than 50%.) The former is commonly referred to as HF with reduced ejection fraction (HF-rEF) and the latter as HF with preserved ejection fraction (HF-pEF), also previously called diastolic HF.

Reports of the proportion of HF-pEF sufferers within the HF population vary between 30% and 70%. The characteristics of the HF-rEF and HF-pEF populations differ: compared to HF-rEF sufferers, HF-pEF sufferers tend to be older, more often women, and have a history of hypertension and atrial fibrillation (Ponikowski et al., 2016). Nevertheless, there is overlap between the populations, and it would be a mistake to jump to conclusions based on the age, gender, and clinical history of the HF patient.

Once diagnosed with HF, the prognosis is grim, with a survival rate less than many cancers, frequent episodes of hospitalization and poor quality of life accompanied by high costs of care (Stewart et al., 2001). Strategies that reduce the high HF hospitalization rates and support the increasing ambulatory care may have a profound effect on reducing economic and humanistic burdens.

Pathophysiology of HF With Reduced Ejection Fraction

The current concept of the pathophysiology of HF involves an unrelenting vicious cycle of neurohormonal activation and ventricular remodeling that leads to amplification of reduced cardiac output, further myocardial damage, arrhythmia potential, vasoconstriction, water and salt retention, and possibly other vascular structural and skeletal muscle changes.

The seminal event of HF is a loss of ventricular functionality resulting in reduced cardiac output. This seminal event may have a sudden onset such as after a myocardial infarct or a slow and subtle onset such as occurs after long-standing hypertension. At some point in time, the patient becomes symptomatic, and morbidity and mortality dramatically increase. Accompanying this transition into symptomatic HF is a marked increase in neurohormonal activity involving systems such as the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) and other neurohormones such as natriuretic peptides and cytokines as well as a series of maladaptive changes within the myocardium, labeled "ventricular remodeling" (Mann, 2004). The neurohormonal activation and overexpression that result in a direct toxic effect on the cardiovascular system describe the "neurohormonal" model of HF (Katz, 2000; Mann, 2004; Packer, 1992). It provides an explanation as to why no one drug is sufficient to inhibit or control the multiple pathways that lead to and progress HF (Bleske, 2000; Mann, 2004).

Pathophysiology of HF With Preserved Ejection Fraction

The pathophysiology of HF-pEF is poorly understood. The symptoms of diastolic dysfunction relate to alterations in ventricular stiffness. Rather than a single distinct pathophysiological entity, it likely reflects a wide range of heterogeneous cardiovascular problems (Desai, 2007). The applicability of the "neurohormonal" model in HF-pEF is unclear. To date, none of the major clinical trials have identified therapies that improve survival, although beneficial effects on hospitalization have been reported (Ezekowitz et al., 2017; Ponikowski et al., 2016).

Clinical Presentation

HF is a clinical syndrome characterized by shortness of breath, fluid retention, and fatigue. Unfortunately, HF symptoms can be nonspecific, and diagnosis may be delayed. **Table 1** displays typical HF symptoms and signs.

Diagnosis

HF is the final consequence of the multitude of diseases that can affect the heart including ischemic heart disease, hypertension, and toxic or viral cardiomyopathies. The workup to diagnose HF includes identification of (1) the underlying cause of HF, (2) the precipitating cause for acute decompensation, (3) the predominant pathophysiology, (4) the presence of any reversible or treatable causes, (5) comorbidities, and (6) the goal(s) of treatment.

A number of national guidelines provide diagnostic algorithms (Atherton et al., 2018; Ezekowitz et al., 2017; Ponikowski et al., 2016; Yancy et al., 2013).

Echocardiography is the most useful tool for initial diagnosis and to guide subsequent management. It is able to provide information of the mechanism and severity of the underlying cardiac dysfunction. Echocardiography is often underutilized, and improving access to and use of echocardiography are important remediable measures that are required to improve HF patient outcomes (Krum et al., 2001).

HF presentations to hospitals may be as new-onset HF following an acute event such as myocardial infarct, occur more gradually following slow worsening of symptoms (over weeks to months) such as in dilated cardiomyopathy or may be an episode of decompensation in the chronic stable HF patient (Ponikowski et al., 2016). Occasionally, a patient may have HF due to a condition that could resolve completely such as acute viral myocarditis or tachycardiomyopathy. However, the vast majority of patients will

Table 1 Typical symptoms and signs of heart failure

Symptoms	*Signs*
Ankle swelling	Cognitive impairment/delirium[a]
Bloated feeling	Elevated jugular venous pressure
Breathlessness (usually with exertion)	Hepatomegaly
Confusion[a]	Nocturia
Cool extremities	Oliguria
Fatigue, increased time to recover postexercise	Peripheral edema (ankle, sacrum)
Nocturnal cough	Pulmonary crepitations
Orthopnea	Tachycardia
Paroxysmal nocturnal dyspnea	Third heart sound (gallop rhythm)
Palpitations	Weight gain (>2 kg/week)
Reduced exercise tolerance	Weight loss in advanced HF

[a]More common in elderly.

Source: Adapted from Ezekowitz, J.A., O'Meara, E., McDonald, M.A., Abrams, H., Chan, M., Ducharme, A., Giannetti, N., Grzeslo, A., Hamilton, P.G., Heckman, G.A., Howlett, J.G., Koshman, S.L., Lepage, S., Mckelvie, R.S., Moe, G.W., Rajda, M., Swiggum, E., Virani, S.A., Zieroth, S., Al-Hesayen, A., Cohen-Solal, A., D'Astous, M., DE, S., Estrella-Holder, E., Fremes, S., Green, L., Haddad, H., Harkness, K., Hernandez, A.F., Kouz, S., Leblanc, M. H., Masoudi, F.A., Ross, H.J., Roussin, A., Sussex, B., 2017. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can. J. Cardiol., 33, 1342–1433;, Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G. F., Coats, A.J. S., Falk, V., Gonzalez-Juanatey, J.R., Harjola, V.-P., Jankowska, E.A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J.T., Pieske, B., Riley, J.P., Rosano, G.M. C., Ruilope, L.M., Ruschitzka, F., Rutten, F.H., Van Der Meer, P., Filippatos, G., McMurray, J.J. V., Aboyans, V., Achenbach, S., Agewall, S., Al-Attar, N., Atherton, J.J., Bauersachs, J., Camm, A.J., Carerj, S., Ceconi, C., Coca, A., Elliott, P., Erol, C., Ezekowitz, J., Fernandez-Golfin, C., Fitzsimons, D., Guazzi, M., Document, R. & Authors/Task Force, M. 2016. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. J. Heart Fail., 18, 891–975; Atherton et al., 2018)

experience a patient journey characterized by slow deterioration and chronic limitation with episodic exacerbations requiring emergency hospitalizations over 5–10 years and ending with a death that appears sudden and unexpected (Levenson et al., 2000; Lynn et al., 1997). Such patient journeys differ to those suffering incurable cancer or frailty and dementia. Prognosis determination is notoriously challenging in the HF patient.

There are a variety of International Classification Disease (ICD) codes for HF. ICD-10 coding and reporting should document the type (diastolic, systolic, or mixed) and acuity of heart failure. If these details are not specified, the code 150.9 Heart Failure is documented. Additional coding should indicate HF etiology.

Detection and Management of Precipitating Factors

The underlying precipitants should be considered during the workup of a HF patient and during any subsequent episodes of decompensation. There is often more than one precipitant. If the precipitants are not identified and managed, episodes of decompensation due to these precipitants are likely to reoccur. **Table 2** shows significant precipitating factors that may lead to HF decompensation and hospitalization.

Pharmacists in both hospital and community settings have an important role in identifying and managing medication-related precipitants. This includes recognizing medications that should be avoided; ensuring HF patients are up to date with influenza and pneumococcal immunization; and, monitoring adherence to evidence-based management and self-care strategies.

Common Comorbidities

The comorbidity burden is high in HF patients. Reasons include the fact that HF is the end condition of all heart disease, that HF predominantly affects the elderly, and that many of the risk factors, for example, smoking and obesity that have contributed to HF development may also cause other conditions such as chronic airways limitation and obstructive sleep apnoea. HF should not be considered an isolated condition. Conditions such as renal impairment, hepatic impairment, anemia, and cachexia should also be considered as they are common and negatively affect prognosis. Risk of hospitalization and potentially preventable hospitalizations are known to increase with the number of conditions such as CAL, renal failure, diabetes, and depression. HF itself and some HF therapies may lead to the development of other comorbidities such as arrhythmias, gout, thyroid disorders, and renal impairment. Some first-line therapies for HF may compromise the treatment of other comorbidities and vice versa. Comorbidities in the presence of HF have important ramifications for diagnosis of HF, polypharmacy, and self-care strategies. Consultation with generalist health-care professionals such as geriatricians and pharmacists may be useful during decision-making processes to ensure that proper consideration of comorbidities and their therapies is given. Awareness of a comorbidity's impact on HF management or vice versa has meant that HF-specific guidelines are now more likely to discuss the ways in which HF may change the usual management of common comorbidities (Ezekowitz et al., 2017; Ponikowski et al., 2016).

Table 2 Precipitating factors for worsening HF

Precipitating factor category	*Details*
Medical conditions	
	Arrhythmia including atrial fibrillation
	Infection
	Ischemia/infarction
	Anemia
	Pulmonary thromboembolism
	Chronic airways limitation
	Thyroid dysfunction
	Renal dysfunction
	Uncontrolled hypertension
Nonadherence	
	Medications
	Salt and fluid restriction
Concomitant medicines	
	Nonsteroidal anti-inflammatories including COX-2 inhibitors
	Corticosteroids
	Beta-blockers
	Nondihydropyridine calcium antagonists
	Class 1 antiarrhythmics
	Moxonidine
	Thiazolidinediones
	High-salt medications
Inadequate EBM prescription	
	Nonprescription of EBM
	Inappropriate reduction in dosing of EBM or diuretics
Other	
	Delay in seeking help
	Poor social support
	Poor continuity of care

EBM, Evidence-based medicine; includes ACE inhibitors and HF-specific beta-blockers in HF-rEF.

Source: Adapted from Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G. F., Coats, A.J. S., Falk, V., Gonzalez-Juanatey, J.R., Harjola, V.-P., Jankowska, E.A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J.T., Pieske, B., Riley, J.P., Rosano, G.M. C., Ruilope, L.M., Ruschitzka, F., Rutten, F.H., Van Der Meer, P., Filippatos, G., McMurray, J.J. V., Aboyans, V., Achenbach, S., Agewall, S., Al-Attar, N., Atherton, J.J., Bauersachs, J., Camm, A.J., Carerj, S., Ceconi, C., Coca, A., Elliott, P., Erol, C., Ezekowitz, J., Fernandez-Golfin, C., Fitzsimons, D., Guazzi, M., Document, R. & Authors/Task Force, M. 2016. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. J. Heart Fail., 18, 891–975; Ezekowitz, J.A., O'Meara, E., McDonald, M.A., Abrams, H., Chan, M., Ducharme, A., Giannetti, N., Grzeslo, A., Hamilton, P.G., Heckman, G.A., Howlett, J.G., Koshman, S.L., Lepage, S., Mckelvie, R.S., Moe, G.W., Rajda, M., Swiggum, E., Virani, S.A., Zieroth, S., Al-Hesayen, A., Cohen-Solal, A., D'Astous, M., DE, S., Estrella-Holder, E., Fremes, S., Green, L., Haddad, H., Harkness, K., Hernandez, A.F., Kouz, S., Leblanc, M. H., Masoudi, F.A., Ross, H.J., Roussin, A., Sussex, B., 2017. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can. J. Cardiol., 33, 1342–1433;, Maxwell, C.B., Jenkins, A.T., 2011. Drug-induced heart failure. Am. J. Health-Syst. Pharm., 68, 1791–1804.; Reed, B.N., Rodgers, J.E., Sueta, C.A., 2014. Polypharmacy in heart failure: drugs to use and avoid. Heart Fail. Clin., 10, 577; Rich, M. W., Vinson, J.M., Sperry, J.C., Shah, A.S., Spinner, L.R., Chung, M.K., Davila-Roman, V., 1993. Prevention of readmission in elderly patients with congestive heart failure: results of a prospective, randomized pilot study. J. Gen. Intern. Med., 8, 585–590;, Tsuyuki, R.T., Mckelvie, R.S., Arnold, J.M., Avezum A, JR., Barretto, A.C., Carvalho, A.C., Isaac, D.L., Kitching, A. D., Piegas, L.S., Teo, K.K., Yusuf, S., 2001. Acute precipitants of congestive heart failure exacerbations. Arch. Intern. Med., 161, 2337–2342.

Polypharmacy increases the risk of adverse effects, drug interactions, medication errors, and costs. Both polypharmacy and number of chronic diseases have been implicated in falls risk (Hilmer et al., 2007). Pharmacists can identify inappropriate polypharmacy and also provide advice regarding regimen simplification such as use of once daily dosing medications or formulations.

Goals of Treatment

The major goals of HF therapy are to prolong survival, to reduce the need for hospitalization, and to improve patient quality of life including reduction of activity-limiting symptoms and adverse drug effects from medications. The priority these goals are given may vary between patients and may vary over time.

Pharmacological Management of the Condition

Pharmacotherapy is the mainstay of HF management supported by nonpharmacological management for the large majority of HF patients. There are gaps in the judicious, appropriate, safe, and effective use of medicines in HF and hence pharmacists can make an

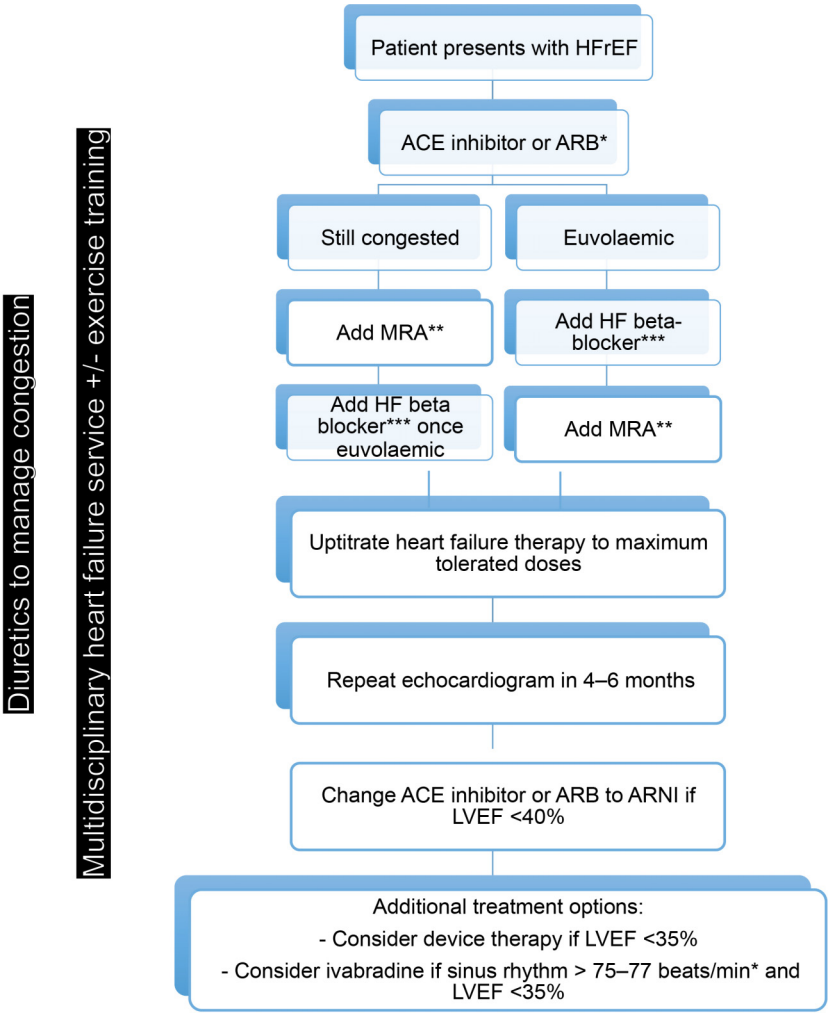

Figure 1 HFrEF management algorithm. *HF*, heart failure; *ACEI*, ACE inhibitor; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor blocker-neprilsyin inhibitor; *LVEF*, left ventricular ejection fraction. *ARB only if ACEI contraindicated or not tolerated. **MRA contraindicated if serum potassium concentration is >5 mmol/L or creatinine clearance is <30 mL/min. *** HF beta-blockers= carvedilol, bisoprolol, metoprolol-modified release, or nebivilol.

important contribution to the management of HF in hospital and community settings. An understanding of the pathophysiology of HF provides an understanding of the mechanisms by which current HF pharmacological management is thought to exert its effect. The therapeutic management of acute decompensated HF (ADHF) will not be discussed, and readers are referred to the latest international HF guidelines for this information.

Pharmacotherapy in HF-rEF

Most of the drugs shown to improve outcomes in HF-rEF patients (improved survival and reduced hospitalizations) modulate neurohormonal systems. Major therapeutic targets are the RAAS and the SNS and more recently the natriuretic peptide system. Inhibitors of these systems, the angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitor (ARNI) and beta-blockers are recommended at various phases of the HF-rEF patient journey unless contraindicated or not tolerated (Atherton et al., 2018; Ezekowitz et al., 2017; Ponikowski et al., 2016; Yancy et al., 2013) (see **Fig. 1**, **Table 3**).

Other Drugs for HF-rEF

Other medications commonly used in HF-rEF patients include amiodarone, warfarin, and antiplatelet medications and relate to the causes or complications of HF. Apart from digoxin, amiodarone is the only antiarrhythmic, which does not have a negative

Table 3 Medicines used in chronic HF with reduced ejection fraction (HF-rEF)

Drug class/medicine and examples	*Dosing strategy*	*Benefits*	*Target HF-rEF population*	*Comments*
Renin-angiotensin-aldosterone system (RAAS) inhibitors				
ACE inhibitors (ACE-Is): perindopril, enalapril, lisinopril	Start low and uptitrate to target dose, if tolerated as reduced HF hospitalization with higher dose (Packer et al., 1999)	Improves survival; reduces HF hospitalizations; improved ejection fraction; improved symptoms, and exercise tolerance (McMurray, 2011)	Indicated for mild, moderate, or severe HF-rEF and asymptomatic LVSD to delay onset of HF.	Dizziness and renal impairment more common at higher doses but do not usually require discontinuation. Also indicated in patients with systolic dysfunction after myocardial infarct. May commence BBs prior to reaching target doses of ACE-I (or ARB). Gaps in current practice include uptitration to target doses and to a lesser extent, prescription of ACE-Is. (Maggioni et al., 2013; Newton et al., 2016)
Angiotensin receptor blockers (ARBs): candesartan, valsartan	Start low and uptitrate to target dose, if tolerated as reduced HF hospitalization with higher dose (Konstam et al., 2009)	Decreases cardiovascular mortality and HF hospitalizations (Cohn et al., 2001; Granger et al., 2005)	Indicated for mild, moderate, or severe HF-rEF in those who cannot tolerate ACE-Is (Pitt et al., 1999) due to cough or angioedema (NB. cautious use in angioedema patients).	Combination of ACE-I and ARB is generally discouraged due to increased risk of adverse effects such as hypotension, hyperkalemia and renal dysfunction. (McMurray, 2006)
Mineralocorticoid receptor antagonists (MRAs): spironolactone, eplerenone	Commence low dose (25 mg daily) and increase to 500 mg after 4–8 weeks.	Improves survival, reduces HF hospitalization (Pitt et al., 1999) (Solomon et al., 2016; Zannad et al., 2011)	Indicated for moderate to severe HF-rEF and consider in mild HF-rEF	May be commenced prior to BB if the patient remains congested despite ACE-I/ARB and diuretic therapy. (Atherton et al., 2018) Requires vigilant electrolyte and renal function monitoring, especially if also taking ACE-I/ARB and/or renal impairment present (Juurlink et al., 2004) Switch to eplerenone if gynecomastia occurs with spironolactone.
ARNI: sacubitril/valsartan	Start low-moderate dose and uptitrate every 2–4 weeks to target dose, if tolerated.	Improves survival, reduces hospitalization (McMurray et al., 2014)	Replaces ACE-I/ARB if persistent HF-rEF with LVEF $<$ 40% despite optimized use of ACE-I/ARB and BB +/− MRA for 3–6 months.	New drug class—sacubitril, a prodrug for a neprilysin inhibitor, promotes the activity of natriuretic peptides and bradykinin leading to vasodilation and sodium and fluid elimination. PARADIGM study demonstrated improved outcomes with sacubitril/valsartan compared to enalapril (McMurray et al., 2014) Must cease ACE-I/ARB at least 36 h prior to ARNI initiation (as increased risk of angioedema). Adverse effects include angioedema, hypotension, hyperkalemia, and renal impairment.
Beta-blockers				
Beta-blockers: carvedilol, bisoprolol, modified release metoprolol, nebivolol	Start low and uptitrate to target dose, if tolerated. Initiate and uptitrate when the patient is clinically stable (not during decompensation).	Improves survival, reduces hospitalizations, improved quality of life (Flather et al., 2005; MERIT-HF Study Group, 1999, CIBIS-II Investigators and Committees, 1999; Packer et al., 1996)	Indicated for mild, moderate, or severe HF-rEF and asymptomatic LVSD to delay onset of HF.	Only listed BB examples are indicated for HF-rEF—other BBs have not shown benefit. Pivotal nebivolol trial recruited HF patients aged $>$70 years—most of whom had reduced LVEF. Ongoing debate whether one HF-specific BB is better than another. (Kaye and Krum, 2007; Poole-Wilson et al., 2003) Usually commenced after ACE-I/ARB but may be commenced before if patient is euvolemic. (Willenheimer and Silke, 2005) Well tolerated if uptitrated slowly. Too rapid uptitration may precipitate acute symptomatic deterioration (due to withdrawal of cardiac adrenergic tone). Adjustment of diuretic dose BB during dose uptitration may be considered, for example, decrease diuretic if symptomatic hypotension and increase diuretic if increasing congestion. Patients (and carers) require counseling regarding uptitration and monitoring of condition and adverse effects during dose adjustments.

Diuretics				
Diuretics: furosemide, hydrochlorothiazide	Use lowest possible dose to achieve euvolemia	Limited mortality or morbidity benefit shown (Faris et al., 2012)	Indicated for symptomatic relief of peripheral edema or pulmonary edema.	Do not use as monotherapy for HF. Loop diuretics most commonly used. Regularly review doses: lower dose or cease once euvolemia achieved. Monitor blood pressure and symptomatic hypotension, renal function and electrolytes (particularly for hypokalemia) closely especially if on loop diuretic. Patients may be educated to use flexible diuretic regimen (requires daily weight monitoring).
Other medicines				
Ivabradine	Start low dose and uptitrate every 2–4 weeks to target dose, if tolerated.	Improved cardiovascular survival and reduced HF hospitalization. (Swedberg et al., 2010)	In symptomatic HF-rEF or those with a LVEF $<$ 35% who are in sinus rhythm and have heart rate $\geq$ 70 bpm, despite optimized use of ACE-I/ARB and BB (unless latter contraindicated) +/− MRA.	Ensure patient is on maximally tolerated BB dose (unless contraindicated). Aim for sinus rhythm 50–60 bpm. Greater benefit seen in those with faster sinus rates. Requires patient to be in sinus rhythm to exert pharmacological effect and unlike BBs does not lower BP or contractility. May cause bradycardia and visual changes. Cease if patient develops persistent/permanent AF.
Combination of hydralazine and isosorbide dintrate	Start low doses and uptitrate over 2–4 weeks to target doses, if tolerated.	Improved survival. (Cohn et al., 1991)	Only indicated in those where ACE-I/ARB contraindicated/not tolerated.	Isosorbide mononitrate usually substituted for the dinitrate formulation to reduce pill burden and improve adherence. May be useful in African-Americans, whose response to ACE-Is is variable. Most common adverse effect is symptomatic hypotension.
Digoxin	Start low dose ($<$0.125 mg daily) aiming for target plasma range	Improved symptoms and reduced hospitalizations but no improvement in survival. (The Digitalis Investigation Group, 1997) Recent analyses have shown increased mortality. (Vamos et al., 2018)	Second-line drug Indicated only in HF-rEF patients in sinus rhythm who remain symptomatic despite optimized use of ACE-I/ARB, BB, MRA and diuretic.	Target plasma range: 0.5–0.9 μg/L (0.6–1 nanomol/L) as higher concentrations associated with increased mortality and hospitalization. (Rathore et al., 2003) May also be useful in HF and atrial fibrillation, particularly if there is a rapid ventricular rate and no other therapeutic options are available.
Omega-3 polyunsaturated fatty acids	$>$850 mg combined DHA and EPA (in 1 g fish oil)/day	Small benefit on death and CV hospitalization. (Tavazzi et al., 2009)	Only as adjunct to optimized ACE-I/ARB & BB +/− MRA.	Wide variety of proprietary fish oil supplements, which may not have required DHA/EPA content. Pivotal study used ratio of approximately 1:1.2 DHA and EPA to fish oil.

AF, Atrial fibrillation; *BP*, blood pressure; *bpm*, beats per minute; *CV*, cardiovascular; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *LVEF*, left ventricular ejection fraction; *LVSD*, left ventricular systolic dysfunction.

inotropic effect on the heart. In the past, it was commonly used in HF with AF and for severe, symptomatic, and sustained ventricular tachycardia. Its benefit does not seem evident with the more widespread uptake of BBs in HF-rEF (Torp-Pedersen et al., 2007b). Amiodarone has multiple effects on the thyroid system and may play a role in the thyroid dysfunction frequently seen in HF patients. Its use is problematic with a long half-life, numerous adverse effects, and interactions with medications such as digoxin and warfarin.

Given that HF is a prothrombotic condition, randomized control trials have compared the efficacy and adverse effects of warfarin versus aspirin or aspirin and clopidogrel in HF-rEF patients in sinus rhythm (Homma et al., 2012; Massie et al., 2009). In general, there has been no difference demonstrated in primary outcomes of death, nonfatal myocardial infarct, or nonfatal stroke. Two meta-analyses also identified that although there were reductions in stroke in the warfarin arm, this was offset by increased major bleeding events (but not intracranial hemorrhage) (Hopper et al., 2013; Kumar and Goyal, 2013). They concluded that there may be benefit in warfarin use to prevent stroke but noted there was no difference in mortality. Routine anticoagulant use in HF-rEF patients in sinus rhythm is now discouraged unless intracardiac thrombus is identified (Ezekowitz et al., 2017). Studies using the non-Vitamin K oral anticoagulants (NOACs) in HF-rEF patients in sinus rhythm are currently being undertaken (Ponikowski et al., 2016).

Aspirin is usually prescribed in HF with ischemic etiology unless they are already taking as an anticoagulant. Given the effects of nonsteroidal anti-inflammatories on renal hemodynamics, controversy surrounds the use of aspirin in patients taking ACEIs (or ARBs), particularly if they are also taking diuretics, have severe symptoms or frequently hospitalized (Cleland et al., 1995; Hall, 2001). Furthermore, aspirin use is associated with a substantial risk of gastrointestinal bleeding, particularly with increasing age.

Statins have not demonstrated any survival benefit in HF-rEF patients (Kjekshus et al., 2007). Their role is restricted to HF patients who require it because of underlying coronary artery disease and/or hyperlipidemia (Ponikowski et al., 2016).

Device Therapy

Device therapy includes pacemakers, biventricular pacing [also called cardiac-resynchronization therapy (CRT)], and implantable cardioverter defibrillators (ICDs) (Ezekowitz et al., 2017; Ponikowski et al., 2016). ICDs have shown a 20%–30% reduction in mortality over a 1–5-year period in patients with LVEF $< 35\%$. CRT reduces symptoms and hospitalizations and mortality in symptomatic patients with dilated cardiomyopathy, low ejection fractions, prolonged QRS intervals, and in sinus rhythm (Bristow et al., 2004). ICD therapy may also be combined with CRT to improve symptoms as well as mortality. Device therapy is expensive but may be applicable to a wide range of HF patients. The means by which to allocate such therapies is an on-going debate. Generally, evidence-based pharmacotherapy would be optimized prior to considering device therapy.

HF With Preserved Ejection Fraction (HF-pEF)

There has been a paucity of trials to evaluate therapies in HF-PSF. Furthermore, results of the few trials that have been undertaken have been disappointing and not provided therapeutic guidance in this large group of HF patients. The goals of therapy are generally to alleviate symptoms and improve well-being given that HF-pEF sufferers are generally older with poor quality of life. Diuretics are indicated to improve the congestion. Thiazide diuretics may be sufficient diuretic therapy. Neither BB nor MRA therapies have demonstrated symptom benefit, and ACEI/ARB therapy has produced inconsistent results on symptom improvement (Ponikowski et al., 2016).

The Candesartan in HF-Assessment of Mortality and Morbidity-Preserved (CHARM-Preserved) trial investigated the prognostic value of candesartan added to standard background HF therapy in 3000 HF-pEF patients (Yusuf et al., 2003). The result was a nonsignificant 11% reduction in the combined endpoint of CV death or HF hospitalization. The investigators attributed the statistical shortfall to a short duration of follow-up (3.5 years). The CHARM-Preserved study did find a significant but modest morbidity benefit (reduced HF hospitalizations). This benefit was not apparent until 6 months after candesartan commencement. Another trial investigating the use of irbesartan in HF-pEF patients (LVEF $> 45\%$, mean LVEF 60%) did not show cardiovascular mortality or morbidity benefit, and there was an increase in adverse events including serious hyperkalemia (Massie et al., 2008). A trial evaluating perindopril therapy in elderly HF-pEF patients reported no significant improvements in all-cause mortality or HF-related hospitalizations (Cleland et al., 2006).

Other therapies assessed in HF-pEF patients include digoxin in the Digitalis Investigators Group (DIG) study and nebivolol, a beta-1 selective BB, in the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with HF (SENIORS) study (Ahmed et al., 2006b; Flather et al., 2005). An ancillary study of the DIG trial (EF $> 45\%$) did not find digoxin had any significant effect on mortality or HF, cardiovascular-related or all-cause hospitalization in HF-pEF patients in normal sinus rhythm (Ahmed et al., 2006a).

Although there is a lack of evidence-based recommendations for the use of BBs in HF-pEF, these patients may gain benefit from the use of BBs if they also have ischemic heart disease or hypertension. Patient may also gain benefit from a reduction in heart rate that allows an increase in diastolic filling time, reduction in sympathetic nervous system activation, relief of ischemia that improves diastolic relaxation, and prevention or attenuation of left ventricular hypertrophy (Yancy et al., 2006). The

SENIORS study, which included a small proportion of HF-pEF patients, found that the significant reduction in the combined endpoint of all-cause mortality and cardiovascular hospitalization in patients allocated to nebiviolol was not influenced by ejection fraction (Flather et al., 2005). However, this trial did not demonstrate a significant effect on all-cause mortality.

The value of spironolactone in HF-pEF was assessed in the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) trial (Pitt et al., 2014). Patients with symptomatic HF and a LVEF > 45% received either spironolactone (15–45 mg daily) or placebo. Of the components of the primary outcome (cardiovascular death, aborted cardiac arrest, or HF hospitalization), only HF hospitalization had a significantly lower incidence in the spironolactone group than in the placebo group, 12.0% vs. 14.2%, $P = 0.04$). Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events.

In summary, there is evidence that nebiviolol, digoxin, spironolactone, and candesartan may reduce HF hospitalizations, but not mortality in HF-pEF patients in sinus rhythm. Thus, despite recent attempts to provide evidence-based recommendations for the management of HF-pEF, there remains a lack of knowledge of the pathophysiology of HF-pEF, a paucity of evidence-based guidance for clinicians, and therapy remains empirical. Despite the high prevalence of HF-pEF, overall quality of HF care lags behind that of HF-rEF and emphasizes the optimal management of comorbidities, symptoms, blood pressure, and heart rate.

Specific Considerations Regarding Pharmacotherapy of Comorbidities in HF Sufferers

Atrial Fibrillation

Atrial fibrillation is common in HF, and patients will require anticoagulation unless contraindicated. The non-Vitamin K oral anticoagulants (NOACs) are contraindicated in moderate to severe renal impairment and given renal impairment is common in HF, renal function will require frequent monitoring if they are used in mild renal impairment and during HF exacerbation. Specialist input regarding the appropriate strategy, rhythm, or rate control is recommended.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is common in HF and complicates the diagnosis of HF and worsening HF. Although beta-blockers are relatively contraindicated in asthma, they may be used in COPD. The more beta-2 specific BBs such as bisoprolol are preferred. Although oral corticosteroids are problematic in HF due to sodium and water retention, inhaled corticosteroids can be used in HF patients.

Depression

Depression is common in HF and is associated with worse outcomes. It also impacts adherence medication and nonpharmacological recommendations. Selective serotonin reuptake inhibitors are thought to be safe in HF. However, it is recommended that tricyclic antidepressants are avoided as they may be arrhythmogenic, lower blood pressure, and worsen HF. Nonpharmacological therapies, such as cognitive behavioral therapy should also be considered.

Diabetes

Diabetes is a common comorbidity in HF patients and is associated with poorer functional status and worse prognosis. The presence of diabetes in a HF patient also has therapy ramifications. Thiazides may not be appropriate depending on diabetic control and while beta-blockers do not have adverse effects on HF outcomes, some beta-blockers may be better in HF than others (Torp-Pedersen et al., 2007a). Contrary to previous recommendations, metformin is now the treatment of choice in patients with HF and diabetes but is contraindicated in HF patients with severe renal or liver impairment because of the risk of lactic acidosis.

Insulin is a necessary therapy for type 1 diabetes and is often required in type 2 diabetes. However, insulin is a potent sodium-retaining hormone and when combined with a reduction in glycosuria can exacerbate fluid retention and lead to worsening HF. Therapies that promote insulin secretion such as sulphonylureas can increase the risk of HF exacerbations and should be used with caution. Thiazolidinediones such as rosiglitazone, also cause sodium and water retention and increase the risk of worsening HF and hospitalization. They should be avoided in HF patients.

Dipeptidyleptidase-4 (DPP-4) inhibitors (gliptins) and GLP-1 analogues also stimulate insulin release. In a recent trial, the DPP-4 inhibitor, saxagliptin, showed an increased risk of HF hospitalizations (Scirica et al., 2013). Other DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin) have not shown this effect but if used, patients should be monitored closely (Green et al., 2015; Rosenstock et al., 2015; Zannad et al., 2015). The sodium-glucose co-transporter 2 inhibitors reduce glucose reabsorption in the kidney and may be used in HF patients if renal function is not significantly impaired. A recent study involving empagliflozin reduced HF hospitalizations and mortality, but not other cardiovascular outcomes in patients with diabetes and high cardiovascular risk, some of whom had HF (Zinman et al., 2015). It is unknown whether this is a class effect.

Gout, Arthritis, and Management of Pain

Gout is common in HF due to the condition itself and diuretic therapy. Allopurinol may be used in HF patients although the dose may need reduction in renal impairment. Colchicine is the preferred agent for treatment of acute gout attacks, but caution is required if renal impairment is severe or the patient suffers diarrhea. Systemic corticosteroids are best avoided although corticosteroid injection to a single joint is permissible. Nonsteroidal anti-inflammatories including COX-2 inhibitors are contraindicated due to their significant adverse effects on fluid status, the cardiovascular system, and renal function. This also means these agents should not be used systemically as analgesics or arthritic therapies in HF patients. Patients should be counseled on how they should best manage pain such as headache or osteoarthritis. Paracetamol is the preferred analgesic in HF patients.

Hypertension

Optimized control of blood pressure is important in HF patients as hypertension is associated with increased adverse events (including death and stroke) in those with new onset HF (Lip, 2015). The negative inotropic calcium channel blockers (CCBs), verapamil and diltiazem, which are often used in IHD and hypertension and have been shown to reduce left ventricular hypertrophy are contraindicated in HF-rEF. Amlodipine has shown no mortality and morbidity benefit in HF-rEF but may be used in HF-rEF if ACEI/ARB, BB, MRA, and diuretic therapy have not adequately lowered blood pressure. Hydralazine is also a consideration. However, uncontrolled hypertension is not normally an issue in HF-rEF if the recommended HF therapies are used. In contrast, optimization of blood pressure control is an important therapeutic strategy in HF-pEF.

Iron Deficiency and Anemia

Iron deficiency (ID) with or without anemia is a common comorbidity in chronic HF. Its etiology is multifactorial and not fully understood (Drozd et al., 2016; McDonagh and Macdougall, 2015). ID may contribute to HF symptoms such as breathlessness and fatigue and may be a precipitant for decompensated HF. ID is associated with poor quality of life and poor prognosis. Patients should be screened for ID, and reversible causes for iron deficiency is corrected.

Supplementation using the intravenous iron formulations, iron sucrose and ferric carboxymaltose, enable more rapid repletion of iron stores and has demonstrated improvement in prognosis, symptoms, quality of life, and exercise tolerance in HF-rEF. They should be considered in patients with symptomatic HF and iron deficiency. The ferric carboxymaltose formulation has the advantage of quicker administration time and reduced fluid load but is significantly more costly.

Currently, the evidence does not demonstrate improved outcomes using oral iron supplementation in iron-deficient patients with HF-rEF. Repletion of iron stores using oral iron supplementation is compromised for a variety of reasons including poor gastrointestinal absorption, adverse effects such as nausea and constipation, and poor adherence. Erythropoietin-stimulating agents are generally not recommended for HF-associated anemia but may be considered when due to renal dysfunction (together with iron supplementation).

Renal Impairment

Renal function is frequently impaired in HF patients and often worsens during exacerbation. The presence of renal impairment worsens outcomes in HF patients. Renal impairment shares the many of the same risk factors as HF. Pharmacists should be aware of medicines such as digoxin and the NOACs that may accumulate and cause toxicity in HF exacerbations. HF patients will require greater doses of diuretics as renal impairment progresses.

Inhibitors of the RAAS are generally well-tolerated in renal impairment. There is often a slight worsening in renal function, especially during ACEI/ARB/MRA initiation and uptitration. No action is necessary as long as the change in serum creatinine is small (<30% change in eGFR), stabilizes within 2 weeks, and the patient is asymptomatic. However, greater changes will necessitate urgent review for potential renal artery stenosis, hyper- and hypovolemia, potentially nephrotoxic medications, and hyperkalemia. Those with preexisting moderate to severe renal impairment when first diagnosed with HF are more susceptible to acute kidney injury if affected by dehydrating illnesses, overdiuresis, and nephrotoxic medications. Patients should be counseled regarding the importance of renal function and electrolyte monitoring and the required testing frequency in general and especially during changes in relevant medications and their doses or during acute illnesses.

Complementary and Alternative Medicines in HF

Although the use of CAM in HF patients is not common, patients who do use them often use a significant number (Bennett et al., 2004). CAMs are often recommended by family members. Their use is often not reported to their treating physicians. As applies to many conditions in which CAM may be promoted, there is a lack of randomized controlled trials of CAM in HF and when they do occur, participant sample sizes are small. Of the CAMs that have been evaluated, coenzyme Q 10, a naturally occurring antioxidant, may have a modest beneficial effect on ejection fraction, decrease symptoms, and HF hospitalizations (Fotino et al., 2013; Weant

and Smith, 2005). No positive effect on survival has been demonstrated. It is an expensive therapy. Its adverse effects are generally gastrointestinal in nature, and it may increase bleeding time. There is potential for interactions with antihypertensives, alkylating agents, and warfarin. International guidelines do not advocate its use.

Other CAMs that are sometimes recommended by CAM proponents include magnesium, hawthorn, selenium, and Vitamins C and E. There is no evidence that they provide benefit and some may compromise the use of evidence-based medicines. For example, magnesium and hawthorn have vasodilatory effects and may reduce blood pressure. Their use may compromise the prescription or uptitration of medicines that also vasodilate but are known to improve outcomes in HF patients such as ACEI/ARBs and beta-blockers. A thorough evaluation of safety, likely effectiveness, convenience, and cost which included discussion with specialist and general physicians and pharmacists should be undertaken prior to considering use on a trial basis, which would include the use of objective measures to determine effectiveness.

Nonpharmacological Management of HF

Nonpharmacological therapies include recommendations regarding fluid management, nutrition, alcohol intake, self-management and education, exercise programs, smoking cessation, psychosocial support, and immunization. Failure to adhere to nonpharmacological therapies may result in increased mortality and morbidity.

Restricting dietary sodium consumption is controversial. An ongoing randomized clinical trial is anticipated to provide guidance on this vexed question (Ezekowitz et al., 2017). It is now generally advised that salt intake should be restricted to less than 3 g/day. Patients and their carers should be taught how to read food labels and select lower sodium content foods.

The restriction of fluid intake is also controversial. High-quality evidence is lacking. It is generally advised to restrict fluid intake to 2–3 L/day; the specific amount will be influenced by the clinical situation, the severity of symptoms, the season, the size of the patient, and their activity. Tighter restrictions may be considered in hyponatremic patients with hypervolemia.

Daily weight monitoring is advised to recognize worsening HF or less commonly, dehydration. An increase of 2 kg (equivalent to 2 L of fluid) in 2–3 days portends HF decompensation. Patients and carers should seek medical attention early as treatment is much easier in the early stages of decompensation and may avoid hospitalization and intravenous therapy. Some patients (or carers) will be able to identify the likely cause of the deterioration (e.g., nonadherence to diet or diuretics, use of contraindicated medicines, infection) and use a flexible diuretic regimen to manage the fluid retention. Electrolyte and renal function monitoring will be required for any prolonged increased diuretic dose. Addressing the precipitant(s) of HF exacerbations will be required.

Alcohol consumption should be limited for all HF patients (maximum of 10–20 g/day) and counted in the fluid allowance. Those whose cardiomyopathy is thought to be due to alcohol toxicity should practice total abstinence.

Infections add an additional load on the heart. Prevention using influenza and pneumococcal vaccinations is an important strategy to reduce the risk of worsening HF.

Obese patients especially those with HF-pEF should be provided with assistance to lose weight.

Last but not least, physical activity (unless decompensated) is advised. Enrolment in an exercise training program, if available and eligible, is encouraged.

Barriers to Effective Heart Failure Management

Several studies have shown that heart failure exacerbations may be attributable to nonmedical factors. Table 4 outlines such factors identified in studies that hinder successful treatment of heart failure management. A number of these may benefit from the input of pharmacists with their expert knowledge in medication adherence and review.

Strategies to Overcome Barriers to Optimal HF Management

A number of strategies have been devised to overcome these barriers and maximize clinical outcomes. Recent strategies to improve outcomes include guidelines developed by cardiology organizations generally directed at other HCPs including the primary care physician; specialist HF clinics; disease state management programs involving a multidisciplinary management team; individualized care; patient education and counseling that ideally also involves family or carers and includes promotion of self-care management; flexible but intensive follow-up particularly postdischarge that may include home visits and telephone follow-up, which may proactively detect and address issues that may hinder optimal outcomes; and patient-initiated access to appropriate advice and support which is available through a variety of channels, for example, telephone, written, and or the Internet. The influence of comorbid conditions, age, symptomatic limitation, the patient's own goals, and the ability to adhere to a complex regimen needs to be taken into account. In some patients, the management plan may focus on improvement in survival and slowing disease progression; while in others, it may be more appropriate to limit symptoms and improve quality of life. A brief discussion of some of these strategies is as follows.

Table 4 Barriers to effective HF management

Drug Related	
	Patient adherence to medication
	Adverse drug reactions from HF medications
	Inappropriate use of medication
	Polypharmacy
	Inadequate medical treatment
Multiple co-morbidities	
	Coronary heart disease
	Hypertension
	Diabetes
	Renal insufficiency
	Respiratory disease
	Arthritis
Non-pharmacological non-adherence	
	Diet including salt, fluid, alcohol, exercise, and other self-care measures
	Failure to recognize early warning signs of decompensation
	Psychosocial problems, depression, social isolation
Financial constraints	
	Inability to work
	Retired from work
Physical limitations	
	Symptomatic limitation
	Reduced visual and auditory acuity, neuromuscular deficits: stroke, arthritis, Parkinsonism
Cognitive impairment	
	Poor understanding of disease and self-care measures
	Low reading age
	Non-English speaking background
	Poor coping skills

Source: Adapted from Rich MW. Heart Failure Disease Management: A Critical Review. Journal of Cardiac Failure 1999,5(1):64-75 (Rich, 1999) and National Heart Foundation of Australia. Multidisciplinary care for people with chronic heart failure: Principles and recommendations for best practice. 2010

HF Management Guidelines

In the last two decades, there has been a concerted effort to develop and disseminate HF management guidelines. Guidelines provide a strategy to improve use of new and existing therapeutic modalities of proven benefit. In order to be implemented, guidelines need to deal not only with therapies that are efficacious but also consider the practical aspects necessary in the day-to-day care of the patient. All major cardiac societies or organizations now publish regularly updated guidelines including the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, the Heart Failure Society of America, the American College of Cardiology and American Heart Association, the Canadian Cardiovascular Society, and the European Society of Cardiology (Atherton et al., 2018; Ezekowitz et al., 2017; Krum et al., 2011; Ponikowski et al., 2016; Yancy et al., 2013, 2016, 2017). These and similar organizations also offer eLearning modules and information for health-care professionals:

- https://www.escardio.org/Education/E-Learning
- https://hfsa.digitellinc.com/hfsa/store/6#cat15
- https://www.heartfoundation.org.au/for-professionals/online-learning
- http://www.heartonline.org.au/

Disease State Management Programs

The management of HF has evolved from that of crisis management to the use of proactive, preventative multidisciplinary disease state management programs that recognize the complexity of medical, psychosocial, behavioral, and financial issues that are faced by many patients and their carers. They attempt to provide a relatively formalized mechanism to overcome many of the barriers to

effective care. Team members may include physicians, general practitioners, nurses, pharmacists, social workers, dietitians, occupational therapists, and physiotherapists and may be hospital, outpatient, or community based.

A landmark study published in 1995 trialled the effect of a nurse-directed multidisciplinary team on rates of readmission within 90 days of hospital discharge, quality of life, and costs of care (Rich et al., 1995). The intervention consisted of comprehensive education of the patient and family, a prescribed diet, medication review, social service consultation, and early discharge planning, as well as intensive follow-up. The number of readmissions for heart failure was reduced by 56.2% in the treatment group ($P = 0.04$). Quality of life scores improved more from baseline in the intervention group ($P = 0.001$), and costs of care were reduced due to the reduction in hospital admissions.

A number of systematic reviews of randomized trials of disease management programs (DMPs) in heart failure have since been published (Gohler et al., 2006; Gonseth et al., 2004; Holland et al., 2005; McAlister et al., 2001, 2004; Phillips et al., 2004; Whellan et al., 2005). Overall, the DMPs showed a consistent and favorable effect on rehospitalization, particularly HF rehospitalization, although the effect on mortality and quality of life was more controversial. (Gonseth et al., 2004; Gwadry-Sridhar et al., 2004; McAlister et al., 2004; Phillips et al., 2004) The interventions vary between the DMPs and evidence is required to identify the components with the greatest impact on adverse outcome. Elements that appear to be efficacious in DMP have been the use of multidisciplinary teams, an emphasis on patient education and self-management and enhanced access to specialist clinics or home visits. The use of home-based intervention strategies had the advantage of not only reinforcing education and compliance but also of detecting clinical deterioration and identifying hitherto unknown problems likely to contribute to poorer long-term outcomes (McAlister et al., 2004). Telephone-based systems designed to enhance follow-up by primary care givers appear to be less effective (McAlister et al., 2004). Team-based disease management care delivery versus single person care delivery and in-person communication versus telephonic delivery was also found to be more effective (reduced HF hospitalizations and length of hospital stay) in a review of HF management programs (Sochalski et al., 2009). The findings of these and other studies have led to the development of a taxonomy for disease management programs. A core component of such programs is medication management (Krumholz et al., 2006).

A recent Cochrane review compared the effects of different HF management interventions (case management, clinic-based models, and multidisciplinary models), which were not solely educational, versus usual care, in terms of death (from any cause or HF), rehospitalizations, quality of life, and cost-related outcomes (Takeda et al., 2019). The analysis included 47 randomized controlled trials (RCTs) involving 10,869 participants. The authors concluded that case management and multidisciplinary interventions probably have an effect on all-cause mortality and rehospitalizations. Clinic-based interventions were of less certain benefit. Unfortunately, the review was hampered by the poor quality of evidence resulting in uncertainty of the various interventions' benefits. The methodology of further RCTs requires optimization to improve the quality of evidence and provide certainty to the benefits (or lack of benefits) of various interventions in HF patients so that scarce health-care dollars are directed appropriately.

Evidence for Pharmacists as Part of the Multidisciplinary Team

While the role a multidisciplinary team in the treatment of HF patients has been established, there is less evidence to characterize the role of specific team members (Gohler et al., 2006; McAlister et al., 2004). In 2008, Koshman et al. published a systematic review of randomized trials that evaluated the effect of pharmacist care on HF patients outcomes (Koshman et al., 2008). Twelve RCTs involving 2060 patients were identified. Pharmacist care was associated with a significant reduction in all-cause and HF hospitalization [OR 0.71 (0.54–0.94) and 0.69 (0.51–0.94), respectively. There was a nonsignificant reduction in mortality [0.84 (0.61–1.15)]. Greater reduction in HF hospitalizations was achieved when the pharmacist was part of a multidisciplinary team rather than when pharmacist care was pharmacist initiated and managed. Details of the activities pharmacists undertook were difficult to identify in the literature, and the investigators contacted primary authors to clarify the activities pharmacists performed. Nevertheless, there were notable differences in the pharmacists' activities and further investigations regarding key elements of pharmacist's activities are warranted. The authors concluded that a pharmacist should be part of the multidisciplinary team caring for HF patients whether it be outpatient or community based.

Current and Future Role of Pharmacists as Part of the Health-Care Team Managing Patients with HF

HF is a chronic condition usually accompanied by numerous comorbidities and treated with multiple medications. The time and effort and possibly costs that a patient (and their carers) may need to spend to ensure optimal self-care of their HF is substantial. The pharmacist has a major role to play in ensuring patients' outcomes are optimized and their goals of therapy are achieved.

The activities pharmacists can play are numerous and include:

1. ensuring prescription of evidence-based medicines,
2. optimizing dosing of medications, including ensuring appropriate uptitration,
3. monitoring for adverse drug effects and HF symptoms and signs,
4. checking for and managing any drug interactions,
5. counseling patients and their carers, as appropriate, about the medicines including potential adverse effects, what to do about forgotten doses,

6. assisting appropriate patients (and carers) with understanding and management of flexible diuretic regimen,
7. providing proactive counseling about management of incidental health issues, for example, pain management, gastrointestinal conditions, and gout,
8. optimizing management of comorbidities,
9. providing supporting written material to verbal counseling,
10. monitoring medication adherence and identifying and managing-related issues,
11. ensuring medicines that should be avoided by the HF patient are avoided,
12. simplifying medication regimens where possible,
13. assisting, providing, and updating medication lists,
14. undertaking medication reconciliation particularly between transitions of care,
15. assisting with dose administration aids where appropriate,
16. to ensuring that patients understand the monitoring requirements for the medications,
17. identifying when a comprehensive medication review may be appropriate,
18. undertaking a comprehensive medication review,
19. ensuring a patients immunization status is up to date,
20. supporting a patient's (and carer's) knowledge of and adherence to nonpharmacological management,
21. undertaking clinical audits of HF therapies in various care settings,
22. support end-of-life care,
23. supporting other health-care professionals and HF team members in their roles,
24. referring to other health-care professionals, and
25. reinforcing other health-care professional's messages and counseling.

These activities can be undertaken in a variety of settings including hospitals and community pharmacies. Newer settings for pharmacists include hospital outpatient clinics, posthospital discharge programs that include home visits, home visits as part of comprehensive medication review programs, and primary care practices (Bennett and Brien, 2002; Hargraves et al., 2008; Kalisch et al., 2010; Lowrie et al., 2011, 2014; Ponniah et al., 2007; Roughead et al., 2009). A retrospective cohort study using data from 2004 to 2006 Australian veteran affairs claims database of veterans aged 65 years or over receiving HF-specific beta-blockers demonstrated the value of comprehensive home medication review (Roughead et al., 2009). The study analyzed subsequent HF hospitalizations of those who received a home medicines review (HMR) and those who did not. At the time of the study, the process of home medication review involved referral from a general practitioner (GP) to an accredited pharmacist via the community pharmacy, a home visit by an accredited pharmacist to identify any medication-related problems, and a pharmacist report to the GP who then consults with the patient regarding the findings and recommendations in the report. The GP is responsible for developing med management plan in collaboration with the patient and following up the patient. When conducting a HMR, the pharmacist is expected to spend between 30 and 60 min with the patient in their home and 2 h writing and sending the report to the GP. Two hundred and seventy-three Australian war veterans and war widows receiving HF-specific BBs received the HMRs, and they were compared with 5444 veterans receiving HF-specific BBs who had not. The age of the two groups was similar, with a mean of almost 82 years, and the HMR group had a median of eight comorbidities compared to the non-HMR group of seven comorbidities. After adjustment, there was a 45% reduction in the rate of HF hospitalization at any time.

The effect of pharmacist intervention on HF-rEF patients under the care of 174 Scottish general practices was investigated by Lowrie et al. (2011). The intervention was delivered by 27 nonspecialist pharmacists who practiced within general practice. These pharmacists received 1-day in-house training from HF pharmacists and a GP with an interest in HF as well as reading material. Patients in the intervention group were offered a 30-min interview with the pharmacist. The intervention's main focus was the optimization of evidence-based medicines. If the patient and the doctor agreed, the medications could be initiated, discontinued, and modified over 3–4 weekly or fortnightly appointments by the pharmacist. Baseline use and dosing of EBM were already fairly high (86% ACE/ARB & 62% BB) (dosing at target levels was 55%) and similar between the two groups. Patients were recruited over 2.5 year and followed-up for a further 2 years. The study showed no difference in the primary outcome of death or HF hospitalization or its component outcomes. However, there were significant differences in the use of EBM with increases in prescription and dosing to target in the pharmacist intervention group. Changes in medications that should be avoided in HF were also noted but were not significant.

Another study conducted in Scotland explored the perspectives of patients receiving and pharmacists delivering an enhanced pay for performance community pharmacy HF service (Lowrie et al., 2014). Pharmacists reported that they were confident in delivering the structured service and valued the repeated contacts with HF patients enabling the opportunity to improve self-care and medicines adherence. Challenging areas were discussion of non-HF comorbidities and persuading patients to modify behavior. HF patients reported that they were comfortable discussing HF symptoms with their pharmacist and that the service assisted them with their self-care and HF medication management strategies and believed that community pharmacists should provide such a service.

Support for nurse practitioner (NP)-led clinics that involve clinical pharmacists (CPs) is growing given the success of community disease state management programs involving CPs given the vulnerable postdischarge phase that HF sufferers often experience (Gheorghiade et al., 2013; Hickey et al., 2016). A recent pilot study demonstrated improved adherence to guideline recommendations, which suggested improved HF readmission rates in those attending the NP-CP clinic (Rheault et al., 2018).

The widespread implementation of extended roles for pharmacists is in its infancy. Evidence to date supports these roles. Health-care policy surrounding and funding for these roles needs to be explored as the focus of pharmacists' roles change from medicines supply to cognitive services. Further research is also required to determine if some pharmacist interventions are of more value than others and how to stratify patients to pharmacist intervention and type of pharmacist intervention.

Specific Pharmacist Activities

Medication Uptitration

Clinical guidelines recommend the use of target doses of evidence-based medicines in HF-rEF. Initially, these medicines are commenced at low doses and product information commonly recommends uptitration of doses every 2–4 weeks. However, in most real-world studies, only 10%–20% of patients achieve target doses in the 3–6 months postinitiation. Furthermore, failure to tolerate an uptitrated dose does not mean this cannot be subsequently reattempted. Many structured postdischarge HF programs provide support to patients and community health-care practitioners during the uptitration phase as these have been shown to increase rates of target dosing in HF-rEF patients. Pharmacists within those programs may take a direct or indirect role in uptitrating doses. Moreover, concomitant medicines that may compromise the ability to uptitrate require identification and a review of their benefit to harm ratio in each patient. For example, previously used antihypertensives such as dihydropyridine calcium antagonists are generally best ceased prior to uptitration of EBM dose uptitration. Close review of diuretic doses is also necessary. Regular, more frequent monitoring of blood pressure, heart rate, volume status, renal function, and electrolyte concentrations are required during uptitration. Supporting information and tool kits for medicine uptitration can be found at http://www.heartonline.org.au/articles/medications/titrating-medications-in-heart-failure and https://www.escardio.org/static_file/Escardio/Guidelines/ehw128_Addenda.pdf

Medications to be Avoided in HF

There are a number of prescriptions, over-the-counter, and complementary medicines that are contraindicated or should be used cautiously in HF (see **Table 5**). Pharmacists should ensure that patients and carers understand that they should obtain advice before commencing over-the-counter and complementary medicines or medicines initiated by other health-care practitioners and periodically check with patients for any medicine changes.

Table 5 Common medicines to be avoided or used cautiously in HF patients

Medicines	*Comments*
Adrenergic agents including pseudoephedrine, amphetamines	Adverse cardiovascular effects including increased blood pressure, tachycardia, proarrhythmic effects. Avoid use. Proactively counsel appropriate management of colds and flus
Antiarrhythmics (Classes I and III)	Negative inotropic and proarrhthymic effects. Avoid all antiarrhythmics except amiodarone and digoxin
Carbamazepine	Negative inotropic and chronotropic effects and anticholinergic effects. Avoid if possible
Caffeine, high dose	Increase systemic vascular resistance, blood pressure. Includes CAM such as guarana, high-energy drinks, and products to keep people awake plus coffee $>$ 4 cups/day. Counseling may be required
Corticosteroids, systemic	Sodium and fluid retention. Consider likely benefits vs potential harm. If beneficial, use for minimal period at lowest effective dose. Monitor for HF symptoms and signs
Itraconazole	Negative inotropic effect. Avoid
Drugs that cause QTc prolongation	Numerous different drug classes. Ensure likely benefit $>$ potential harm. If beneficial, use minimum doses. Also check for drug interactions and drug–disease interactions
High sodium content medicines	Increase fluid retention and contribute to HF exacerbation. Examples include urinary alkalinisers, effervescent medicines, some antacid medicines
Medications requiring accompanying fluid	Examples include bulk-forming agents for constipation. Accompanying fluid needs to be counted in the recommended fluid allowance. Consider alternative
Moxonidine	Avoid. RCT showed increased mortality in HF patients
NSAIDs and COX-2 inhibitors	Increase salt and fluid retention, worsen HF, blunt diuretic effect; worsen renal function, increase blood pressure, increase risk of myocardial infarct. Use of low-dose aspirin controversial (ensure likely benefit $>$ potential harm)
Thiazolidinediones	Sodium and fluid retention. Increase risk of worsening HF and HF hospitalizations. Use other hyoglycemic agents. (See Diabetes section.)
TNF-alfa antagonists	Adalimumab, certolizumab, etanercept, golimumab, infliximab. Weigh likely benefits versus potential risks. Closely monitor. Avoid in NYHA III-IV HF and LVEF $<$ 50%. Use cautiously in mild disease
Tricyclic antidepressants	Negative inotropic effects; increased automaticity; proarrhythmic; slowing of intracardiac conduction. Consider SSRI as alternative for depression and other medicines for neuropathic pain
Verapamil and diltiazem	Negative inotropic effect and neurohormonal activation. Contraindicated in HF-rEF. May have role in HF-pEF

Source: Adapted from Maxwell and Jenkins, Drug-induced Heart Failure (Maxwell and Jenkins, 2011) and Reed et al. Polypharmacy in Heart Failure: Drugs to Use and Avoid (Reed et al., 2014)

Identifying Adverse Effects of Medicines

Some adverse effects are to be expected and can be avoided with appropriate vigilance and action. It is important to ensure that new medicines are not introduced to treat an adverse effect (the prescribing cascade). Patients should be routinely monitored for common adverse effects and encouraged to report them to their usual health-care practitioners. A modification can frequently be made that will not necessitate the cessation of EBM.

Identifying and Managing Drug Interactions

Given the high number of medicines most HF patients will be taken, pharmacists should be alert for potential drug interaction. Combinations of certain medications should also be avoided. For example, an ARB should not be added as therapy to patients already taking an ACEI and MRA due to the increased risk of renal dysfunction and hyperkalemia. The combination of a diuretic, ACEI/ARB, and NSAID/COX-2 inhibitor (known as the "Triple Whammy") is also highly problematic.

Commonly used medicines in HF patients that are frequently involved in drug interactions include amiodarone, digoxin, some proton pump inhibitors, phosphodiesterase inhibitors, and H2 antagonists (Reed et al., 2014).

Pharmacists should ensure HF patients and carers understand that they should obtain advice from their usual health-care practitioners before commencing, ceasing, or changing the doses of any medicines.

Ensuring Optimal Medication Adherence

The HF patient commonly takes at least nine medications, six of which are cardiovascular (Bennett et al., 2004; Masoudi et al., 2005). Multiple dosing throughout the day is usually required. This complexity increases the risks of confusion, drug interactions, adverse effects, and monitoring requirements that impact quality of life. There may also be significant cost burden. Medication nonadherence is associated with an increased risk of all-cause mortality and cardiovascular hospitalizations (Fitzgerald et al., 2011). Medication nonadherence may be as high as 50% in HF patients (Zhang et al., 2013). Although 80% is the common threshold for differentiating between satisfactory and suboptimal medication adherence, investigators identified significantly better patient outcomes when the adherence was greater than or equal to 88% (Wu, 2009). A possible explanation for this high threshold is the need for comprehensive neurohormonal blockade. Nonadherence to dietary recommendations is also common. The reasons for medication nonadherence are complex and vary in different conditions and for different medications. For example, in HF, nonadherence with diuretics is common, particularly elderly women (Riegel and Dickson, 2016).

Nonadherence may be intentional or unintended. Both types may occur in the one patient.

It is important to not only investigate why patients are nonadherent to medicines but also identify factors that promote their adherence.

Concordance with the therapeutic plan can be achieved through shared decision making. Shared decision making is when decisions are made by health professionals and patients together, using the available evidence and considering and respecting the patient's characteristics and values. It is also called "patient-centered care."

Health professional requirements for successful shared decision making
Establish a context in which the patient's beliefs and views about medicines options are valued
Identify patient preferences, so that appropriate therapeutic options can be discussed;
Educate patients about their treatment options, such as potential harms versus likely benefits, in a way that they can understand
Help patients make a treatment decision and make sure that decisions are made based on the correct information and motives (i.e., the facts not misconceptions)

Ideally, a therapeutic alliance (a relationship between the various health professionals and the patient) can be established that leads to the development of an agreed patient-centered treatment plan with an ongoing support to adhere to the plan.

Pharmacists have a critical role in identifying medication nonadherence. Pharmacists should be vigilant in adherence monitoring and take the time to ask the patient or carer about it. **Box 1** displays some indicators that a patient may be nonadherent to medicines.

Apart from questioning the patient or their carer, pharmacists have the advantage of being able to objectively measure adherence. Consider:

- Repeat refills/community pharmacy electronic alert systems
- Pill counts—could perform this on home visits
- Labels on bottles—when was the medicine last dispensed? Is the patient picking up repeat medicines as scheduled? Is there more than one community pharmacy, prescriber involved?
- Consider markers of effect: e.g., blood pressure, heart rate, INR, symptoms (weight increase, breathlessness, angina, palpitations)

Patient-related factors to consider when medication non-adherence in an HF patient is identified, as shown in **Table 6**. When nonadherence is detected, consider how best this may be addressed acknowledging that there may be more than one problem and one solution. Patient/carer education regarding the medicine's benefits and associated information is usually required but is rarely sufficient alone or adequate when only provided once. Both verbal and written information should be provided. Patient-focused interventions appear to be more effective than provider-focused interventions (Ruppar et al., 2015) (**Box 2**).

Box 1 Indicators of potential medication nonadherence

Condition-related
- Asymptomatic disease/mild symptoms
- Cure appears worse than the condition
- Needs medicines that have negative publicity

Treatment-related
- Frequent brand changing
- High cost
- Multiple medications and complex regimen required
- Complaints of adverse effects form medicines

Have poor response or less than anticipated
Missed appointments, missed getting repeats
Forgetful/confused
Depression
Cognitive impairment, mental disorder
Poor health literacy and/or numeracy
Non-native speaking background
Chaotic lifestyle
Lack social support
Lack of or incorrect knowledge about condition/treatment
Belief system, e.g., want "natural" medicines; dislike taking "medicines"

Table 6 Patient-related factors to consider when nonadherence in HF patients is identified.

Patient-related factors	*Examples*
Actual or perceived adverse effects	Need to frequently urinate because of diuretics (especially if away from home); using an ACE inhibitor can cause a persistent cough; some beta-blockers can cause fatigue, dizziness, and shortness of breath during exercise; anticoagulants can cause bruising and excessive bleeding; gynecomastia from spironolactone
Rejection of the diagnosis	Patients may be in denial, especially in the early stages of HF
Limited understanding of the importance of some medicines or their dosing	HF patients may be resistant to uptitration because they believe it indicates severe disease
Loss of faith in medicines	A patient is prescribed spironolactone because the use of diuretics, ACE inhibitors and beta-blockers, hasn't improved their heart failure adequately. If the patient believes that spironolactone is also not going to work, they may not take spironolactone and may stop taking other medicines as well.
Poor sight	Patients with poor sight can't read the medicine's label or the consumer medicines information
Poor memory	Patients with poor memory can't remember the information they read or what was given to them. Poor cognition is common in HF patients.
Lack of self-efficacy	Patients may lack the confidence to make recommended behavioral changes, including taking medicines as prescribed. Adopting and maintaining self-care strategies is complex and time consuming, which may be particularly challenging in socially isolated frail HF patients.
Language or literacy barriers	Patient's medicines information may not be available in their native language, or the level of information may be too high for patients with low literacy levels. Check professional societies and consumer organizations as many provide patient information about various aspects of HF management in a variety of languages.

Box 2 Potential patient-focused interventions to improve adherence

Simplifying regimens—ideally choose once daily formulations, ideally choose medicines that can be taken with meals
Minimising costs—for example, can some medicines be combined into one, or a higher strength formulation cut in half?
Strategies to minimize adverse effects, for example, provide advice on when and how to take a diuretic so that it is effective but does not interfere with quality of life.
Consider alarms, dosette boxes, blister packs.
Event diaries, self-monitoring diaries
Posthospital discharge follow-up
Telephone/videophone follow-up

A meta-analysis of medication adherence interventions in HF patients reported that improvement in medication adherence was more likely when one behavior at a time is targeted rather than attempting to improve adherence at the same time as changing other health behaviors (Ruppar et al., 2015). The National Heart Foundation of Australia provide an e-Learning module for health-care professionals on medication adherence: http://myheartmylife-elearning.com.au/moodle/enrol/index.php?id=5.

Patient Education of Self-Care Strategies by Pharmacists

Pharmacists have an important role in educating patients about potential medication-related strategies including the use of a flexible diuretic regimen, if the HF team/specialist believes the HF patient is appropriate and supporting the uptake and maintenance of nonpharmacological self-care strategies and monitoring medication adherence and providing solutions, if nonadherence occurs.

Disease Monitoring

Pharmacists can assist patients understand and monitor their symptoms. Nonadherence to medications and nonpharmacological recommendations and use of contraindicated medications are frequent reasons for clinical deterioration. HF patents should be provided with an action plan that details their actions if symptoms of deterioration occur. Patients should be advised not to delay seeking help as it is much easier to manage the early stages of deterioration. An example of a HF action plan can be found at https://www.heartfoundation.org.au/images/uploads/publications/CON-035.v5_LWWCHF-2015-web_v2.pdf

Flexible Diuretic Regimen

The aim of a flexible diuretic regimen is to prevent HF exacerbations and hospital admissions. Daily weight monitoring is an essential component when assessing fluid status and is useful in guiding diuretic dosing. Patients should be aware of their "dry" weight and the action required if their weight increases or decreases by 2 kg within a few days. The dose of diuretic that will be required to address the exacerbation will depend on whether a diuretic is currently being used of not: if on a diuretic, the dose is usually doubled, if not 20 mg of furosemide/kg gained is a common recommendation. Patients should be counseled to watch for dizziness. Vomiting and/or diarrhea is the usual reason for a sharp decrease in weight. In these cases, the diuretic should be temporarily stopped to avoid dehydration and renal function deterioration. A diary is a useful tool for patients to monitor their weight and symptoms and adjust diuretic dosing. An example can be found at http://www.heartonline.org.au/media/DRL/Weight_and_symptom_diary.pdf. A tool to assist patients monitor their fluid intake is useful for patients:

https://www.heartfoundation.org.au/images/uploads/main/AusPAnet/My_fluid_plan.PD

Practical Guidance

Given evidence that there issues related to the real-world implementation of evidence-based therapy in HF and the acknowledged complexity of the HF patient, professional societies and hospital/community HF programs have developed practical guidance to assist uptake of evidence-based recommendations. The European Society of Cardiology has useful online practice guidance for prescription of and problem solving with ACEI/ARBs, BBs, MRAs, diuretics, and ivabradine. https://www.escardio.org/static_file/Escardio/Guidelines/ehw128_Addenda.pdf. The Canadian and Australian guidelines also provide practical tips. The American College of Cardiology have also published practical guidance that addresses key gaps in optimal care of HF-rEF patients. In Australia, the Heart Online website provides information and problem-solving plans and information to assist health-care professionals apply guideline-recommended HF management. http://www.heartonline.org.au/

Patient Resources

Professional societies and related organization provide a number of useful resources for patients and can also be used by health-care professionals when counseling patients.

- European Society of Cardiology: Heart Failure Matters-Website for patients that highlights lifestyle adjustments that enable HF sufferers and their carers to improve their quality of life.
  - https://www.escardio.org/Sub-specialty-communities/Heart-Failure-Association-of-the-ESC-(HFA)/Advocacy/heart-failure-matters-website-for-patients
- Heart Failure Society of America—provides a number of self-contained patient learning modules and information about other relevant organizations
  - http://www.hfsa.org/patient/patient-tools/educational-modules/
  - http://www.hfsa.org/patient/patient-resources/
- The National Heart Foundation of Australia
  - https://www.heartfoundation.org.au/images/uploads/publications/Living_well_with_heart_failure_2017.pdf

End-of-Life Care

HF is a progressive condition. Prediction of the specifics of the individual patient journey is challenging. Increasingly frequent recurrent hospitalizations, declining functional status, deteriorating renal function, increasing diuretic dosage, and the appearance of malignant arrhythmia indicate the HF patient is entering the terminal phase although this may last over a year. Discussion of the likely patient journey and documentation of the patient's advance-care directives should occur early and involve family members and the health-care team members. The involvement of a palliative care team may also be considered. Although EBM such as ACEIs and BBs should be continued if possible because they can help alleviate HF symptoms, hypotension, renal impairment, electrolyte derangements can necessitate their withdrawal. Diuretics for congestive symptoms and opioids for breathlessness, pain, and anxiety are useful. Cessation of medications that will not have any immediate effect on symptoms or quality of life should be considered. These include osteoporosis medicines and statins.

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Management of Cerebrovascular Disease and the Pharmacist's Role: Stroke

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Learning Objectives:

- To understand the epidemiology of stroke.
- To identify the pathophysiology and etiology of stroke.
- To explain the treatment used for acute ischemic stroke and its secondary prevention.
- To identify the nonpharmacological approaches in preventing ischemic stroke attack.

Take Home Messages

- Stroke is the second leading cause of death, and approximately 42.4 million people suffered from stroke globally in 2015.
- Stroke that is caused by reduced blood flow to the brain can either be hemorrhagic or ischemic in nature.
- Atherosclerosis due to plaque formation in blood vessels is the main factor that leads to reduced blood flow to the brain.
- Early reperfusion with thrombolytic agents such as alteplase may reduce the sequela and disabilities associated with stroke attack.
- Therapy with antiplatelet, antihypertensive, and anticholesterol agents is the cornerstone in the prevention recurrence of stroke.
- Blood pressure lowering and cholesterol-lowering therapy regardless of blood pressure and baseline cholesterol level had been proven to reduce recurrence of stroke episodes.

Introduction

According to the Global Burden of Disease Study 2015 (GBD 2015), prevalence of stroke was reported at 42.4 million in 2015 (Vos et al., 2016). Although the global age-adjusted mortality rate for stroke decreased, the absolute number of people who have stroke increased between 1990 and 2015 (Benjamin et al., 2018). In 2016, stroke is the second leading cause of death globally and has remained the leading cause of death in the past 15 years (WHO, 2018).

Stroke is a cerebrovascular disease affecting the central nervous system, resulting either from insufficient blood flow to the brain or hemorrhage into the parenchyma or subarachnoid space of the central nervous system. Stroke patients may develop focal or global cerebral function disturbances lasting more than 24 h or death. Stroke survivors may experience various complications such as loss of vision, loss of speech, paralysis, and confusion (Koda-Kimble et al., 2013). High blood pressure and atrial fibrillation are the two important risk factors for stroke (Hörnsten et al., 2016).

Stroke can be either classified as ischemic or hemorrhagic. According to the American Heart Association report 2015, 87% of all strokes are ischemic, while 13% is hemorrhagic (Mozaffarian et al., 2015). Although hemorrhagic stroke is less common, it is more fatal than ischemic stroke with up to 46.5% of fatality rates compared to 9%–23% for ischemic stroke (Godoy et al., 2015).

Transient ischemic attack (TIA) is due to inadequate cerebral or ocular blood flow. The inadequate blood supply may be caused by low blood flow, thrombosis, or embolism, which leads to loss of cerebral or ocular function with symptoms lasting less than 24 h (George Rudd et al., 2017). The symptoms appear rapidly, and the clinical presentations depend on the portion of the cerebrovascular branch affected. The symptoms include slurred speech, aphasia, weakness or paralysis of a limb, or blindness (Koda-Kimble et al., 2013). Approximately 20% of TIA patients experienced at least one symptom (Godoy et al., 2015).

Ischemic stroke is caused by occlusion of cerebral artery, leading to decreased cerebral blood flow. The occlusion of blood vessels is caused either by local thrombus formation or by embolic phenomena. Atherosclerosis is a causative factor in most cases of ischemic stroke (DiPiro et al., 2017). Emboli can arise from intracranial or extracranial origin. Cardiogenic embolism is prone to happen in patients suffering from atrial fibrillation, valvular heart disease, or other heart conditions that lead to clot formation (Mozaffarian et al., 2015).

Hemorrhagic strokes include subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) (DiPiro et al., 2017). SAH involves leakage of blood into the brain and the space surrounding the brain or subarachnoid space. Cerebral artery aneurysm, arteriovenous malformation, hypertensive hemorrhage, and trauma are among the major causes of SAH (Koda-Kimble et al., 2013). ICH occurs when a blood vessel ruptures within brain parenchyma, resulting in the formation of hematoma. Uncontrolled high blood pressure and antithrombotic or thrombolytic therapy are among the risk factors for ICH (DiPiro et al., 2017). The leakage may be typified by sudden onset of severe headache and vomiting (George Rudd et al., 2017).

Severe neurological deficits happen as stroke progresses and thus, timely initiation of appropriate therapy for stroke patients is important (Saver, 2006). Involvement of pharmacists in stroke care team reduces the door-to-needle time (Kevin Brandon et al., 2018; Rech et al., 2017). Besides, pharmacists also play an essential role in providing counseling and education to stroke patients in order to ensure poststroke treatment adherence (Rhoney, 2011), minimize the impact of stroke-related complications (Rhoney, 2011; Sreenivasan, 2012), and improve patients' health-related quality of life (Hohmann et al., 2009).

Epidemiology

According to the GBD 2015, the incidence of both ischemic and hemorrhagic stroke increased by 15.8% and 14%, respectively, from 2005 to 2015 globally (Vos et al., 2016). In the United States, on average, someone suffers from stroke every 40 s (Mozaffarian et al., 2015). In 2015, every 3 min 45 s, one patient died of stroke, which accounted for approximately 1 of every 20 deaths in the United States. It is projected that by 2030, nearly 4% of the United States' population will have a stroke attack (Ovbiagele et al., 2013).

Stroke events are more likely in those patients with lower income and lower educational level (Ovbiagele et al., 2013). Around 70% of stroke cases and more than 85% of stroke-related deaths and disability-adjusted life years are found in low- and middle-income countries, and the incidence has been on the increasing trend over the past 40 years (Feigin et al., 2009; Owolabi et al., 2015; Strong et al., 2007). On the other hand, the incidence of stroke decreased by 42% in high-income countries (Owolabi et al., 2015; Strong et al., 2007). High-income countries such as Austria and Switzerland have reported a relatively low stroke mortality rate, although a large proportion of their population is elderly (aged more than 65 years old) (Thrift et al., 2017). According to Owolabi et al. (2015), stroke occurs 15 years earlier in people living in low- and middle-income countries and causes more deaths compared to people living in high-income countries. Furthermore, up to 84% of patients in low- and middle- income countries die within 3 years of stroke diagnosis, making the mortality rate five times higher than in patients with stroke living in high-income countries (Owolabi et al., 2015). Besides, 34% of stroke patients in low- and middle-income countries are diagnosed with hemorrhagic stroke, which is almost four times higher when compared with the hemorrhagic stroke incidence reported in high-income countries (Owolabi et al., 2015).

The risk of having stroke varies with race or ethnicity, age, and gender. Generally, the incidence of having first stroke attack was higher in black individuals than with white individuals (Howard et al., 2016). Male generally has lower lifetime risk of stroke than female (Centers for Disease Control and Prevention, 2012). Furthermore, the lifetime risk of stroke among those 55–77 years of age is 1–5 for women and approximately 1–6 for men (Seshadri et al., 2006). In the United States, there have been approximately 55,000 more females suffering from stroke attack when compared to male patients (Persky et al., 2010). Age-specific stroke incidence rate is almost similar in older age group; however, the incidence rate is lower in female than in male in younger and mid-age populations (Benjamin et al., 2018).

In the United States, the estimated prevalence of TIA is around 0.5 million annually and affects 1.1 per 1000 of the population (Panuganti and Dulebohn, 2018). There are important racial, ethnic, gender, and age differences in incidence rates for TIA. The incidence increases with age. Male, African American and Mexican Americans showed higher incidence rate when compared to the female, non-Hispanic white populations (Kissela et al., 2004; Kleindorfer et al., 2005; Morgenstern et al., 2004). There is an

established correlation between the occurrence of TIA and increased risk of subsequent stroke. Around 12% of all stroke events reported is associated with TIA (Hankey, 1996). Stroke attack is reported to be the highest within the first 30 days after TIA event and the TIA risk of stroke within 90 days is reported at 3.7%–17% (Amarenco et al., 2008; Giles and Rothwell, 2007; Johnston et al., 2000; Wu et al., 2007).

In the United States, the total medical cost of stroke (both direct and indirect medical cost) incurred in 2012 to 2013 was $33.9 billion with the estimated direct medical cost being $17.9 (Agency for Healthcare Research and Quality, 2014). It is projected that by the year 2030, the total direct medical stroke-related costs will be $184.1 billion (Ovbiagele et al., 2013). Recurrent stroke patients had 38% higher cost per patient a year after discharge from hospital as compared to new stroke patients (Engel-Nitz et al., 2010). From 2001 to 2005, the average cost involved in stroke rehabilitation was $11,145 (Godwin et al., 2011). Besides, health-care costs associated with stroke survivors with complications such as spasticity are fourfold higher than those without spasticity (Lundström et al., 2010).

Poststroke depression and stroke-related disability are those factors affecting stroke survivors' health-related quality of life (HRQoL). Nearly 30% of stroke survivors suffered from poststroke depression (Abubakar and Isezuo, 2012; Hackett and Anderson, 2005). Poststroke depression has been found to be associated with higher chances of suicidal ideation (Fuller-Thomson et al., 2012). Depression also slows down the rehabilitation process and negatively affects patients' HRQoL (Gray et al., 2007; Williams et al., 1999). However, poststroke depression is a treatable condition, and early diagnosis may prevent the progression to chronic depressive disorder. The degree of stroke-related disability measured by Modified Rankin Scale (MRS) also has negative impact on patients' quality of life (QoL). Patients who remained disabled 3 months after stroke had poor QoL (Godoy et al., 2015; Hackett & Anderson, 2005), although another study has reported poor QoL even in patients without disability after stroke (Lai et al., 2002).

Pathophysiology

Stroke may arise due to local damage to a vessel wall from atherosclerosis. Development of atherosclerosis begins with endothelial injury and inflammation, leading to plaque or clot formation which affects the cerebral blood flow of the brain. The clot may form near the infarcted area in the brain or it might have migrated to the brain from a distant source. Clot arising from a distant source is considered as embolus. However, if the clot is formed near the infarcted area, it is considered a thrombus (Frizzell, 2005).

Thrombotic infarction is mainly due to atherosclerosis. The release of adenosine diphosphate (ADP), thrombin, epinephrine, and a variety of other substances due to tissue injury or turbulent blood flow may stimulate platelet migration. Adhesion of platelet to the damaged blood vessel wall is enhanced by the exposure of collagen and other subendothelial surfaces of the blood vessel wall. Phospholipase is activated as a result of platelet adhesion and aggregation, which leads to the formation of thromboxane A_2 (TXA_2). TXA_2 induces platelet release and aggregation, which results the formation of clot in blood vessel (Sangkuhl et al., 2011).

The pathophysiology of ischemic stroke due to embolic event is similar to ischemic stroke due to thrombotic event. Embolus composes of platelet, clot, or plaque debris that can be either originated from the heart or major blood vessels. Portions of these clots may break away and travel through the blood to the brain, which occlude the intracranial arteries leading to partial or totally occlusion of blood flow. Atherosclerotic plaque is commonly found in the carotid artery that accounts for up to 20% of ischemic stroke, while cardiac embolus accounts for up to 30% (Arboix and Alió, 2010). Cardiac events such as myocardial infarction, atrial fibrillation and flutter, rheumatic and prosthetic valves, and infective endocarditis are among the major risk factors for embolus formation (Arboix and Alió, 2010; Koda-Kimble et al., 2013). Other risk factors of ischemic stroke are listed in **Table 1**.

Inflammatory process is responsible for the development of ischemic stroke. Within hours of infarction, substances such as adhesion molecules, C-reactive protein, proinflammatory cytokines, such as tumor necrosis factors-alpha, interleukin-I, interleukin-6, free oxygen radicals, and chemokines increase and lead to inflammation. Inflammation enhances the development of thrombotic lesions and causes occlusion of blood vessels (Jin et al., 2010).

Normal cerebral blood flow in a healthy adult is 30–70 mL/100 g/min. The reduction of cerebral blood flows to less than 20 mL/100 g/min causes an electrical silence and irreversible neuronal injury including neuron cells death might happen if the cerebral blood flow continues to reduce to less than 10 mL/100 g/min (Hakim, 1998; Jones et al., 1981). There are three mechanisms that lead to cell death during brain ischemic events, namely, excitotoxicity and ionic imbalance, oxidative and nitrosative stresses, and apoptotic-like cell death (Carbonell and Rama, 2007). Excitotoxicity and ionic imbalance and oxidative and nitrosative stresses cause cell death in the central core. Apoptotic like cell death normally happens in the penumbral region of the brain.

Intracerebral hemorrhage (ICH) refers to bleeding in the brain parenchyma and surrounding meningeal spaces. ICH is a manifestation of underlying small vessel disease. Hypertension and cerebral amyloid angiopathy (CAA) are the important risk factors for ICH. The risk of hypertension-related ICH increases with increasing blood pressure (Matsukawa et al., 2012), whereas CAA-related ICH tends to occur in elderly (Ariesen et al., 2003). Other risk factors include cerebral artery aneurysm, arteriovenous malformation, and trauma (Koda-Kimble et al., 2013). Hypertensive vasculopathy due to longstanding hypertension changes the walls of the small and medium penetrating vessels. CAA leads to deposition and accumulation of amyloid-beta peptide in the walls of small vessel (Vinters, 1987). These subsequently result in the changes in the vessel wall characterized by the loss of smooth muscle cells, wall thickening, luminal narrowing, microaneurysm formation, and microhemorrhages (Viswanathan and Greenberg, 2011). Vessel rupture leads the leakage of blood into the brain and its surrounding structures. Neurologic dysfunction in ICH is due to the direct irritant effects of blood that is in contact with the brain tissues (Gund et al., 2013).

Table 1 Risk factors for ischemic stroke

Modifiable risk factors:
- Cardiovascular disease
- Hypertension
- Atrial fibrillation
- Asymptomatic carotid stenosis
- Dyslipidemia
- Diabetes mellitus
- Sickle cell disease
- Postmenopausal hormone replacement therapy
- Obesity
- Cigarette smoking
- Physical inactivity

Potentially modifiable:
- Metabolic syndrome
- Alcohol abuse
- Hyperhomocysteinemia
- Drug abuse
- Hypercoagulability
- Oral contraceptive use
- Inflammatory process
- Acute infection

Non-modifiable risk factors:
- Age
- Race
- Sex
- Low birth weight
- Family history of stroke

Adapted from Koda-Kimble, Anne Marry, Young JY, 2013, Applied Therapeutics: The clinical use of drugs, Philadelphia, Wolters Klumer Health/Lippincott Wiliams & Wilkins, p1421. Copyright 2013 by Wolters Klumer Health/Lippincott Wiliams & Wilkins

Clinical Presentations and Diagnosis of Ischemic Stroke

Clinical signs and symptoms of stroke or TIA are determined by the location of the brain area that is affected. For example, if the left side of the brain that controls the motor function is affected, then the muscle strength or movement on the right side of the body will be disturbed. The clinical signs and symptoms of stroke or TIA include paresis or paralysis of the limbs, slurred speech, blurred vision, facial drop, dizziness, and difficulty in swallowing (DiPiro et al., 2017; Koda-Kimble et al., 2013).

Resumption of adequate blood perfusion to the affected blood vessels is the immediate primary treatment goal of stroke. According to the American Heart Association/American Stroke Association 2018 guideline (Powers et al., 2018), formal stroke scores based on NIH Stroke Scale (NIHSS) is recommended to be performed. The formal stroke scores quantify the degree of neurological defects that may aid in the decision of type of treatment and identify those patients who are at higher risk of intracerebral hemorrhage and other complications (Adams et al., 1999; Fonarow et al., 2012; Frankel et al., 2000; Wahlgren et al., 2008). Brain imaging evaluation using noncontrast computerized tomography (NCCT) is recommended over diffusion-weighted magnetic resonance imaging (DW-MRI) for all patients admitted to hospital suspected of acute stroke to exclude the use of antithrombotic agents in intracerebral hemorrhage (Powers et al., 2018). Blood glucose assessment should be performed prior to the initiation of IV alteplase in all patients, while other tests such as baseline ECG assessment, international normalized ratio (INR), activated partial thromboplastin time, and platelet count may be needed in certain circumstances; however, the treatment with IV alteplase should not be delayed while pending for these investigations (Powers et al., 2018).

Management of Ischemic Stroke

The immediate approach to the management of a stroke patient is to ensure that the patient is supported from a respiratory and cardiac standpoint and to determine whether the patient is having ischemic or hemorrhagic stroke. The goals of treatment of ischemic stroke are to (1) re-establish adequate blood perfusion in the occluded vessel, (2) reduce the ongoing neurological injury, (3) decrease mortality and long-term disability, (4) prevent complications to immobility and neurologic dysfunction, and (5) prevent stroke recurrence (DiPiro et al., 2017; Koda-Kimble et al., 2013). The treatment algorithm for ischemic stroke is summarized in Fig. 1.

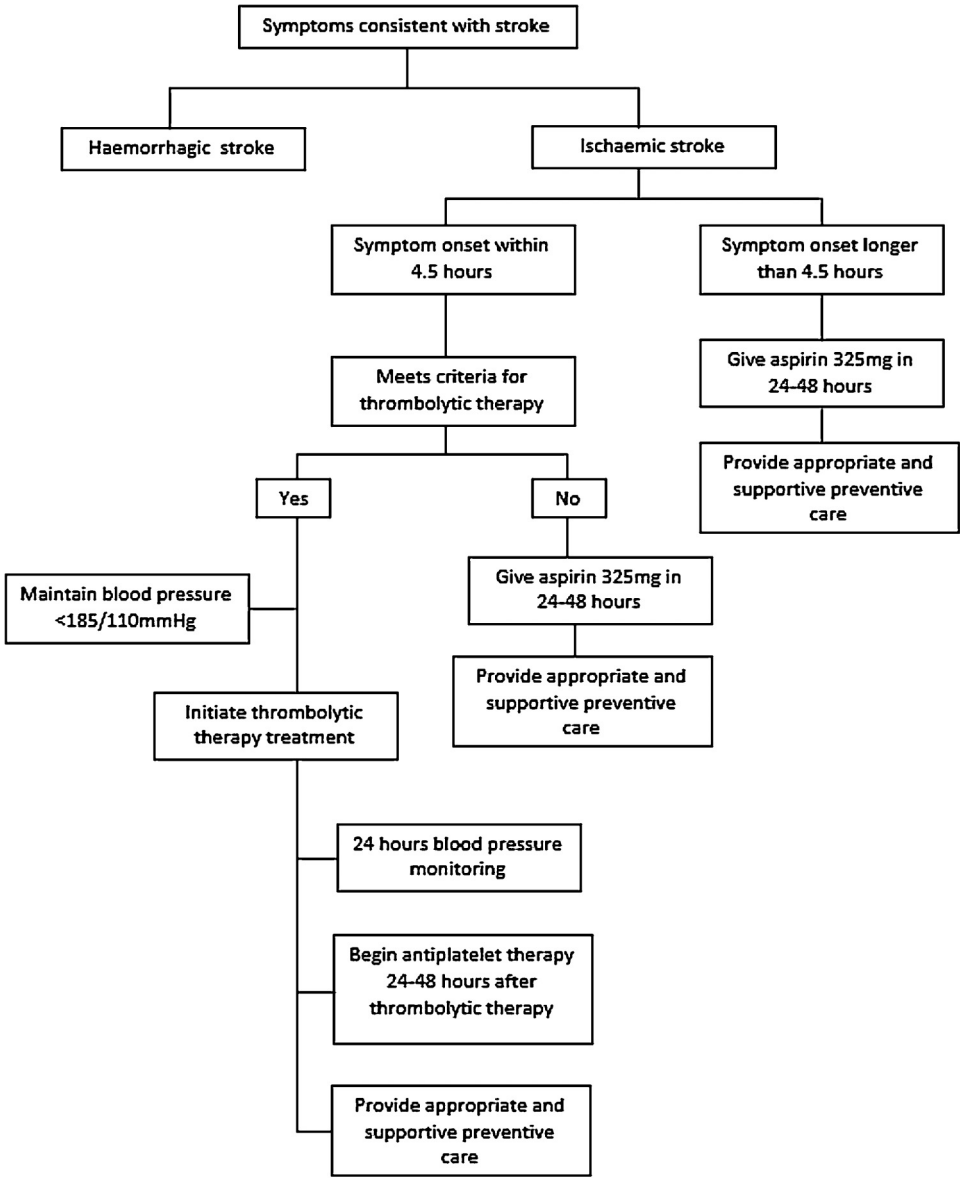

Fig. 1 Treatment algorithm for ischaemic stroke. *Adapted from Koda-Kimble, Anne Marry, Young JY, 2013, Applied Therapeutics: The clinical use of drugs. Philadelphia, Wolters Klumer Health/Lippincott Wiliams & Wilkins, p. 1430. Copyright 2013 by Wolters Klumer Health/Lippincott Wiliams & Wilkins*

Acute Treatment of Ischemic Stroke

Thrombolytic Agent

Blood clot that causes blockage to the brain artery is one of the main causes of ischemic stroke. Timely initiation of thrombolytic agent, which dissolves blood clot, ensures blood perfusion to the blocked area before a major damage to the brain occurs (Wardlaw et al., 2014). Time is brain and early blood reperfusion leads to better recovery from ischemic stroke. However, the use of thrombolytic agent may cause hemorrhage in the brain, which could be fatal in severe cases. The use of thrombolytic agent is contraindicated in hemorrhagic stroke. Thus, it is important to exclude patients with hemorrhagic stroke from initiating thrombolytic therapy.

Alteplase (i.e. tPA) is one of the thrombolytic agents used in ischemic stroke patients. The benefit of the treatment is time dependent. For better outcome, thrombolytic agent should be administered to suitable ischemic stroke patients as fast as possible after the onset of symptoms (Ettehad et al., 2016; Wardlaw et al., 2014). The efficacy of alteplase is proven if administered within 3–4.5 h after ischemic stroke onset (The ATLANTIS, ECASS, 2004; Wahlgren et al., 2007; Wardlaw et al., 2014, 2012).

Thrombolytic treatment is strongly recommended for patients with ischemic stroke caused by large vessel occlusion and those who are candidates for endovascular thrombectomy (Goyal et al., 2016). For ischemic stroke patients who meet specific eligible

Table 2 Contraindication of thrombolytic treatment

- Active systemic bleeding
- Systemic coagulopathy with
  - Platelet count $< 100{,}000\ mm^3$
  - INR > 1.7
  - Elevated ATPP with unfractioned heparin use within 48 h
  - Abnormal antifactor Xa activity with low molecular weight heparin use within 24 h
  - Abnormal coagulation profile with direct oral anticoagulant use within 24 h
- Infective endocarditis
- Acute intracranial hemorrhage

Adapted from Sandercock. Peter AG, Counsell. Carl, Mei-Chiun. Tseng and Cecconi. Emanuela, 2014, Oral antiplatelet therapy for acute ischemic stroke. Cochrane Database of Systematic Reviews, 3, Art No.: CD000029. Copyright 2014 by the Cochrane Collaboration

criteria, alteplase 0.9 mg/kg (maximum 90 mg) administered intravenously over 1 h with initial 10% of the dose given as bolus injection over 1 min should be initiated (Goyal et al., 2016; Wardlaw et al., 2014).

Tenecteplase, a more fibrin-specific agent with longer duration of action, is another thrombolytic agent used in ischemic stroke management. Both alteplase and tenecteplase are associated with intracerebral hemorrhage risk (1%). According to a clinical trial involving 1100 patients, tenecteplase failed to demonstrate superiority over alteplase in patients with minor neurological impairment (NIHSS score 4) and no major intracranial occlusion (Logallo et al., 2017). Contrary, based on the study conducted by Campbell et al. (2018), tenecteplase performed better than alteplase before thrombectomy for ischemic stroke patients with better 90-day functional outcome and better MRS score. Although the safety profile of tenecteplase appears to be similar to alteplase, whether it is as effective as or more effective than alteplase still remains unclear due to the lacking of sufficient clinical evidence (Haley et al., 2010; Huang et al., 2015; Logallo et al., 2017; Parsons et al., 2012).

If a patient is not a candidate for thrombolytic therapy, antiplatelet therapy should be initiated after hemorrhagic stroke is excluded (Sandercock et al., 2014). Bleeding risk or potential bleeding risk is one of the contraindications to thrombolysis. Other contraindications of thrombolytic treatments are listed in **Table 2**.

There are few clinical conditions that do not exclude the use of thrombolytic agents; however, these make the initiation of thrombolytic agents to be carefully considered due to risk and benefit. Those clinical conditions include (Sandercock et al., 2014):

- Uncontrolled high blood pressure with systolic and diastolic blood pressure more than 185 mmHg and 110 mmHg, respectively
- History of intracranial hemorrhage
- Major head trauma or spinal or cranial surgery within 3 months
- Major surgery or trauma within 14 days
- Gastrointestinal or genitourinary tract bleeding within 21 days
- Ischemic stroke within 3 months
- Central nervous system neoplasm

Treatment with thrombolytic agent should only be initiated if the BP $< 185/110$ mmHg and should have the BP monitored in the first 24 h after the treatment (Powers et al., 2018). Regardless of diabetic status, antihyperglycemic therapy should be started when blood glucose level is greater than 10 mmol/L (Middleton et al., 2011).

There are insufficient data to support the safe use of intravascular thrombolytic agents and direct oral anticoagulants within 48 h of stroke onset. However, this is not an absolute contraindication to stop using thrombolytic agents. There are several ways to initiate thrombolytic treatment in patients who use direct oral anticoagulant within 48 h, and these include reversal of anticoagulant with specific antidote, appropriate coagulation testing, and immediate thrombectomy (Hankey et al., 2014).

Antiplatelet Therapy

Antiplatelet therapy with aspirin as the most commonly known agent, is part of the antithrombotic therapy in stroke management. Antiplatelet agents inhibit platelet adhesion and aggregation in intracerebral artery. They decrease the neurological complications, risk of morbidities and mortalities, as well as risk of early recurrent stroke (Sandercock et al., 2008, 2014). Although increased risk of intracerebral hemorrhage may offset its benefit, recent clinical trials reported a relatively low risk of major bleeding with the use of aspirin in embolic stroke compared to an anticoagulant (Hart et al., 2018; Sandercock et al., 2014). Thus, aspirin is highly recommended in ischemic stroke patients who are not candidates for reperfusion therapy after brain imaging excludes hemorrhage (Powers et al., 2018).

Administration of aspirin is highly recommended in acute ischemic stroke patient within 24–48 h after symptoms onset. Aspirin given at the dose between 150 mg and 300 mg has been proven to be safe and effective (Castillo et al., 1998; Sandercock et al., 2014; Sandercock and Group, 1997). Rectal or nasogastric administration is further recommended in a patient who is unable to swallow (Powers et al., 2018). Combination use of aspirin and alteplase within 24 h significantly increases the risk of intracranial hemorrhage with no apparent benefit (Zinkstok et al., 2012). Although the evidence is not strong, acute antiplatelet therapy is recommended to be deferred at least for 24 h after administration of alteplase (Powers et al., 2018).

Clopidogrel inhibits platelet aggregation induced by ADP. Based on CAPRIE trial (Clopidogrel vs Aspirin in Patient at Risk of Ischaemic Event) (CAPRIE Steering Committee, 1996), relative risk of ischemic event reduction of 7.3% was observed in patients receiving clopidogrel 75 mg/day as compared to those patients receiving aspirin 325 mg/day. Clopidogrel is associated with higher incidence of rash and diarrhea than aspirin. Reduction in neutrophils counts and thrombocytopenia purpura are reported in patients receiving clopidogrel (Azarm et al., 2011; Rubano et al., 2015). Clopidogrel is considered as an alternative to aspirin in secondary prevention of stroke (Koda-Kimble et al., 2013).

Dual antiplatelet regimen with aspirin and clopidogrel has shown to reduce recurrent stroke and its associated morbidities and mortalities with no increased risk of bleeding compared with aspirin monotherapy, as reported in CHANCE trial (Clopidogrel in high-risk patients with acute nondisabling cerebrovascular events) (Wang et al., 2015). However, this trial mainly focused on Asian Chinese population, making the benefit of the dual antiplatelet therapy uncertain to the non-Asian population. This gap nonetheless has recently been filled by Claiborne Johnstan et al (S. Claiborne Johnston et al., 2018) where they conducted a randomized trial on international population with ischemic stroke or high risk of TIA. The result showed that those patients receiving dual antiplatelet therapy had lower risk of major ischemic events although they experienced higher risk of major bleeding than those receiving aspirin monotherapy in the 90-day trial period (S. Claiborne Johnston et al., 2018).

Ticlopidine is an antiplatelet agent, which is chemically related to clopidogrel. It works by inhibiting ADP-induced platelet aggregation. According to two large clinical trials, TASS (Ticlopidine Aspirin Stroke Study Group) (Hass et al., 1989) and CATS (Canadian American Ticlopidine Study) (Gent et al., 1988), which recruited a total of 4141 patients, ticlopidine significantly reduced risk of stroke by 21%–33.5%. However, hematological and gastrointestinal adverse effects limit its use. The risk of adverse effects is greater with ticlopidine than aspirin (Hass et al., 1989). Fatal thrombotic thrombocytopenia purpura (TTP) has been associated with ticlopidine. Among the 60 cases of ticlopidine-induced TTP reported to the U.S. Food and Drug Administration (FDA) in 1998, approximately one-third of the patients had died from TTP (Bennett et al., 1998). Other potentially fatal types of hematologic adverse effects such as agranulocytosis, aplastic anemia, neutropenia, pancytopenia have been reported (Paradiso-Hardy et al., 2000). Due to the severe adverse effects, a complete blood count should be performed prior to the initiation of ticlopidine therapy and every 2 weeks for the first 3 months of the therapy (Koda-Kimble et al., 2013).

Ticagrelor, a platelet aggregation inhibitor, is found to be inferior to aspirin. The primary outcomes measured in SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) (S. Claiborne Johnston et al., 2016) including the time to the composite end point of stroke, myocardial infarction, and death up to 90 days suggest that ticagrelor is not as effective as aspirin. However, based on its safety profile, which is similar to aspirin, ticagrelor might be considered a reasonable alternative in patients who have contraindications to aspirin (S. Claiborne Johnston et al., 2016; Powers et al., 2018).

Glycoprotein IIb/IIIa Receptor Antagonists

The efficacy of glycoprotein IIb/IIIa receptor antagonists such as abciximab, tirofiban, and eptifibatide in the management of acute ischemic stroke are not well established (Adeoye et al., 2015a, 2015b; Pancioli et al., 2008; Siebler et al., 2011). Administration of glycoprotein IIb/IIIa receptor antagonists in the treatment of acute ischemic stroke is harmful with associated increased risk of intracerebral hemorrhage (Ciccone et al., 2014). The increased risk of intracerebral hemorrhage with the use of abciximab in acute ischemic stroke patients in AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patient With Acute Ischaemic Stroke) led to early termination of the trial (Harold P. Adams et al., 2008).

Anticoagulants

Common anticoagulants such as heparin and warfarin are part of the antithrombotic therapies for patient with cardioembolic acute ischemic stroke (Powers et al., 2018). They reduce the propagation of a thrombus in an intracerebral artery and reduce early recurrent thromboembolic stroke. Oral anticoagulation is the treatment of choice for the prevention of stroke in patients with atrial fibrillation. Atrial fibrillation is an independent risk factor for stroke, and it increases the risk by about fivefold (Wolf et al., 1991). In the European Atrial Fibrillation Trial (EAFT), patients with nonvalvular atrial fibrillation and prior stroke were randomized to warfarin, aspirin, or placebo (European Atrial Fibrillation Trial, 1995). A reduction of risk of cardiovascular events including stroke and death was reported in up to 53% of patients treated with an anticoagulant (European Atrial Fibrillation Trial, 1995). However, risk of major bleeding is a limiting factor to its use (Sandercock et al., 2008, 2014). Nevertheless, SPAF III trial (Stroke Prevention in Atrial Fibrillation) suggested that targeting INR of 2.5 in patients with nonvalvular atrial fibrillation in preventing stroke was associated with lowest risk of bleeding (Kernan et al., 2014; Meschia et al., 2014). Due to its high risk of major bleeding, anticoagulant is recommended only in TIA/stroke patient associated with cardioembolism (Sandercock et al., 2008).

The use of heparin, either the unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for deep vein thrombosis prophylaxis in immobilized patients with acute ischemic stroke, is not well established. Prophylactic use of UFH or LMWH is associated with significant reduction of pulmonary embolism and deep vein thrombosis, but it also associated with significant increases in intracranial hemorrhage and extracranial hemorrhage. Due to the risk of hemorrhage, intermittent pneumatic compression (IPC) should be considered as deep vein thrombosis prophylaxis in immobilized stroke patients (Dennis et al., 2016). The usefulness of novel oral anticoagulants (NoACs) such as dabigatran, direct thrombin inhibitor such as argatroban (Barreto et al., 2012, 2017; Kate et al., 2015), and factor Xa inhibitor, such as rivaroxaban, apixaban, and edoxaban (Gioia et al., 2016) in the treatment of acute ischemic stroke either as a single or an adjunct therapy to alteplase are not well established.

Acute Blood Pressure-lowering Agents

High blood pressure is one of the risk factors for ischemic stroke and hemorrhagic stroke (Geeganage et al., 2012) and up to 70% of those stroke patients admitted to hospital have a history of high blood pressure (National Stroke Foundation, 2015). Patients with acute ischemic stroke can present with several acute comorbidities such as acute heart failure, aortic dissection, preeclampsia/eclampsia, which demand emergency blood pressure reduction to prevent serious complications. However, drastic blood pressure lowering in the acute phase care to systolic blood pressure (SBP) < 140 mmHg increases the risk of renal adverse effects (Qureshi et al., 2016) and does not benefit the patient on death or functional outcome (Geeganage et al., 2012). For acute ischemic stroke patients with blood pressure greater than 220/120 mmHg, blood pressure should be gradually reduced to 20% over the first 24 h (Powers et al., 2018) and subsequently to the target level of SBP of 140 mmHg (Barreto et al., 2012).

BP is an important monitoring criterion to decide the optimal timing for the initiation of thrombolytic therapy. For candidates who meet the criteria for treatment with IV alteplase, their SBP and diastolic blood pressure (DBP) should be less than 185 mmHg and less than 110 mmHg, respectively, before the treatment is given. The BP should be maintained at <180/105 mmHg for the first 24 h after the treatment (Powers et al., 2018). Studies suggest that there is greater risk of hemorrhage in patients with high BP (Butcher et al., 2010; Endo et al., 2013; Mazya et al., 2012; Perini et al., 2010; Waltimo et al., 2016; Wu et al., 2016). According to the American Heart Association/American Stroke Association 2018 management of acute ischemic stroke guideline (Powers et al., 2018), thrombolytic agent should not be initiated if BP is more than 185/110 mmHg. For patients meeting the criteria of IV alteplase treatment with BP > 180/110 mmHg, the following antihypertensive treatment regimen is recommended (Powers et al., 2018):

1. IV Labetalol 10–20 mg over 1–2 min may repeat 1 time OR
2. IV Nicardipine 5 mg/h, titrate up 2.5 mg/h every 5–15 min, with maximum dose of 15 mg/h OR
3. IV Clevidipine 1–2 mg/h, titrate by doubling the dose every 2–5 min until desired BP with maximum dose of 21 mg/h OR
4. Other agents such as hydralazine and enalapril may be considered.

Patient's BP should be monitored closely for the first 24 h from the start of IV alteplase to maintain at ≤180/105 mmHg. BP should be checked every 15 min for 2 h from the initiation of IV alteplase treatment followed by every 30 min for 6 h and then every hour for 16 h. If the SBP is more than 180–230 mmHg or the DBP is more than 105–120 mmHg, the following therapy may be considered (Powers et al., 2018):

1. IV Labetalol 10 mg followed by IV continuous infusion 2–8 mg/min OR
2. IV Nicardipine 5 mg/h, titrate up by 2.5 mg/h every 5–15 min to desired blood pressure, with maximum dose of 15 mg/h OR
3. IV Clevidipine 1–2 mg/h, titrate by doubling the dose every 2–5 min to desired blood pressure, with maximum dose of 21 mg/h

IV sodium nitropruside may be considered if DBP > 140 mmHg or patient's BP is not controlled with the abovementioned therapy.

General Supportive Care

Antipyretic treatment should be given to lower body temperature in stroke patients with hyperthermia as the risk of death is greater for patient with body temperature above 39̊C (Saxena et al., 2015). However, there is lacking of evidence of benefit of inducing hypothermia in ischemic patient. Some studies have proven that inducing hypothermia is associated with higher risk of pneumonia and other types of infections (Geurts et al., 2017; Hemmen et al., 2010; Lyden et al., 2016; Piironen et al., 2014).

Patient's blood glucose should be monitored and treated accordingly to the range of 140–180 mg/dL as poor blood glucose control leads to worse outcomes during the first 24 h after acute ischemic stroke. Since hypoglycemia and hyperglycemia may mimic the ischemic stroke presentations, determining blood glucose level is needed prior the initiation of thrombolytic agent (Powers et al., 2018).

Dysphagia screening is recommended before allowing oral administration of food and medications preferably within 4 h after an acute stroke attack (Bray et al., 2017). Behavioral approaches such as swallowing exercise and dietary modification are recommended for stroke survivors who have swallowing difficulties (Geeganage et al., 2012).

Secondary Prevention of Ischemic Stroke

Poststroke patients exhibit an accumulated risk of up to 43% of having recurrent stroke in 10 years of time (Hardie et al., 2004). Early stroke symptoms identification by the patients or family members are crucial in seeking for timely medical assistance or treatment. FAST test has been a well-accepted stroke screening test for health-care professionals and general public (Harbison et al., 2003), although some stroke patients may have a negative FAST test (Powers et al., 2018). Secondary prevention with pharmacological agents and through nonpharmacological approach is able to manage or minimize the risk factors of recurrent stroke. In this context, medication adherence is one of the important aspects.

Pharmacological Approach

Antihypertensive therapy

High BP is a modifiable risk factor for stroke and should be included in the secondary stroke prevention treatment regimen as a discharge medication (Thrift et al., 2017). Poststroke survivors with BP more than 140/90 mmHg should be considered as the

Table 3 Drugs for preventing transient ischemic attack (TIA) and ischemic stroke

Drugs	*Action*	*Dose*
Aspirin	Antiplatelet	50–300 mg/day
Clopidogrel	Antiplatelet	75 mg/day
Ticlopidine	Antiplatelet	50 mg/day
Dipyridamole	Antiplatelet (in combination with aspirin)	200 mg sustained-released twice daily
Warfarin	Anticoagulant	Titrate to INR 2-3

Adapted from Koda-Kimble, Anne Marry, Young JY, 2013, Applied therapeutics: the clinical use of drugs. Philadelphia, Wolters Klumer Health/Lippincott Wiliams & Wilkins, p. 1428. Copyright 2013 by Wolters Klumer Health/Lippincott Wiliams & Wilkins

candidate for long term BP-lowering therapy with the target SBP between 120 mmHg to 140 mmHg (Costas Thomopoulos, 2016; Ettehad et al., 2016). Among the antihypertensive agents, beta blocker should be considered as first-line agent for patient with ischemic heart disease. Angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist should be considered as the drug of choice for patient with diabetes mellitus (Shrout et al., 2017). Calcium channel blockers and thiazide diuretics are also acceptable as antihypertensive therapy for poststroke patients (Lakhan and Sapko, 2009; Mukete et al., 2015).

Antiplatelet and anticoagulant therapy

Antiplatelet therapy has been the cornerstone in preventing recurrent stroke. It reduces the risk of stroke due to the formation of blood clots. There are several therapeutic options that could be used to prevent blood clot, including low dose of aspirin, clopidogrel, and combination of low dose aspirin and modified release dipyridamole. Long-term antiplatelet therapy is highly recommended to all stroke survivors (Rothwell et al., 2016; Sandercock et al., 2014). Aspirin is generally given at 300 mg as a STAT dose followed by 100–150 mg daily. A loading dose of 300 mg followed by 75 mg daily of clopidogrel would be considered as well if dual antiplatelet regimen is to be used. Both aspirin and clopidogrel proved to reduce recurrent ischemic stroke events (Rothwell et al., 2016; Sandercock et al., 2014).

Anticoagulant is an agent of choice for stroke survivors after cardioembolic stroke event secondary to atrial fibrillation. Warfarin has been widely used as an anticoagulant, especially for those who suffered from valvular atrial fibrillation or renal impairment (Tawfik et al., 2016). The introduction of novel direct oral anticoagulants (NoACs), such as dabigatran, apixaban, and rivaroxaban, which do not require routine monitoring of INR, is preferred over warfarin in nonvalvular atrial fibrillation patients with prior stroke attack (Ruff et al., 2014). The doses of antiplatelet agents and anticoagulants used in preventing TIA and ischemic stroke are summarized in **Table 3**.

Cholesterol lowering agents

Regardless of patients' baseline cholesterol level, a cholesterol-lowering agent should be prescribed for secondary prevention of stroke or cardiovascular events. Statins, especially high intensity therapy with atorvastatin 80 mg or rosuvastatin 40 mg, should be considered along with lifestyle changes and dietary modifications (Amarenco et al., 2008; Manktelow and Potter, 2009). It should be considered as first-line therapy in women and men ≤ 75 years old who have atherosclerotic cardiovascular disease (Powers et al., 2018).

Nonpharmacological Approach

Lifestyle modification is a crucial management to prevent recurrent stroke. Behavioral changing strategies focusing on daily lifestyle activities should be conveyed to public especially poststroke patients. However, according to the National Stroke Audit of Acute Services, only about half of those stroke survivors were counseled about the lifestyle modification approach to minimize the risk of recurrent stroke (National Stroke Foundation, 2015). Thus, all poststroke patients should be assessed and counseled on the risk factors for recurrent stroke and approaches to modify the risk factors (Powers et al., 2018).

Smoking cessation

Smoking has been identified as one of the major risk factors of stroke (Aldoori and Rahman, 1998). Stroke survivors who smoke are highly advised to stop smoking. Health-care professional should support and assist those tobacco dependent stroke survivors to stop smoking through smoking cessation programs.

Diet

Patient should be advised to consume at least five servings of fruit and vegetables daily because diet high in fruit and vegetable reduces the risk of stroke (Dauchet et al., 2005; He et al., 2006). BP reduction in patient with cardiovascular diseases through sodium restriction has proved to be effective in preventing stroke attack (He et al., n.d.). Excessive alcohol intake increases the risk of stroke, but light alcohol consumption with one to two standard drinks is protective against stroke (Reynolds et al., 2003; Ronksley et al., n.d.). Limiting the intake of alcohol, restricting the consumption of food, which is high in saturated fat and high sugar content, and maintaining healthy body weight may help to prevent stroke (Government National Health and Medical Research Council Department of Health and Aging, 2013).

Physical activity

Overweight and obesity are modifiable risk factors of ischemic stroke (Strazzullo et al., 2010). Healthy diet pattern and exercise are both effective ways to maintain body weight. To prevent stroke and other cardiovascular diseases, patients are advised to be physically active (Warburton et al., 2006). Adults in the age range of 18–64 years old should do at least 150 min moderate intensity or 75 min of vigorous intensity exercise weekly. For those aged 65 years old and above, 30 min daily of moderate intensity exercise is recommended (Government Department of Health Ageing, 2005).

Medication adherence

Medication adherence issue is generally high in elderly patients with the prevalence up to 43% (McKenzie et al., 2015). Nonadherence to prescribed medication is a major barrier to effective secondary prevention of stroke. Lacking of information, burden of the treatment, concerns about medication side effects, beliefs toward medication, difficulties in taking medication, and inability to self-care are some of the factors contributing to nonadherence (Kronish et al., n.d.).

Monitoring and Complications Associated With Stroke

Monitoring of Alteplase Administration

The recommended treatment regimen of alteplase is 0.9 mg/kg infused over 60 min with 10% of the total dose given as a bolus injection over 1 min. During and after the administration of IV alteplase, measurement of BP and neurological assessment should be performed every 15 min for 2 h, followed by every 30 min for 6 h then every hour until 24 h after the treatment initiation. If the patient develops severe headache, acute hypertension, nausea and vomiting, or showed worsening neurological examination stop the IV infusion. BP monitoring should be more frequent if patient's SBP is >180 mmHg or DBP is >105 mmHg. Starting antihypertensive treatment should be considered to maintain desired BP. A follow-up CT or MRI scan at 24 h after the infusion is performed before starting antiplatelet or anticoagulant therapy (Powers et al., 2018). If symptomatic intracranial bleeding (sICH) develops within 24 h after alteplase therapy, infuse 10U cryoprecipitate over 10–30 min and administer additional dose to achieve a fibrinogen level of ≥150 mg/dL (Powers et al., 2018; Yaghi et al., 2017). Platelet transfusion is considered only in patients with thrombocytopenia with platelet count <100 000/μL (Yaghi et al., 2017).

Glycemic Control

Blood glucose level in poststroke patients fluctuates in the first 72 h in diabetic and nondiabetic patients (Allport et al., 2006). Glucose intolerance is commonly noted in poststroke patients (Allport et al., 2006; Vancheri et al., 2005). Although there have been huge variation from 8% to 83% incidence rate, the development of hyperglycemia after stroke attack is not uncommon (Vermeer et al., 2006) and is linked to higher recurrent stroke (Vermeer et al., 2006). Regardless of the patient's diabetic status, all stroke patients should be initiated with appropriate antihyperglycemic therapy if the blood glucose level is greater than 10 mmol/L followed by close blood glycemia monitoring at the first 72 h after hospital admission (Middleton et al., 2011). Monitoring blood glucose level and treating the blood glycemic level to the target are associated with better outcomes at 90 days (Middleton et al., 2011). However, tight range of glycemic control at 4–7.5 mmol/L is not recommended as it does not improve mortality or functional outcomes but increases the risk of hypoglycemia in patient treated with intravenous insulin (Bellolio et al., 2014; Ntaios et al., 2014).

Body Temperature

Poorer outcome is associated with patients who develop pyrexia (Greer et al., 2008) with body temperature greater than 37.5°C and up to 50% of poststroke patient develop pyrexia (Castillo et al., 1998). Thus, monitoring patients' body temperature every 6 hourly for 72 h is recommended (Middleton et al., 2011).

Complications

There are various complications that may arise due to stroke. Besides weakness of the limbs and losing strength of the affected muscle, seizure may occur in up to 20% of poststroke patients. In addition, pneumonia, pulmonary edema, arrhythmias, and deep vein thrombosis may be seen in stroke patients (Koda-Kimble et al., 2013). Stroke-associated psychological disorders such as depression may affect up to 30% of the patients (Abubakar and Isezuo, 2012; Hackett and Anderson, 2005).

Role of Pharmacist in Health-Care Team: Stroke Management

Acute ischemic stroke is a severe neurological event that needs timely treatment. Patients who survive from stroke may experience complications and the risk of recurrence stroke is higher than patients who did not experience stroke. Stroke patients may interact with different health-care providers, including physicians, nurses, pharmacists, and physiotherapists, throughout their course of disease management and rehabilitation process.

Pharmacist is a member of the multidisciplinary health-care team in providing pharmaceutical care to stroke patients. Timely administration of thrombolytic agents within 3 h after the onset of ischemic stroke with a door-to-needle time of 60 min is associated with better clinical outcomes (Powers et al., 2018). Involvement of pharmacist in the emergency department in reducing the door-to-needle time is promising. A study was conducted to evaluate the door-to-needle time in stroke patients with the presence of pharmacist and without the presence of pharmacist. In the presence of pharmacist, the door-to-needle time was reduced from 73 min to 43 min, and the goal of door-to-needle time of ≤ 60 min was achieved in 71% of patients (Rech et al., 2017).

Administration of thrombolytic agents involves careful dose calculation based on patient's body weight and proper drug reconstitution process to prevent unwanted side effects such as hemorrhage owing to overdose. Brandon et al conducted a study to evaluate the involvement of pharmacists in calculating the dose of thrombolytic agent to be administered to stroke patients and the expanded role of pharmacists in mixing thrombolytic agent at bedside together with nurses in the hospital emergency department. The study reported reduction of decision-to-needle thrombolytic administration time in the presence of pharmacists. Besides, up to 78% of the cases achieve zero minute decision-to-needle time with the involvement of pharmacists in managing stroke patients (Kevin Brandon et al., 2018).

Medication treatment in stroke patients is complicated and may cause wide range of drug-related problems (DRPs), which eventually result in morbidity, mortality, prolonged hospital stay, and incur additional treatment cost. Identifying the DRPs is one of the primary roles of in-patient pharmacist or clinical pharmacist to prevent unwanted side effects and promote optimal therapeutic outcomes. According to a study conducted by Hohmann et al. (2012), DRPs happened in almost 70% of stroke patients admitted to hospital with at least two medications given in the ward and at discharged. Those DRPs identified by pharmacist in ischemic stroke patients are associated with the issue of under treatment, and most of the missing drugs were stroke-related secondary prevention therapies (Hohmann et al., 2012). Besides, Lindblad et al. (McAlister et al., 2014) reported an average of 2.8 pharmaceutical interventions made per patient encountered in stroke prevention clinic and up to 64% of the interventions made by the pharmacists were accepted by the physician. These findings support the role of pharmacist in the stroke management team within hospital setting.

Antithrombotic agents together with antihypertensive agents and lipid-lowering agents have been the mainstay in preventing recurrent stroke in poststroke survivors. Uncontrolled high blood pressure and consistently high level of low density lipoprotein are among the modifiable risk factors leading to stroke. Better achievements of SBP and low-density lipoprotein to the targeted level have been reported in stroke patients who receive monthly follow-up by pharmacist (Chiu et al., 2008; McAlister et al., 2014; Nguyen et al., 2011). On top of that, studies showed pharmacists' interventions resulted in a significant increase in the prescribing of antihypertensive and antithrombotic agents to ischemic stroke patients (Khalil et al., 2015). These findings accentuate the significant role of pharmacist in enhancing the adherence of stroke treatment guidelines by medical doctors in order to prevent recurrence of stroke in stroke survivors (Khalil et al., 2015).

Although warfarin is not commonly used in the majority of ischemic stroke patients, there is beneficial effect of warfarin in preventing recurrent stroke in patients suffering from atrial fibrillation (Shah et al., 2014). The role of pharmacist in deciding the rational use of warfarin and providing counseling service on the proper use of warfarin to patients reduces the bleeding risk associated with warfarin use. A study reported the pharmacist-led anticoagulant review clinic reduces the inappropriate use of anticoagulant and the risk of atrial fibrillation-related stroke incidents (Dowling et al., 2016). In terms of cost-effectiveness in running this pharmacist-led anticoagulant review clinic compares to the cost incurred in atrial fibrillation-related stroke associated health-care cost, pharmacist-led anticoagulant review clinic is considered cost-effective if it is able to prevent only two incidents of stroke per year (Dowling et al., 2016).

Appropriate medication counseling increases drug adherence. Adherence to prescribed treatment regimen reduces recurrence of stroke and minimizes unwanted side effects of drugs. Stroke patients are always discharged with multiple medications including antithrombotic agents, antihypertensive agents, and lipid-lowering agents. Most of the time, the discharged medications are different from the medications used before their hospital admission. Complex and large amounts of discharged medications make patients confused with the treatment. The issue is further worsened when patients consult multiple health-care professionals for different health conditions. The lacking of proper and effective communication between health-care professionals may eventually lead to polypharmacy and over-prescribing. Effective communication between the hospital and primary care physician is important for the continuity care of stroke patients after discharge from hospital. Providing detailed information on medication changes by pharmacist to primary care physician showed significant improvement with regard to the adherence of post stroke-treatment regimen (Hohmann et al., 2013).

Proper and adequate stroke education and prevention strategies provided to the public especially the post stroke patients are needed. Pharmacists play a role in identifying patients at risk of first strokes attack or recurrent TIA or recurrent stroke. Proper education to high-risk patients on the signs and symptoms of TIA or stroke and the need for urgent evaluation and treatment are keys to early stroke detection and timely management. Identifying and overcoming barriers to timely diagnosis and treatment are associated with better clinical outcomes. Besides, ensuring appropriate primary and secondary stroke prevention strategies would minimize the impact of stroke-related complications. Study showed an increased in stroke patients' overall satisfaction with the present of pharmacist in providing stroke-related education in multidisciplinary health-care team (Rhoney, 2011; Sreenivasan, 2012). Involvement of pharmacist in the education of stroke patient on risk factors and stroke prevention further reduced the hospital readmission rate (Bruner, 2012; Hooker and Evans, 2018).

Care for post stroke patients does not end after hospital discharge and thus the role of pharmacists in stroke management is not just limiting at hospital setting. Community pharmacists play an equally important role as hospital pharmacists in promoting

optimal pharmaceutical care in post stroke patients. Easy access to community pharmacy setting provides a platform for the public and the post stroke patients as well as their care givers to seek medications and medical advices. Participation of community pharmacists in providing medication reviews and education for post stroke patients who were discharged home showed positive impact on patient health-related quality of life (Hohmann et al., 2009). A study to measure stroke medication adherence was conducted through examining the number of days that the patients were late for prescription refills. With the intervention of community pharmacist, there was significant reduced in the average number of days patients were late for stroke medication prescription pickup (Fincham and Wallace, 2000).

Using mobile medical applications in managing patients' clinical conditions has been widely accepted in recent years. Atrial fibrillation increases risk of stroke. Early identification of undetectable atrial fibrillation in the community and subsequently initiating appropriate antithrombotic treatment could reduce stroke burden. A study was conducted to investigate the feasibility of community screening for unknown atrial fibrillation through an iPhone electrocardiogram (iECG) in pharmacies and to determine the cost-effectiveness of this approach. The study found that screening with iPhone electrocardiogram (iECG) was both feasible and cost-effective. The high and largely preventable risk of stroke of those with newly identified atrial fibrillation reported in this study highlights the potential benefits of atrial fibrillation screening in community pharmacy setting (Lowres et al., 2014). Available evidence proves the significant role of pharmacist in both the hospital setting and community pharmacy setting.

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Management of Cardiovascular Disorders and the Pharmacist's Role: Venous Thromboembolism

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Learning Objectives

- Identify modifiable and nonmodifiable risk factors of venous thromboembolism (VTE).
- Describe the appropriate pharmacological management of VTE.
- Identify the applicability of the different nonpharmacological strategies in VTE management.
- Design a personalized guideline-driven anticoagulant therapeutic and monitoring plan for patients with VTE.
- Describe the roles of pharmacist in VTE management.

Take Home Messages

1. Dabigatran is as effective as warfarin at reducing VTE recurrence and is associated with less bleeding risk in acute settings.
2. Rivaroxaban is noninferior to warfarin in preventing VTE recurrence and is associated with similar bleeding rates in acute pulmonary embolism (PE).
3. Apixaban is noninferior to low-molecular-weight heparins (LMWHs) and vitamin K antagonist-based therapy for VTE recurrence and VTE mortality, but showed greater reduction in bleeding rates.

4. In patients with VTE who have completed 6–12 months of anticoagulation, rivaroxaban 10 mg/day reduces the risk of recurrent VTE without significantly increasing the risk of bleeding compared to aspirin.
5. Pharmacists are well-positioned to educate and guide providers and patients on the benefits and risks of various anticoagulants. Patients also need to be counselled on adherence, drug interactions, and what to do when doses are missed.

Introduction

Thrombosis refers to abnormal, life-threatening blood clots that form in the artery or vein. Thrombosis can affect any venous or arterial circulation. Venous thromboembolism (VTE) is a fairly common condition in which blood clots form most often in the deep veins of the leg (known as deep vein thrombosis, DVT) and can travel through blood circulation and lodge in the lungs (known as pulmonary embolism, PE) (Di Nisio et al., 2016). VTE is a pathological condition that is associated with significant morbidity and mortality. The spectrum of disease ranges from a clinically unsuspected silent disease to a massive embolism causing long-term sequelae. It is a leading cause of hospital-associated premature death and disability worldwide (Jha et al., 2013). VTE burden consumes an estimated cost of more than USD 1.5 billion per year in the United States (US) and more than €3 billion per year in Europe (Dobesh, 2009). It claims more lives than acquired immune deficiency syndrome (AIDS), breast and prostate cancer, and motor vehicle crashes combined in the United States and Europe (Cohen et al., 2007). However, it is considered a preventable cause of morbidity and mortality (Jha et al., 2013). Around 60% of VTE cases occur during or after hospitalization (Jha et al., 2013). Patients are at high risk for VTE events after surgery due to the associated inflammatory state, endothelial vascular injury, or venous stasis. Other predisposing factors have been identified, each conferring differing degrees of VTE risk (**Table 1**).

Anticoagulants are the mainstay of VTE management and are given in three phases: acute, maintenance, and extended treatment phases. Pharmacists, particularly clinical pharmacists, are well-positioned to play a significant role in VTE risk assessment, management, and provision of guideline-driven patient care (Bauer et al., 2008; Davis et al., 2013; Gharaibeh et al., 2017).

Epidemiology

VTE is a significant vascular disease. The precise number of people affected by DVT/PE is unknown due to lack of data, although as many as 900,000 symptomatic and asymptomatic cases of VTE (1 to 2 per 1000) occur annually in the United States (Beckman et al., 2010). Worldwide, the annual incidence rates range from 0.75 to 2.69 per 1000 individuals (ISTH Steering Committee for World Thrombosis Day, 2014). The incidence increases to between 2 and 7 per 1000 among individuals aged ≥70 years. Although the incidence is lower in individuals of Chinese and Korean ethnicity, their disease burden is not low because of ageing population (ISTH Steering Committee for World Thrombosis Day, 2014). Furthermore, one-third of VTE patients will have a recurrence within 10 years (Heit, 2015).

Independent predictors of recurrent VTE include old age, high body mass index (BMI), male gender, active neoplastic condition, and leg paresis-related conditions (Heit, 2015). Furthermore, pathologists believe that up to 63% of DVT cases are missed clinically (Beckman et al., 2010). The survival rates after VTE are not promising. The survival of PE incidence in the absence of DVT history is significantly lower than the one of PE incidence after DVT by 20%. The risk of early death is 18-fold higher in patients having PE than in those with DVT alone (Heit, 2015). Without adequate treatment, VTE can cause serious complications such as venous ulcers, chronic thromboembolic pulmonary hypertension (CTEPH), and postthrombotic syndrome (PTS) (Winter et al., 2017). PTS occurs in up to 20%–50% of adults with DVT. It includes long-term pain, swelling, skin problems, and in severe cases, ulcers on the calf (Winter et al., 2017). CTEPH occurs frequently after pulmonary embolic events, but is less common after DVT (Martinez et al., 2018). Also, VTE represents a significant risk of substantial mortality, with reported mortality rates of up to 40% in a period of 10-year postdiagnosis (Winter et al., 2017). Among elders with DVT, 21% will die within a year, as will 39% of those with PE (ISTH Steering Committee for World Thrombosis Day, 2014; Winter et al., 2017). Twenty-five percent of PE patients progresses to sudden death (Beckman et al., 2010).

Etiology and Risk Factors

Many transient and persistent risk factors have been identified in the past two decades. However, a third to half of VTE cases do not have an identified provoking risk factor. This segment of VTE cases is classified as unprovoked VTE (*i.e., VTE of unknown cause*). The risk factors are additive or multiplicative. The higher the number of risk factors, the higher the likelihood of thrombosis (Di Nisio et al., 2016; Piazza et al., 2009). These risk factors are of different strength [e.g., strong factors are of high odds (>10), e.g., hip or knee replacement surgeries, others are of moderate odds (~2–9) such as chemotherapy or heart failure disease, and others are of weak odds (<2) like obesity or hypertension] (Anderson Frederick and Spencer Frederick, 2003). Collectively, these factors actively increase the risk of VTE by inducing simultaneous stasis, hypercoagulability state, and endothelial damage that encourage clot formation. **Table 1** lists the risk factors for VTE (Di Nisio et al., 2016; Piazza et al., 2009). Many conditions increase the risk of thromboembolic events such as history of hypercoagulability disorders (e.g., protein C or S deficiency, presence of antiphospholipid antibodies, antithrombin deficiency, or activated protein C resistance), arterial or venous thrombosis within the previous month,

Table 1 List of risk factors for venous thromboembolism

Risk factor	*Strength*	*Modifiability*
1. *Injury to a vein:*		
a. Fractures	Strong	–
b. Severe muscle injury	Strong	–
c. Major surgery (particularly involving the abdomen, pelvis, hip, or legs)	Strong	–
d. Varicose veins	Moderate	Modifiable
2. *Slow blood flow:*		
a. Confinement to bed	Weak	–
b. Limited movement (e.g., a cast on a leg to help heal an injured bone)	Weak	Modifiable
c. Sitting for a long time, especially with crossed legs	Weak	Modifiable
d. Paralysis/spinal cord injury	Strong	–
e. Acute heart failure or atrial fibrillation hospitalization	Strong	–
3. *Increased estrogen:*		
a. Oral contraceptive pills	Moderate	Modifiable
b. Hormone replacement therapy (HRT)	Moderate	Modifiable
c. Pregnancy, for up to 6 weeks after giving birth	Weak	Modifiable
4. *Certain chronic medical illnesses:*		
a. Heart disease	Strong	Modifiable
b. Lung disease	Strong	Modifiable
c. Cancer and its treatment	Moderate	Modifiable
d. Inflammatory bowel disease (Crohn's disease or ulcerative colitis)	Moderate	–
e. Autoimmune disease	Moderate	–
5. *Other concomitant risk factors:*		
a. Previous DVT or PE	Strong	–
b. Family history of DVT or PE	Moderate	–
c. Age (risk increases as age increases)	Weak	–
d. Obesity	Weak	Modifiable
e. A catheter located in a central vein	Moderate	Modifiable
f. Inherited clotting disorders, e.g., thrombophilia	Moderate	–
g. Air embolism	Weak	Modifiable

DVT, deep venous thrombosis; *PE*, pulmonary embolism.

Source: Anderson Frederick, A., Spencer Frederick, A., 2003. Risk factors for venous thromboembolism. Circulation, 107, I-9-I-16; Piazza, G., Fanikos, J., Zayaruzny, M., Goldhaber, S.Z., 2009. Venous thromboembolic events in hospitalised medical patients. Thromb Haemost., 102, 505–510; Di Nisio, M., Van Es, N., Buller, H.R., 2016. Deep vein thrombosis and pulmonary embolism. Lancet, 388, 3060–3073

thromboembolism associated with malignancy, mechanical mitral valve in conjunction with atrial fibrillation, previous stroke, poor ventricular function, or coexisting mechanical aortic valve.

Hospitalized medical and surgical patients are significantly at increased risk of VTE. There are several scores to estimate the burden of the risk factors. These scores aim to risk stratify patients who have a potential risk for VTE occurrence, not to diagnose VTE disease. For example, Padua score (**Table 2**) is an explicit tool to stratify the risk in medically hospitalized patients (Barbar et al., 2010). On the other hand, Caprini score (**Table 3**) stratifies VTE risk in surgical patients (Caprini et al., 1991). These at-risk patients should be identified as soon as possible after admission to the hospital in order to provide appropriate thromboprophylaxis. Thromboprophylaxis is the most important patient safety strategy in patients admitted to the hospital. If VTE risk outweighs the bleeding risk, an appropriate pharmacological VTE prophylaxis should be considered (**Table 4**) (Piazza et al., 2009).

Diagnosis

Deep Venous Thrombosis Diagnosis:

1) *Wells' score*: The score assesses the clinical pretest probability (risk) of DVT. In those with suspected DVT, a clinical assessment of probability can be useful to determine which tests to perform. The Wells' score should only be applied to those patients who have been deemed at risk for DVT. If there is no concern for DVT, then there is no need for risk stratification. Wells' scores can be

Table 2 Risk factors for venous thromboembolism in hospitalized medical patients

Risk factor	*Points*	*Patient score*
Active cancer	3	
Previous VTE involving deep veins	3	
Reduced mobility	3	
Thrombophilia	3	
Trauma or surgery within 30 days	2	
Age ≥ 70 years	1	
Heart and/or respiratory failure	1	
Acute myocardial infarction or ischemic stroke	1	
Acute infection or rheumatologic disorder	1	
Obesity (BMI ≥ 30 kg/m^2)	1	
Hormone replacement therapy	1	
Total Patient's Padua score =	**20**	
• Padua Score < 4 points →		
◦ *Pharmacologic (anticoagulant) prophylaxis is **not** indicated.*		
◦ *Consider using mechanical (nonpharmacological) prophylaxis.*		
• Padua Score ≥ 4 points →		
◦ *Pharmacologic prophylaxis is indicated.*		
◦ *If high risk of bleeding, use mechanical prophylaxis.*		

BMI, Body mass index; *VTE*, venous thromboembolism.

Source: Padua Score adapted from Barbar, S., Noventa, F., Rossetto, V., Ferrari, A., Brandolin, B., Perlati, M., De Bon, E., Tormene, D., Pagnan, A., Prandoni, P. 2010. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J. Thromb. Haemost. 8, 2450-2457 (Barbar et al., 2010)

Table 3 Risk factors for hospitalized surgical populations

Caprini score calculation

1 *point each for:*	2 *point each for:*	3 *points each for:*	5 *points each for:*
• Age 41–60 years	• Age 61–74 years	• Age ≥ 75 years	• Stroke (<30 days)
• Minor surgery	• Arthroscopic procedure	• History of VTE	• Elective arthroplasty
• BMI > 25 kg/m^2	• Major open surgery (>45 min)	• Family history of VTE	• Hip, pelvis, or leg fracture, or spinal cord injury (<30 days)
• Swollen legs	• Laparoscopic procedure (>45 min)	• Thrombophilia	
• Varicose veins	• Malignancy		
• Pregnant or postpartum	• Confined to bed >72 h,		
• History of unexplained or recurrent abortion	• Plaster cast		
• Hormone replacement therapy (HRT)	• Central venous access		
• Sepsis (<30 days)			
• Lung disease including pneumonia (<30 days)			
• Abnormal pulmonary function			
• Acute myocardial infarction (AMI)			
• Congestive heart failure (CHD)			
• History of inflammatory bowel disease			
• Medical patient at bed rest			

Patient total risk factor score	Caprini Score	Estimated risk without prophylaxis
	0	Very Low
	1–2	Low
	3–4	Moderate
	≥5	High

BMI, Body mass index; *GI*, gastrointestinal; *VTE*, venous thromboembolism.

Source: Caprini Score adapted from Pannucci, C.J., Bailey, S.H., Dreszer, G., Fisher Wachtman, C., Zumsteg, J.W., Jaber, R. M., Hamill, J.B., Hume, K.M., Rubin, J.P., Neligan, P.C., Kalliainen, L.K., Hoxworth, R. E., Pusic, A.L., Wilkins, E.G., 2011. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. J. Am. Coll. Surg. 212, 105–112 (Pannucci et al., 2011); Bahl, V., Hu, H.M., Henke, P.K., Wakefield, T.W., Campbell, D.A., JR., Caprini, J.A., 2010. A validation study of a retrospective venous thromboembolism risk scoring method. Ann. Surg. 251, 344–350 (Bahl et al., 2010)

Table 4 Pharmacological profile of warfarin and new oral anticoagulants

	Warfarin	*Dabigatran*	*Rivaroxaban*	*Apixaban*	*Edoxaban*
Mechanism of action	Vitamin K antagonist	Direct thrombin (factor IIa) inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Adult treatment dosing regimen	Individualize dosing to target INR 2–3	CrCl >30 mL/min: LMWH or UFH x 5–10 days, then dabigatran 150 mg BID CrCl ≤30 mL/min or on dialysis: Dosing recommendation cannot be provided Extended treatment to prevent VTE recurrence with CrCl >30 mL/min: 150 mg BID	CrCl ≥ 30 mL/min: 15 mg BID x 21 days with food, then 20 mg daily with food. CrCl <30 mL/min: Avoid Extended treatment to prevent VTE recurrence: 20 mg daily	10 mg BID x 7 days, then 5 mg BID No dose adjustment recommended for renal function Extended treatment to prevent VTE recurrence: 2.5 mg BID	CrCl >50 mL/min: LMWH or UFH x 5–10 days, then edoxaban 60 mg daily CrCl 15–50 mL/min: 30 mg daily CrCl <15 mL/min: use is not recommended Patients ≤60 kg: 30 mg daily
Adult prophylactic dosing regimen	2–5 mg for 2 days, or 10 mg for 2 days in healthy individuals	CrCl >30 mL/min: 110 mg OD 1–4 h after surgery or hemostasis on first day, then 110 mg bid For 28–35 days	CrCl >30 mL/min: 10 mg OD 6–10 h after surgery or hemostasis For 35 days	2.5 mg OD 12–24 h after surgery or hemostasis For 12–35 days	Not indicated
With or without food	With or without	With or without	With food	With or without	With or without
Missed dose	Take it immediately	Take it immediately	[a]*Footnote*	Take it immediately	Take it immediately
Pregnancy FDA category	X (Contraindicated in pregnancy)	C (risk not ruled out)	C (risk not ruled out)	B (No risk in noncontrolled studies)	C (risk not ruled out)
Factor affecting the agent selection in acute VTE	• ODA therapy preferred • Renal disease (CrCl < 30 ml/min) • Dyspepsia • History of GI bleeding • Poor adherence • Reversal agent needed • CAD	• Reversal agent needed	• Parenteral therapy to be avoided • ODA therapy preferred • CAD • Reversal agent needed	• Parenteral therapy to be avoided • CAD • Dyspepsia • History of GI bleeding	• ODA therapy preferred
Pharmacokinetics					
Oral bioavailability	79%–100%	3%–7%	80%–100% (10 mg) 66% (20 mg)	50%	~60%
T_{max} (h)	4	1.25–3	2–4	3–4	1–2
$t_{1/2}$ (h)	40	12–17; Up to 27 in severe renal impairment	5–9; 11–13 in elderly patients	12	10–14
Food effect	Yes (narrow therapeutic index drug)	Delayed absorption	Delayed absorption	No	No

Metabolism	CYP2C9 (primary), CYP3A4, 1A2, 2C19 (minor pathways)	Conjugation (no CYP involvement)	Oxidation (via CYP3A4 and CYP2J2) and hydrolysis	Oxidation (via CYP3A4) and conjugation	Minimal by oxidation, conjugation and hydrolysis
Elimination	Renal, primarily as metabolites	Renal (80% unchanged drug)	Renal (36% unchanged drug)	Renal (27% unchanged drug)	Renal (35% unchanged drug)
Antidote options (reversal)	1. Vitamin K 2. Fresh Frozen Plasma 3. PCC 4. Recombinant activated factor VIIa (rFVIIa)	1. Idarucizumab 2. PCC 3. Recombinant activated factor VIIa (rFVIIa) 4. Hemodialysis	1. Andexxa (factor Xa) 2. PCC 3. FEIBA 4. Recombinant activated factor VIIa (rFVIIa)	1. Andexxa (factor Xa) 2. PCC 3. FEIBA 4. Recombinant activated factor VIIa (rFVIIa)	1. PCC 2. FEIBA 3. Recombinant activated factor VIIa (rFVIIa)
Coagulation monitoring	Target INR= 2 – 3	No	No	No	No
Dosage Forms, Administration, Storage					
Strengths (mg)	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10	75, 110, 150	10, 15, 20	2.5, 5	30, 60
Dosage form	Tablet	Capsule	Tablet	Tablet	Tablet
Splitting, crushing, or chewing	May split tablet in half May crush tablet and mix with water or applesauce immediately before use	No; will increase exposure to medication	May crush tablet and mix with water or applesauce immediately before use Do not administer via feeding tubes placed distal to the stomach due to decreased absorption	May be crushed and suspended in 60 mL D_5W and immediately delivered through nasogastric tube	No recommendations provided
Drug interactions					
Shifting from VKA to a NOAC agent		1) Stop VKA 2) Initiate dabigatran once INR $\leq$2.0	1) Stop VKA 2) Initiate rivaroxaban once INR $\leq$2.5	1) Stop VKA 2) Initiate apixaban once INR $\leq$2.0	1) Stop VKA 2) Initiate edoxaban once INR $\leq$2.5
Shifting from NOAC to VKA		CrCl $\geq$ 50 mL/min: **Start warfarin 3 days before discontinuing dabigatran** CrCl 31–50 mL/min: **Start warfarin 2 days before discontinuing dabigatran** CrCl 15–30 mL/min: **Start warfarin 1 day before discontinuing dabigatran** CrCl $<$ 15 mL/min: **No dosing recommendations are available**	• Discontinue the NOAC agent. • Begin both a parenteral anticoagulant and warfarin at the time the next dose of the NOAC would have been taken. • Discontinue the parenteral anticoagulant when the INR reaches an acceptable range.		[b]*Footnote*
Food interactions	Yes	No	No	No	No

(*Continued*)

Table 4 Pharmacological profile of warfarin and new oral anticoagulants (*cont.*)

	Warfarin	*Dabigatran*	*Rivaroxaban*	*Apixaban*	*Edoxaban*
Drug–drug interactions	For patients taking CYP2C9, CYP3A4, CYP1A2 inhibitors and inducers: consider avoiding concomitant use or adjusting warfarin dose with close INR monitoring For initiation or changes with medications that have high protein binding: consider increased INR monitoring	p-GP inhibitors: CrCl <50 mL/min: avoid concomitant use – p-GP inducers (e.g., rifampin): avoid concomitant use	Dual p-GP inhibitors and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, indinavir, conivaptan): avoid concomitant use – Dual p-GP inducers and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St.John's wort): avoid concomitant use	Dual p-GP inhibitors and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin): - for patients receiving doses of 5 or 10 mg BID, reduce dose by 50%; for patients taking 2.5 mg BID, avoid coadministration – Dual p-GP inducers and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort): avoid concomitant use	p-GP inhibitors (e.g., verapamil, quinidine, or short term-concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole): reduce dose to 30 mg daily – p-GP inducers: avoid concomitant use with rifampin
Discontinuation prior to elective or invasive surgery procedures	At least 5 days	24–48 h 3–5 days if CrCl <50	at least 24 h Black box Warning of epidural/ spinal hematomas	24–48 h	at least 24 h

BID, Twice daily; *CAD*, coronary artery disease; *CrCl*, creatinine clearance; *CYP*, cytochrome; *D_5W*, 5% dextrose; *FDA*, US Food and Drug Administration; *GI*, gastrointestinal; *INR*, international normalized ratio; *kg*, kilogram body weight; *LMWH*, low-molecular-weight heparin; *NOAC*, new oral anticoagulant; *OD*, once daily; *ODA*, once daily administration; *p-GP*, p-glycoprotein; *PCC*, prothrombin complex concentrates; *$t_{½}$*, half-life; *T_{max}*, time to maximum effect; *UFH*, unfractionated heparin; *VKA*, vitamin K antagonist; *VTE*, venous thromboembolism.

[a]Rivaroxaban missed dose: If a dose is missed during the 15 mg twice daily treatment phase (days 1–21), the patient should take the missed dose immediately and take the next dose on time (if the next dose is due two 15 mg tablets can be taken together). The patient should then continue with 15 mg twice daily. If a dose is missed during the once-daily treatment phase (day 22 and onward), the patient should take the missed dose immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

[b]Conversion of edoxaban to warfarin: (1) Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. The INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and warfarin continued. (2) Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued

Source: Hull, R.D., Gersh, M.H., 2015. The current landscape of treatment options for venous thromboembolism: a focus on novel oral anticoagulants. Curr. Med. Res. Opin., 31, 197–210 (Hull and Gersh, 2015); Jaffer, A., Bragg, L., 2003. Practical tips for warfarin dosing and monitoring. Cleve Clin. J. Med., 70, 361–371 (Jaffer and Bragg, 2003); Makaryus, J.N., Halperin, J.L., Lau, J.F., 2013. Oral anticoagulants in the management of venous thromboembolism. Nat. Rev. Cardiol., 10, 397 (Makaryus et al., 2013); Douketis, J.D., Spyropoulos, A.C., Spencer, F.A., Mayr, M., Jaffer, A.K., Eckman, M.H., Dunn, A.S., Kunz, R., 2012. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141, e326S–e350S (Douketis et al., 2012); Steuber, T., 2017. The role of direct oral anticoagulants in the management of venous thromboembolism. Am J Manag Care, 23, S383–S390 (Steuber, 2017) and summary of product characteristics (SPC) of each medication listed in the table.

categorized as high if >2, moderate if 1 or 2, and low if <1, with likelihoods of 53%, 17%, and 5%, respectively. Confirmation of diagnosis may require a further diagnostic study, particularly in patients with a high Wells' score (Wells et al., 1997).

2) *Physical examination*: The physical examination of the patient's signs and symptoms significantly improves the diagnostic accuracy of noninvasive tests and should be routinely performed. DVT is mainly asymptomatic, but if symptoms do occur, they can include: pain, swelling, and tenderness in one legs (usually the calf), a heavy ache in the affected area, warm skin in the area of the clot, or red skin, particularly at the back of the leg below the knee (Bates et al., 2012).
3) *D-Dimer test*: D-Dimer is a byproduct of fibrin degradation. This is a diagnostic (not screening) test. The normal range is lower than or equal to 500 ng/mL Fibrinogen Equivalent Units (FEU). D-Dimer is almost always elevated during acute VTE. It is of note that other conditions may increase the D-Dimer results such as disseminated intravascular coagulation (DIC), recent surgery, trauma, pregnancy, cancer, and age older than 65 years. A positive result requires further diagnostic verification. D-Dimer values ≤500 ng/mL FEU in conjunction with clinical pretest probability (<2) exclude VTE diagnosis (Bates et al., 2012).
4) *Doppler ultrasonography*: This is the most common diagnostic imaging method (test of choice) for DVT and preferred to venography. However, it is not the gold standard diagnostic method. The advantage of color flow Doppler ultrasonography is the ability to determine motion and the direction of blood flow. An absence of blood flow confirms the diagnosis of DVT. It indicates the presence of thrombus within a vein. However, it cannot reliably detect small blood clots in distal veins. This noninvasive test does not carry the adverse effects of venography (hypotension, cardiac arrhythmias, vessel wall irritation, and nephrotoxicity caused by the contrast medium). A positive Doppler ultrasound finding in combination with a moderate to high clinical pretest probability or a positive D-Dimer result can be used to confirm the diagnosis. Negative test result does not exclude DVT, particularly in calf veins. Doppler ultrasound successfully identifies 95% of DVT cases that occur in the large veins above the knee. The ability to diagnose a new DVT can be difficult in patients with a past history of DVT (Bates et al., 2012).
5) *Contrast venography*: Venography is the gold standard diagnostic method for DVT. It is used when the ultrasound does not provide a clear definitive diagnosis. It is an invasive test where a contrast medium is injected into a vein, and then an X-ray of the leg is taken. The medium makes the vein visible on the X-ray. The X-ray will show whether blood flow is slow in the vein. Thrombus is depicted as an intraluminal filling defect. This test is expensive and can cause anaphylaxis and nephrotoxicity. Thus, the use of iodinated contrast is not advised in patients with a history of contrast allergy or in patients with impaired renal function. Other than medications, the patient should be advised to not to eat or drink anything for several hours before the procedure (Bates et al., 2012).

Pulmonary Embolism Diagnosis:

1) *Wells' score*: A clinical pretest probability stratifies patients according to the likelihood of PE occurrence (Wells et al., 2001). Confirmation of diagnosis requires a further diagnostic study.
2) *Physical examination*: Physical examination of PE manifestations significantly improves the diagnostic accuracy of noninvasive tests. The patient may have acute onset of the following symptoms: chest pain, which may get worse upon deep breathing or coughing; coughing, coughing up blood, dizziness or even fainting, tachypnoea and tachycardia, irregular rhythm, and shortness of breath (Beckman et al., 2010).
3) *Laboratory tests*: Serum concentrations of D-Dimer are almost always elevated. A plasma D-Dimer level of <500 ng/mL FEU and a Wells' score lower than 4 essentially exclude PE. The patient may have an elevated erythrocyte sedimentation rate (ESR) and high white blood cell (WBC) count. The arterial blood gases (ABG) on room air demonstrate hypoxemia (partial arterial oxygen tension, PaO_2 <80 mmHg) and an elevated alveolar-arterial oxygen gradient. Acid–base status may demonstrate respiratory alkalosis (Bates et al., 2012; Konstantinides et al., 2014).
4) *Helical computed tomography (HCT)*: HCT is the most commonly used method to diagnose PE because it is minimally invasive and allows concurrent visualization of the parenchyma, pleura, and mediastinum of lungs. It is the preferred option for PE diagnosis unless contraindications exist. Contrast medium is typically used, which can make the test unsuitable for patients with impaired renal function. Positive scan results have good specificity and generally confirm the diagnosis of PE. Negative scan results may require further diagnostic studies if PE seems likely because of clinical pretest probability scoring and/or D-Dimer results. Both the sensitivity and specificity of the scan are improved with central clots compared with those that are more peripheral (Bates et al., 2012; Konstantinides et al., 2014).
5) *Ventilation/perfusion (V/Q) scanning*: V/Q scanning is the most common screening technique for PE diagnosis; it measures the distribution of blood flow and airflow in the lungs. The ventilation part of the test looks at the ability of air to reach all parts of the lungs, while the perfusion part evaluates how well blood circulates within the lungs. When there is a large mismatch between blood flow and airflow in one area of the lung, the probability is high that the patient has a PE. The test scans with positive findings have good sensitivity and help to confirm the diagnosis. Specificity can be impaired by chronic obstructive pulmonary disease (COPD), asthma, and heart failure. A scan with negative findings also has good specificity and generally rules out the diagnosis. V/Q scanning is often preferred in patients with renal insufficiency or with allergies to contrast media. It is preferred rather than pulmonary HCT to minimize radiation exposure unless patients have preexisting lung disease. For that latter group, an HCT scan is preferred (Bates et al., 2012; Konstantinides et al., 2014).
6) *Pulmonary angiography*: This is the gold standard diagnostic method for PE. It is a minimally invasive procedure, but requires the administration of intravenous contrast medium into the pulmonary artery. This test is expensive and can cause anaphylaxis and nephrotoxicity (Bates et al., 2012; Konstantinides et al., 2014).

7) *Pulmonary embolism severity index (PESI) or simplified PESI score*: PESI score determines PE severity to stratify mortality risk after the confirmation of PE diagnosis (Aujesky et al., 2005; Jimenez et al., 2010).

Venous Thromboembolism Management and Therapeutic Regimens

Goals of Therapy

There are four general goals of therapy for VTE: (1) improving patient's quality of life and exercise capabilities; (2) preventing DVT complications into PE or PTS; (3) preventing VTE recurrence; and (4) reducing further PE causing morbidity occurrence as pulmonary hypertension (Coleman and MacCallum, 2010).

Treatment Modalities

The mainstay of VTE management is the pharmacologic anticoagulation therapy since the introduction of unfractionated heparin (UFH) in 1930 (Ita, 2015). Many other anticoagulants such as vitamin K antagonist (VKA), low molecular weight heparins (LMWHs), and thrombolytic agents have been subsequently developed. These agents have been added to the treatment algorithms of VTE. All these medications aim to either dissolve or stop clotting (Ita, 2015). Immediate initiation of therapeutic anticoagulation is crucial for patients with suspected DVT or PE. Heparin-induced anticoagulation reduces the mortality rate from 30% to less than 10%. VTE treatment modalities include many other nonpharmacological strategies such as compression stocking and vena-vaca filters.

The therapeutic regimen of a parenteral anticoagulant (UFH, LMWH, or fondaparinux) plus a VKA (warfarin) has been the most frequently prescribed regimen for VTE management before the introduction of the new oral anticoagulants (NOACs), (Akl et al., 2014). Recently, NOACs such as dabigatran, rivaroxaban, apixaban, or edoxaban are recommended over VKA (e.g., warfarin) therapy in several clinical settings. In long-term anticoagulant therapy settings, VKA therapy is recommended over LMWH or UFH for VTE in the absence of concomitant cancer disease. However, LMWH is still suggested over VKA or NOACs for VTE and concomitant cancer (Thein et al., 2016). The updated CHEST guidelines in 2016 recommended against an inferior vena cava filter (IVCF) for VTE treated with anticoagulants (Kearon et al., 2016). Also, routine use of compression stockings is not recommended for the prevention of PTS. Close monitoring is recommended over pharmacological anticoagulation for patients having a low risk of recurrent VTE (Kearon et al., 2016).

Treatment at home is an available option for patients with uncomplicated DVTs and low-risk PEs. Patient medical awareness and adequate home circumstances are required for home VTE treatment, which includes well-maintained living conditions, strong support from family or friends, telephone access, and ability to return to the hospital quickly if deterioration occurs (Kearon et al., 2016). However, patients with acute massive PE causing hemodynamic instability should be treated initially in the hospital with a thrombolytic agent (Sharifi et al., 2013). Tissue plasminogen activators (t-PA) are the first-choice thrombolytic agents (Meyer et al., 2014). For instance, alteplase is administered as 100 mg intravenous infusion over 2 h. Then, heparin could be introduced after the infusion ends (Kearon et al., 2016; Konstantinides et al., 2016).

Pharmacological Treatment Practicalities

Treatment Approach

The pharmacologic treatment of VTE includes three sequential phases: the acute phase (first 5–10 up to 21 days since the diagnosis has been made), a maintenance phase (first 3–6 months after the acute phase), and an extended phase (following the initial 3–6 months) (Mazzolai et al., 2017). The duration of therapy depends on the clinical situation of each patient. Long-term anticoagulation is necessary to prevent the high frequency of recurrent venous thrombosis or thromboembolic events. There are several drug regimens for this threefold treatment timescale.

Therapeutic Regimens

Apixaban and rivaroxaban are the only NOACs that are approved for use in the acute phase of VTE treatment as monotherapy without being preceded by a parenteral anticoagulant (Agnelli et al., 2013; Buller et al., 2012; Robertson et al., 2015). Apixaban should be prescribed as a 10-mg bid for the first 7 days, then tapered to a 5- or 2.5-mg bid beyond 6 months upon the patient's risk and clinical factors. Rivaroxaban regimen is a 15-mg bid for the first 21 days, then, 10 up to 20-mg beyond 6 months according to patient risk and clinical factors.

Other regimens must include an immediate-acting parenteral anticoagulant (e.g., LMWH) for the first 5–10 days as initial treatment followed by maintenance treatment with an oral anticoagulant agent. This oral agent can be one of the following agents: (i) a VKA, e.g., warfarin; (ii) dabigatran 150-mg bid; or (iii) edoxaban 60-mg OD (if creatinine clearance $>$ 50 mL/min. and in absence of any concomitant proton pump inhibitors). **Table 4** presents the different characteristics of the various oral anticoagulants.

Initial treatment with a parenteral anticoagulant (UFH, LMWH, or fondaparinux) should continue for at least 5 days to allow the shift to the oral route (Guyatt et al., 2012; Robertson et al., 2015). However, only bridging with the VKA should be initiated on the third day of parenteral treatment start. When intravenous UFH infusion is used, achieving a therapeutic aPTT (1.5–2.5 times baseline) in the first 24 h has been linked to decreased VTE recurrence rates (Smythe et al., 2016). Dosing of heparin is very crucial and its adjustment deemed one of the pharmacist's responsibilities before administration. The therapeutic regimen of (LMWH + VKA) is affordable to the low budget health-care settings (Middeldorp et al., 2014). **Table 5** discusses the prescribing tips of the various parenteral anticoagulants.

Black Box Warning

Epidural or spinal hematomas, which may result in long-term paralysis, may occur in patients who are anticoagulated with LMWHs or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture.

Management: Stop all heparins 8–12 h prior to spinal puncture + close monitoring of this type of patients for any neurological impairment.

The warfarin dose should be adjusted based on the patient's INR. An initial dose of 5–10 mg is preferred for otherwise healthy patients (Garcia et al., 2016). Lower doses may be needed in some populations that are sensitive to warfarin (e.g., malnourished, drug interactions, elderly). Higher initial treatment doses (e.g., 10 mg) have been associated with obtaining a more rapid therapeutic INR in DVT outpatients. The therapeutic target INR range is 2–3. Higher INR levels have been associated with higher bleeding events without a greater benefit of VTE risk reduction. Lower INR levels (1.5–2) are not as effective with no clear benefit on bleeding outcomes. Warfarin maintenance dose can be adjusted by determining the weekly dose and reducing the weekly maintenance dose by 10%–25% based on the degree of INR elevation. Maintenance dosing of warfarin is preferred to be tailored to the patient's genotype for better achievement of optimum therapeutic doses (Bazan et al., 2012). Personalization of warfarin dosing through genetic testing reduces the risk of combined adverse events in patients undergoing orthopedic surgery (Do et al., 2012). On the other hand, warfarin resistance is a problematic condition in which individuals have a high tolerance for the drug. The health-care team should assess the type and reasons for this resistance. Warfarin resistance does not appear to cause any health problems other than those associated with warfarin drug treatment (Azzam et al., 2016; Osinbowale et al., 2009).

Selection of the Oral Anticoagulants

There are many clinical and patient-related factors that influence the selection of the most suitable anticoagulant agent and regimen (**Table 4**). These factors include the patient's adherence, socioeconomic level, renal function, history of gastrointestinal (GI) bleeding, concomitant medications, and age (Kearon et al., 2016; Konstantinides et al., 2016). For instance, dabigatran and rivaroxaban are not preferred for VTE management in patients with a history of GI bleeding of unclear etiology. Also, the dosing regimen is another important factor to consider. Rivaroxaban has the advantage of once-daily administration. Furthermore, VKAs are preferred over NOACs in several different settings. NOACs are not used in patients with prosthetic heart valves because of a greater risk of valve thrombosis (Vandvik et al., 2012). In patients with renal insufficiency, warfarin may be the preferred oral agent. For patients with creatinine clearance (CrCl) <30 mL/min, there is insufficient evidence compared with warfarin, and the NOACs must be dose adjusted. Furthermore, NOACs are not recommended in patients with CrCl <15 mL/min (Steuber, 2017).

It is important to recognize some general contraindications to the anticoagulation therapies: (1) active major bleeding, (2) hemophilia or other hemorrhagic tendencies, (3) severe liver disease with elevated baseline prothrombin time, (4) severe thrombocytopenia (platelet count < 20,000/mm^3), (5) malignant hypertension, and (6) inability to meticulously supervise and monitor treatment.

Management of Recurrent Thromboembolic Events

In the absence of contraindications, aspirin 80–100 mg once daily is recommended to prevent recurrent VTE in patients with an unprovoked proximal DVT or PE following anticoagulation cessation (Becattini et al., 2012; Brighton et al., 2012). Furthermore, among patients undergoing total knee arthroplasty, low-dose aspirin as monotherapy was found to provide protection against postoperative VTE that is not inferior to that of other anticoagulants (Hood et al., 2018). Although some prescribers expressed some concerns about aspirin safety in certain vulnerable populations such as congestive heart failure and ischemic cardiomyopathies, robust evidence showed the benefit of aspirin continuation in such populations (Bermingham et al., 2014; Cleland et al., 2004; Homma et al., 2012; Massie et al., 2009).

Patients with recurrent VTE while on treatment with a non-LMWH anticoagulant should first be assessed. This segment of patients should be switched to LMWH therapy. Those who suffer from recurrent VTE in spite of administration of LMWH therapy should receive an increased dose of LMWH (Kearon et al., 2016). In cancer patients at risk of recurrent VTE, LMHW is strongly recommended over VKA (Akl et al., 2014). Recently, once-daily rivaroxaban was found to lower recurrence of VTE according to SELECT-D trial (Young et al., 2018).

Table 5 Prescribing tips of parenteral anticoagulants used for the management of acute venous thromboembolism

Unfractionated heparin (UFH)	*Low-molecular-weight heparins (LMWHs)*	*Factor Xa inhibitor: Fondaparinux*
IV administration: √ treatment of choice for those with end-stage renal failure. √ preferred route because of improved dosing precision. *Laboratory workout:* 1) baseline aPTT, PT, CBC with platelet count. 2) CBC with platelet count every day. 3) STAT aPTT 6 h post-IV bolus. 4) aPTT every day starting from the 3rd day of heparin administration. 5) Order aPTT 6 h after any dose change adjusting heparin infusion by the sliding scale until aPTT is within the therapeutic range (46–70 s). 6) When 2 consecutive aPTT are within therapeutic range, order aPTT and readjust heparin drip as needed every 24 h. Initial bolus and the initial rate of the continuous infusion can be either weight adjusted (80 units/kg IV bolus, followed by 18 units/kg/h infusion) or a fixed dose (bolus 5000 units, followed by 1000 units/h). Adjust subsequent doses to attain a goal aPTT based on the institution-specific therapeutic range. *Subcutaneous administration:* - 17,500 units (250 units/kg) given every 12 h (an initial 5000-unit IV bolus dose is recommended to attain rapid anticoagulation). - Adjust subsequent doses to attain a goal aPTT based on the institution-specific therapeutic range. *Heparin sodium preparation:* * Usual diluent: dextrose 5% (D_5W) or 0.9% normal saline solution (NSS) * Standard dilution: 250,000 units/ 250 or 500 mL titration * Loading Dose: IV push or add to 50 mL D_5W * Expiry date: 1 day * Administration: When heparin is added to an infusion solution for continuous IV administration, the container should be inverted at least six times to ensure adequate mixing and prevent pooling of the heparin in the solution. *Calcium heparin preparation:* Same preparation as the sodium salt, but not to be diluted with Ringer's solution as this may precipitate calcium.	√ Gold standard antithrombotic agent. √ Allows for outpatient treatment of uncomplicated DVT. √ Start 12 or more hours preoperatively or 12 h or more postoperatively √ preferred in cancer, liver disease, coagulopathies, pregnancy, or pregnancy risk. *Dalteparin:* 200 units/kg subcutaneously once daily or 100 units/kg subcutaneously twice daily. Not FDA approved for treatment of VTE in patients without cancer. Dosage form: single-dose syringes *Enoxaparin:* √ The only LMWH licensed for both VTE prophylaxis and treatment. 1.5 mg/kg subcutaneously once daily or 1 mg/kg subcutaneously twice daily; if CrCl < 30 mL/min: 1 mg/kg subcutaneously once daily Dosage form: prefilled syringes *Tinzaparin:* 175 units/kg subcutaneously once daily. √ Safer in pregnancy than other LMWHs. Dosage form: prefilled syringes	√ Licensed for VTE prophylaxis in surgical patients and the treatment of acute DVT For body weight < 50 kg (110 lb), use 5 mg subcutaneously once daily For body weight 50–100 kg (110–220 lb), use 7.5 mg subcutaneously once daily For body weight > 100 kg (220 lb), use 10 mg subcutaneously once daily
Contraindications Hypersensitivity to UFH History of HIT	*Contraindications* Hypersensitivity to LMWH, unfractionated heparin, pork products, methyl-paraben, or propyl-paraben History of HIT or suspected HIT	*Contraindications* Hypersensitivity to fondaparinux Severe renal insufficiency (CrCl < 30 mL/min) Body weight < 50 kg (110 lb) Bacterial endocarditis Thrombocytopenia with a positive in vitro test for antiplatelet antibodies in the presence of fondaparinux
Antidote options (reversal)		
Protamine sulfate is the full reversal agent of UFH and "partial" reversal agent for LMWHs. Protamine neutralizes around 60% of the antifactor Xa activity if LMWH was given in the previous 8 h, then 1 mg of protamine should be administered for every 100 units (or 1 mg) of the LMWH. If the LMWH dose is given in the previous 12 h, a 0.5-mg dose of protamine should be given for every 100 antifactor Xa units. Use of protamine sulfate is not recommended if the LMWH was administered more than 12 h earlier due to LMWH metabolism. Protamine administration induces risk of hypersensitivity reactions and anaphylaxis.		No specific antidote

aPTT, Activated partial thromboplastin time; *CBC*, complete blood count; *CrCl*, creatinine clearance; *FDA*, US Food and Drug Administration; *HIT*, heparin-induced thrombocytopenia; *IV*, intravenous; *kg*, kilogram body weight; *lb*, pound; *LMWH*, low-molecular-weight heparin; *PT*, prothrombin time; *UFH*, unfractionated heparin; *VTE*, venous thromboembolism. √, refer to an advantage.

Source: Fareed, J., Adiguzel, C., Thethi, I., 2011. Differentiation of parenteral anticoagulants in the prevention and treatment of venous thromboembolism. Thromb J., 9, 5–5 (Fareed et al., 2011); Hull, R.D., Gersh, M.H., 2015. The current landscape of treatment options for venous thromboembolism: a focus on novel oral anticoagulants. Curr. Med. Res. Opin., 31, 197–210; Douketis, J.D., Spyropoulos, A.C., Spencer, F.A., Mayr, M., Jaffer, A.K., Eckman, M.H., Dunn, A.S., Kunz, R., 2012. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141, e326S–e350S) and summary of product characteristics (SPC) of each medication listed in the table.

Gaps in Evidence

To date, there are still some gaps in evidence. First, little is known about the optimal length of treatment of patients having unprovoked VTE (Robertson et al., 2017). Herein, the physicians in collaboration with the clinical pharmacists are in a position to decide upon extended treatment based on benefit (i.e., prevention of VTE recurrence) and risk (i.e., bleeding) associated with treatment. Particularly, in the elderly population, there are several clinically important unmet needs such as the definition of the real risk of VTE recurrence after a first event. While it is possible that initial treatment is associated with a lower risk of recurrence, the bulk of information to date is drawn from observational studies that were published long time ago. Up-to-date studies are warranted to better address this issue. Furthermore, more information is needed on the use of low-dose NOACs for extended treatment in elderly patients. The data appear promising, but more research is warranted to evaluate their use over longer periods of time and to assess bleeding risks. Additional treatment options also need to be evaluated in order to effectively reduce the risk of bleeding while protecting against VTE recurrence (Palareti and Poli, 2018).

Second, there are no large-scale trials addressing the direct comparison between LMWH and NOAC agents in terms of efficacy and safety in patients with cancer and concomitant VTE (Carrier et al., 2018). Current trials are highly selective and controlled studies. Patients at high risk of bleeding or worsening renal functions are excluded for safety reasons. In addition, none of the studies was specific to cancer patients. Thus, their results should be interpreted with caution (Aronis Konstantinos and Hylek Elaine, 2018; Raskob et al., 2017). Also, there is a lack of data about NOACs use in patients at high risk of acute renal injury such as advanced heart failure patients (Steinberg et al., 2016). To date, the full safety profile of the NOAC agents is not very clear (Salazar et al., 2010; Steinberg et al., 2017).

Third, there is considerable uncertainty of warfarin initial daily dose (Garcia et al., 2016). Early achievement of the therapeutic INR (2–3) is highly recommended to minimize the duration of parenteral anticoagulant administration (Garcia et al., 2016). Although a 5-mg loading-dose tends to prevent excessive anticoagulation, a 10-mg loading-dose may achieve a therapeutic INR more quickly (Quiroz et al., 2006). Also, there is a lack of evidence to recommend genotype-guided initiation. Thus, adequately powered trials to detect effects on adverse events are warranted (Heneghan et al., 2010).

Moreover, the impact of patient adherence with the prescribed NOAC has not been rigorously assessed (Steinberg et al., 2018). The frequency of patients' nonadherence in VTE is considerable. A recent report showed that 50% of patients who were prescribed an anticoagulant were not adherent to their therapy. Also, the achievement of the recommended target dose of oral anticoagulants represents a challenge to routine clinical practice fear of medication's adverse drug reactions or medication initiation burden (Aronis Konstantinos and Hylek Elaine, 2018; Byrne and Weaver, 2013). This prescribing problem is clearly revealed in the landmark clinical trial ORBIT-II (Outcomes Registry For Better Informed Treatment Of Atrial Fibrillation II). Hence, 12.5% of patients have been prescribed a lower dose than the recommended (Steinberg et al., 2016, 2018).

Thrombolytic Therapy

If PE causes severe instability due to high pressure on the heart (massive PE) and leads to low blood pressure or shock-related symptoms (acute manifestations), recombinant tissue plasminogen activators (t-PA) are highly recommended for management. Streptokinase, tenecteplase, alteplase, and urokinase are thrombolytic agents that the Food and Drug Administration (FDA) has approved for use in PE (Guyatt et al., 2012). This therapeutic thrombolysis prevents hemodynamic decompensation, but increases the risks of major hemorrhage and stroke (Meyer et al., 2014; Sharifi et al., 2013). The outcome of this therapy is optimal when the patient arrives at the hospital within 3 h of the emboli occurrence.

Absolute and Relative Contraindications to Thrombolytic Agents (Konstantinides et al., 2014)

1. Absolute contraindications
    a. GI bleeding within the past 6 months
    b. Active or recent internal bleeding
    c. History of hemorrhagic stroke
    d. Intracranial or intraspinal disease
    e. Recent cranial surgery or head trauma
    f. Pregnancy
2. Relative contraindications
    a. Major surgery or trauma within the past 2 weeks
    b. Biopsy within 10 days
    c. Other invasive procedures
    d. Procedures in a location inaccessible to external compression
    e. Uncontrolled coagulation defects such as thrombocytopenia
    f. Nonhemorrhagic stroke

Nonpharmacological Strategies

Physical Activity and Ambulation

Regular physical activity and weight loss are essential prophylactic measures against VTE events. Frequent intensive exercise does not provide further prevention of VTE risk than a regular moderate one (Armstrong et al., 2015). It is important to encourage early ambulation as tolerated by the patient during the acute treatment phase. Patients on any anticoagulants should avoid aggressive activities that could cause trauma (Liu et al., 2015).

Vena Cava Filters

These are a type of vascular filters (net) that are implanted by interventional radiologists or vascular surgeons into a major vein (inferior vena cava) to prevent the blood clot from travelling to lungs causing life-threatening PE while maintaining vena cava patency. IVCFs are often used as an alternative to anticoagulation (Haut et al., 2014; Konstantinides et al., 2016; Weinberg et al., 2013).

Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) is an adjunct approach for prophylaxis and treatment of VTE (Feldman et al., 2012; Liu et al., 2017). IPC devices are used to help prevent blood clots in the deep veins of the legs. The devices use cuffs around the legs that fill with air and squeeze patient's legs. The graduated sequential compression devices produce sequential compression from distal to proximal veins. This increases blood flow through the veins of the legs and helps prevent blood clots (Zhao et al., 2014).

Medical Elastic Stockings

This type of compression stockings can improve venous flow and reduce vessel wall damage caused by passive venous dilatation or during surgery. Routine use of compression stockings is not recommended for the prevention of PTS (Kearon et al., 2016). They are recommended as an adjunct in moderate and high-risk cases. They should be applied preoperatively and continued throughout hospitalization. However, it is crucial to avoid improper fitting stockings. The ankle pressure should be 30–40 mmHg to help prevent PTS, if possible. There are several types of stocking where the physicians and pharmacists should select the most comfortable stockings size for their patient on an individual basis (Mazzolai et al., 2017; Zhao et al., 2014).

Diet

High intake of folate and omega-3 fatty acids has been associated with lower levels of homocysteine, which may lower the risk of VTE. Omega-3 fatty acids have positive effects on vascular function, which may also lower VTE risk (Steffen et al., 2007). In general, there are no special dietary requirements or restrictions for VTE. Diet should be as tolerated per patient. An exception, however, applies to patients prescribed oral warfarin therapy, who must avoid vitamin supplements that contain vitamin K and must limit foods that are rich in vitamin K (e.g., broccoli, cabbage, red and green lettuce, onion, peppers, spinach, oils, mayonnaise, black and green leaf teas). These nutrients can lessen warfarin's effectiveness (Mahtani et al., 2014). For the patients who are prescribed oral warfarin therapy, the diet should remain steady, with no drastic changes in content in order to facilitate accurate and regular monitoring of the INR (Nutescu et al., 2006).

The Role of Pharmacist in the Management of Venous Thromboembolism

Pharmacist in Venous Thromboembolism Management

There is a considerable lack of appropriate VTE prophylaxis and treatment in clinical practice (Byrne and Weaver, 2013; Cohen et al., 2008; Trujillo-Santos et al., 2017). Failure to prevent an avoidable VTE event is associated with a substantial clinical and economic burden due to not only the initial event but also to VTE recurrence and its long-term sequelae (Bungard et al., 2009). From a clinical perspective, the management of VTE with or without concomitant diseases is complex and multifaceted. The prescriber faces various prescribing challenges due to the complex drug regimens, monitoring procedures, as well as the broad range of drug interactions and patient's adherence issues (Aronis Konstantinos and Hylek Elaine, 2018; Konstantinides et al., 2014; Schmerge et al., 2018).

Pharmacists herein have a threefold technical role to improve health system's compliance with the guideline-driven VTE quality measures. The first role is the provision of patient-specific services including the appropriate selection, dosing and monitoring of anticoagulant agents, screening of drug–drug and drug–food interactions, review of drug utilization, and provision of drug and clinical information to prescribers. The second role is the provision of facility-specific services such as design and review of management algorithms, policy development, medication safety, and implementation of VTE quality measures. Third, clinical pharmacists can have a global contribution to the national and international organizations, medico-legal consultations, and public health initiatives (Dunn et al., 2015).

Anticoagulant Drug Therapy Problems

The pharmacist is uniquely positioned to manage drug-therapy problems in order to optimize the quality of VTE care (Schmerge et al., 2018; Vande Griend et al., 2018). Anticoagulants are highly associated with preventable adverse drug reactions (Gray et al., 2007; Steinberg et al., 2016). Among studies that reported pharmacist-led interventions in VTE management, the cumulative results are significantly promising in favor of pharmacy service (Schmerge et al., 2018).

Pharmacists are competent to select the appropriate doses and duration of treatment and able to reconcile the VTE risk assessment with the clinical practice guidelines (Schnipper et al., 2006). At the Colchester Hospital University – NHS Foundation Trust, VTE risk assessments increased from zero in 2007 up to 70% in 2009 by the incorporation of clinical pharmacists in the VTE health-care team (Eradiri, 2011). Pharmacists are well-positioned to communicate VTE priorities to clinical colleagues and can screen those patients who have not been risk-assessed, those who have been risk-assessed and not prescribed, and those not administered the prescribed prophylaxis. The pharmacists showed positive outcomes when involved in root cause analysis, and identification of VTE cause in patients developing the condition while in the hospital or soon after discharge. A recent meta-analysis including 17 studies showed the lower likelihood of bleeding and recurrence of VTE events in the pharmacist-led arm of patients (Hou et al., 2017).

Pharmacists are experts in selecting the most appropriate regimen of thromboprophylaxis for patients identified to be at risk of VTE (Dunn et al., 2015). They can offer several strategies to optimize VTE prevention via passive dissemination, audit and feedback, documentation aids, computer-based decision aids, continuous education, quality assurance activities, or advertising (Dunn et al., 2015; Tooher et al., 2005). For instance, the inclusion of pharmacist in critical care settings had optimized the number of critically ill patients receiving VTE prophylaxis according to the recommendations of the guidelines upon discharge and at one-year postdischarge (Vervacke et al., 2014). The pharmacists are concerned to investigate the potential reasons for inappropriate thromboprophylaxis such as inappropriate dose, insufficient or incomplete duration of guideline-directed prophylaxis, application of mechanical prophylaxis only, or absence of prophylaxis (Amin Alpesh et al., 2009). Also, the pharmacist should track patients who are not receiving the indicated thromboprophylaxis due to bleeding risk factors. This segment of patients needs a continual reassessment of their risk level, whereas thromboprophylaxis should be initiated when appropriate and feasible.

Elsewhere, the pharmacist significantly showed a higher rate of NOAC uptitration at baseline and over a 6-month period of follow-up by 15% (Ashjian et al., 2017). Once VTE therapy is initiated, pharmacists have a critical role in monitoring and uptitration of the prescribed therapies (Davis et al., 2013). The inclusion of a clinical pharmacist in the VTE health-care team results in a reduction of medication errors, adverse drug events, and improved outcomes (Schnipper et al., 2006). The review of the patient's daily chart by pharmacist identifies omitted doses, interactions, adverse events, and biochemical and hematological changes. Chilipko and Norwood showed the advantage of the pharmacist-managed inpatient anticoagulation service over physician-managed service in terms of lower incidence of supra-therapeutic INRs and longer time of target INR achievement (Chilipko and Norwood, 2014).

Patient Education and Adherence

A large number of cancer patients are not aware of the increased risk of thromboembolism (53% in one study) (Sousou and Khorana, 2010). Patients who are well aware of the risk are more likely to use the prescribed prophylaxis and accept its negative sides, such as daily injections or frequent monitoring (Sousou and Khorana, 2010). Pharmacists are unequivocally well-positioned to advise patients on the indications, contraindications, and side effects of their medications. This role is particularly useful when dealing with high-risk medications, such as LMWH, narrow therapeutic index medications, such as warfarin, or medications of short half-lives, such as NOACs.

Medication nonadherence and missed doses expose patients to a considerable risk of VTE (Aronis Konstantinos and Hylek Elaine, 2018). The pharmacist is able to enhance patient's adherence via several strategies: (1) provision of pill organizers, blister packs, calendars, and dose counters; (2) verbal reinforcement and detailed written information of medications; (3) periodical telephone call assessment of refill dates and compliance; (4) encouraging family support; (5) informing the patient about the possible most common side effects and self-monitoring indices; and (6) encouraging patient's participation in regular physical activity programs and in Anticoagulation Management Service. The beneficial outcomes of this role were clearly illustrated in the anticoagulation management service of Michigan University Hospitals. The continuous pharmcist-led education has increased the patient's adherence level by 12% over a 6-month follow-up (Ashjian et al., 2017).

Prescribers Education

The NOAC agents have the advantage of predictable and safe pharmacokinetics. However, appropriate prescription of these agents requires a comprehensive assessment of patient-specific factors such as age, renal function, weight, history of GI or intracranial bleeding, patient's adherence, and literacy levels (Di Palo et al., 2018; Steinberg et al., 2016). Hence, it is important to consider that underdosing of anticoagulant agents is significantly associated with an increased risk of adverse events (Chopard et al., 2018). A 2017 report involving more than 1500 patients who were being treated for VTE with a NOAC highlighted the lack of clinicians familiarity with the recommended dosing (Trujillo-Santos et al., 2017). Herein, the pharmacists are in a position to

provide continuous educational service to clinicians to optimize prescribing outcomes (Schmerge et al., 2018; Di Palo et al., 2018). Vyas et al. reported the positive impact of pharmacist-led education to improve prescribers' behaviors by 16% in 2 months (Vyas et al., 2013).

Transition of Care

Pharmacists represent an important part of the health-care team responsible for the design of VTE management and monitoring guidelines because of their clinical and pharmacological knowledge as well as their oversight of patient care as patients are transferred from one service to another during the hospital stay or at discharge (Davis et al., 2013). The pharmacists have to ensure the full compliance of the prescribed anticoagulation therapy with the guideline-driven quality measures (Schnipper et al., 2006). When parenteral or oral anticoagulants are withheld before procedures, the pharmacists should ensure that they are resumed when patients are transferred to recovery units or another service. This transition of care should cover the following points: follow-up INR scheduled if warfarin is prescribed, prescriber's awareness of discharge and transition plans, and patient education. Herein, the pharmacist should provide a comprehensive education to the patient about VTE, its management, and monitoring (Davis et al., 2013).

Outpatient Settings

Many patients will continue with therapy after hospital discharge. This is an important opportunity to introduce and reinforce complex information at discharge point and at regular occasions in the outpatient settings (Sousou and Khorana, 2010; Vyas et al., 2013). This also needs to be communicated to general practitioners (GPs) via accurate discharge letters to ensure that treatment continues and that patients are appriopriately monitored. Home treatment of VTE is now feasible in several settings. Similar to the inpatient settings, the community pharmacists have the same opportunities for counselling the ambulatory patients about risks, preventive measures for and management of VTE at home, or upon their transfer to long-term care facilities (Sousou and Khorana, 2010). Pharmacists in each of these outpatient settings (long-term care settings and community pharmacy) should first assess patient's VTE risk and should intervene and make appropriate recommendations when necessary. Also, they have to reconcile the patient's medications and manage any possible adverse drug reactions. The community pharmacists have an essential role to select the affordable drug product and provide the medication-related information to the patients or their caregivers to ensure their adherence.

Economic Justification

A large economic report showed the cost-saving benefit of a pharmacist-led anticoagulation clinic where the pharmacist's services saved $505,349 in terms of events and related expenditures of hospitalization and emergency department (ED) visits versus the nurse-led services (Gray et al., 2007). The benefit of events reduction that represented an odds ratio (OR) of 7.68 (95%CI = 1.1–55.9) was in favor of the pharmacist-led arm (Bauer et al., 2008). Similar benefits were rationalized in Gary and colleagues analysis (Gray et al., 2007).

Conclusion

Overall, there is sufficient evidence of benefit of clinical pharmacy services for better clinical outcomes in terms of reduction of VTE occurrence, recurrence, bleeding complications, and mortality, while reducing excess hospitalization and health-care costs (Dager and Gulseth, 2007; Dunn et al., 2015; Gray et al., 2007). Pharmacists are well-positioned to enhance many facets of VTE prevention and management (Dunn et al., 2015; Strand et al., 1990). They are able to develop or expand the anticoagulation management services (Dager and Gulseth, 2007).

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Further Reading

1. Clot Care Online Resource: http://www.clotcare.com
2. Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278060/
3. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report http://journal.chestnet.org/article/S0012-3692(15)00335-9/pdf
4. International Society on Thrombosis and Haemostasis: https://www.isth.org/default.aspx
5. World Thrombosis Day (WTD): http://www.worldthrombosisday.org/
6. Pathophysiology of Venous Thromboembolism http://www.pathophys.org/vte/
7. Centres For Disease Control And Prevention: Venous Thromboembolism (blood clots) Section: https://www.cdc.gov/ncbddd/dvt/index.html
8. Thrombosis Journal: https://thrombosisjournal.biomedcentral.com
9. Thrombosis And Embolism: From Research To Clinical Practice: Volume 1 (Advances In Experimental Medicine And Biology) 1st Edition 2017.
10. Summary of product characteristics (SPC): https://www.medicines.org.uk/emc/; https://www.ema.europa.eu/en/medicines

Management of Respiratory Disorders and the Pharmacist's Role: Asthma

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Learning Objectives

By the end of the chapter, the reader will be able to:

- Discuss the etiology, epidemiology, and clinical presentation of asthma.
- Provide clinical recommendations for the management of asthma using evidence-based principles. Recommendations include, self, pharmacist, and interdisciplinary delivery of both pharmacotherapeutic and nonpharmacotherapeutic care.
- Describe current and future roles of the pharmacist in the provision of care to individual patients with asthma as well as to the wider population with asthma.

Take Home Messages

- Asthma is a chronic condition with a high global prevalence, affecting over 330 million individuals worldwide.
- Asthma may occur in the presence of other diseases of the respiratory system such as allergic rhinitis and chronic obstructive pulmonary disease.
- Inhaled corticosteroids remain the mainstay of treatment however the therapeutic gains resulting from these are limited by poor adherence to treatment.
- There is a shift in focus from underuse of controller therapy to overuse of reliever treatment—optimal pharmaceutical management should focus on both types of treatments.
- There are many opportunities for pharmacists to be involved in optimizing the care of individuals with asthma—from optimizing treatment to improving adherence, particularly around addressing concerns around treatment and need for ongoing regular therapy.

Introduction to Condition

Asthma is a well-known common chronic condition of the airways. Historically, mention of breathlessness or troubled and noisy breathing was found in the earliest known ancient Chinese and Egyptian medical writings, however it is to the Greek we must look for the first mention of asthma by Hippocrates (460–377 BCE) in reference to breathlessness, with the Change to Aretaeus first accurate characterization of asthma as a disease was by Aretaeus the Cappadocian (circa 81–138 CE) (Cohen, 1992; Diamant et al., 2007).

We are now in an era in which the characterization of asthma has evolved from this idea of asthma as a single disease to a respiratory condition that is heterogeneous in nature. Currently, there is still a lack of a definitive definition of asthma, however there is consensus in definitions on asthma being characterized as a heterogeneous condition that has acute periods of variable expiratory airway limitation. These exacerbations may result in symptoms of shortness of breath of variable frequency, duration, and severity as well as associated symptoms such as chest tightness, wheeze, and cough (Global Initiative for Asthma, 2018; National Asthma Council Australia, 2017; World Health Organization, 2018).

Epidemiology, Burden and Pharmacoeconomics

It is estimated that asthma affects up to 334 million people worldwide (Global Asthma Network, 2014). Prevalence is increasing with a prediction of over 400 million affected in 2025 as a result of increasing urbanization (Akdis and Agache, 2013). The burden of disease is shifting to low-income countries with the majority of people with asthma located in developing nations, with such nations reporting higher mortality rates due to asthma (Global Asthma Network, 2014). The burden of disease as measured by disability adjusted life years is greatest in the elderly peaking in the 75–79 year age group with a secondary peak in adolescence in the 10–14 year age group (Global Asthma Network, 2014). Economically, asthma that is poorly controlled results in higher economic costs to both patients as well as to the wider society. Limited data from low-income countries does not allow an accurate picture of the global economic costs of asthma to be estimated. In the US, asthma costs in 2013 were estimated at US$81.9 billion as a result of lost productivity, health care utilization, and mortality (Nurmagambetov et al., 2018).

Etiology

The etiology of asthma has been revised in recent years, yet the specific cause of asthma remains unknown. Traditionally, it was thought that asthma was due to atopy or hypersensitivity to an allergen or "trigger." The inflammatory response was mediated by an increased production of T-helper 2 (T_H^2) cells because of hypersensitivity to a specific allergen. When exposed to the allergen, a primarily cytokine mediated inflammatory cascade ensues, resulting in rapid mast cell degranulation in the presence of IgE,

followed by infiltration of eosinophils and other inflammatory mediators into the airways (de Groot et al., 2015; Wenzel, 2012). However, this process does not explain all asthma disease. An emergent approach to classification of asthma is that of asthma phenotypes (Wenzel, 2012). Asthma phenotypes recognize the heterogeneity of asthma in individuals by grouping according to age of presentation, etiology, and pathophysiology. Broadly, phenotypes can be clustered according to the type and level of inflammation. The most common phenotype is that of "allergic asthma." This phenotype is considered to have the classical T_H^2 cell inflammatory response described above. Other asthma phenotypes may not exhibit a T_H^2 cell inflammatory cascade, e.g., obesity-related and smoking-related phenotypes (Wenzel, 2012). Similarly adult-onset eosinophilic asthma demonstrates independent eosinophilic inflammation and pulmonary infiltration without allergen-dependent activation of T_H^2 lymphocytes (de Groot et al., 2015). A recent metaanalysis suggests that while early-onset asthma is more likely to be due to atopy, late-onset asthma is more related to environmental risk factors suggesting that preventative strategies may be employed in these phenotypes (Tan et al., 2015).

Clinical Presentation

Asthma is not readily distinguishable from other diseases in which airflow obstruction may occur. People typically access health care services with symptoms suggestive of an acute asthma exacerbation or a "flare-up" prior to formal diagnosis of asthma. Such symptoms typically include but are not limited to wheeze, breathlessness, chest tightness, and cough (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

Differential diagnosis include conditions such as airway obstruction due to a foreign body, alpha1-antitrypsin deficiency, bronchiectasis, congenital heart disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary embolism, and vocal cord dysfunction (Global Initiative for Asthma, 2018). Untreated asthma is often characterized by chronic inflammation related to various cells and cellular elements, airway hyperresponsiveness, and intermittent airway narrowing due to bronchoconstriction, congestion or edema of bronchial mucosa, or a combination of these. However, asthma is now thought to have significant overlap with features of other respiratory diseases such as COPD and allergic rhinitis (National Asthma Council Australia, 2017). Recently, the concept of "united airway disease" has emerged as a term to integrate coexistent asthma and rhinitis as an airway-hypersensitivity syndrome due to the shared underlying pathophysiological nature of both diseases (Passalacqua et al., 2000).

Diagnosis

The diagnosis of asthma fundamentally relies on clinical judgment as unfortunately there is no reliable diagnostic test or criteria by which all asthma can be diagnosed. This is compounded by the nonspecific nature of respiratory symptoms which may be caused by other respiratory conditions, instead of, or even in addition to asthma. Another issue in the diagnosis of asthma is the situation of delayed presentation due to some patients delaying presentation with their respiratory symptoms.

Due to the importance of clinical judgment in the diagnosis of asthma, when asthma is suspected, it is essential to obtain a detailed history from the patient and/or their caregiver. The second diagnostic activity involves a careful physical examination including auscultation of the chest. It is important to establish the presence or absence of other conditions that may affect the diagnosis and treatment of the symptoms such as allergic rhinitis and/or COPD.

Diagnosis is made according to two criteria (Global Initiative for Asthma, 2018):

- History of variable respiratory symptoms and
- Confirmed variable expiratory airflow limitation

The second criterion requires the confirmation of airflow limitation preferably by spirometry, as well as confirmation of excessive variability in lung function by lung function testing, e.g., positive bronchodilator reversibility test, exercise challenge test, bronchial challenge test, excessive variability in peak expiratory flow (PEF) over a two-week period or significant improvement in lung function after four weeks of anti-inflammatory therapy. However, if there is a high probability of asthma, a trial of treatment should be given if clinical urgency is present.

Other tests that may provide additional information such as assisting in identification of triggers or asthma phenotype include allergen testing and measurement of the fractional concentration of exhaled nitric oxide (FENO). Allergen testing can be performed by skin prick testing or by measuring the level of specific IgE in serum. Either method may aid in identification of the allergic asthma phenotype, however are not specific tests for asthma. Likewise, FENO is a test that is sensitive for asthma phenotypes that result in increased eosinophil expression in sputum and blood. It is also useful for predicting response to inhaled corticosteroid therapy (Global Initiative for Asthma, 2018).

The diagnosis of asthma in very young children (i.e., those under 5 years of age) is often difficult due to the difficulty in performing lung function testing. In this population, the presence of prognostic markers including symptoms (most commonly disturbed sleep or limitation of activities associated with coughing or wheezing), atopy or a clear provoking stimulus, together with patient history may be all the information a practitioner has to make a diagnosis in the very young.

Traditionally asthma was categorized according to severity of symptoms (see "Introduction" section), however the current approach is to initially assess asthma control (Global Initiative for Asthma, 2018). The following questions may be asked to assess control over the last 4 weeks in patients over 6 years of age:

- Daytime asthma symptoms more than twice/week?
- Any night waking due to asthma?
- Reliever needed for symptoms (except prior to exercise) more than twice/week?
- Any activity limitation due to asthma?

Asthma control is rated as "well controlled," "partly controlled," or "uncontrolled" according to having no symptoms, 1–2 symptoms, or 3–4 symptoms respectively (Global Initiative for Asthma, 2018) (see "Role of the Pharmacist" section).

Asthma disease severity is currently assessed after a patient is stable and has been on regular controller treatment for several months. Severity is rated as "mild," "moderate," or "severe" based on the level of pharmacotherapy required (Global Initiative for Asthma, 2018).

For categorization purposes, asthma is listed under ICD-10 Chapter 10: Diseases of the respiratory system in several categories including J45: Asthma. Asthma is subcoded as intermittent or persistent, with mild, moderate, or severe as descriptors. In addition, a fifth digit is used to describe asthma as uncomplicated, with exacerbation or with *status asthmaticus* (World Health Organization, 2016). Asthma can also be coded in two other categories for specific types of asthma; J46: *Status asthmaticus* and J82: Pulmonary eosinophilia, not elsewhere classified, in which eosinophilic asthma is categorized. It should be noted however that current clinical coding systems including ICD-10 and SNOMED do not align with current clinical terminology with ICD-10 presenting confusion for how acute severe asthma (*status asthmaticus*) should be coded (Lougheed et al., 2017; McKenzie and Wood, 2005).

Place of Pharmacotherapy in Context of Treatment Options

Asthma pharmacotherapy can be broadly classified into two categories—controller treatment which should be taken regularly except in the mildest of asthma cases, and acute short-term reliever treatment for the immediate relief of asthma exacerbations (Global Initiative for Asthma, 2018).

Controller treatment is used in asthma in a stepped approach depending on the symptoms experienced by the patient and the response to the prescribed therapy (see **Fig. 1**) (Global Initiative for Asthma, 2018).

This stepped approach is used as treatment aims to achieve early control—hence treatment should be started at the level most appropriate to the individual's initial clinical presentation—and then for the treatment to be adjusted to the individual's ongoing control. The choice of treatment for maintenance depends on patient factors such as age, ability to use the inhaled device (e.g., inhaler technique) or prescribed formulation, patient preference and goals, severity of asthma, clinician experience (as some therapies are recommended for use only under specialist supervision), and any comorbidities. At any stage of treatment, it is recommended that adherence, inhaler technique, and individual trigger factors be reviewed before any change in therapy (see also "Role of the Pharmacist" section) (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018; National Institute for Health and Care Excellence, 2017).

Controller Treatment

Inhaled Corticosteroids

The mainstay of asthma treatment for both adults and children (with the exception of nonatopic children under five—who often do not have chronic atopic asthma) are the inhaled corticosteroids (ICS) (Adams et al., 2001, 2005; Calpin et al., 1997). Professor Peter Barnes first reported on the use of ICS as first-line treatment for people with persistent asthma (World Health Organization, 2016), highlighting that the use of ICS is associated with improved asthma symptoms, lung function, and reduced risk of exacerbations, hospitalization, and asthma mortality (Barnes, 1998). The mechanism of action of ICS is through the anti-inflammatory effects of the corticosteroid; this suppresses the multiple inflammatory cascades which are activated in the airways of a person with asthma. This inflammation leads to increased mucus production and airway constriction, which contributes to asthma symptoms. Reduction in underlying inflammation through sustained use of ICS can result in symptom improvement and reduced asthma-related morbidity and mortality (Barnes and Adcock, 2003; Barnes and Ulrik, 2015). ICS thus form the basis of most of the controller treatment regimens, with other controllers considered as add-on treatments if response to ICS alone is inadequate (Global Initiative for Asthma, 2018).

Guidelines may vary in terms of when ICS should be started (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018; National Institute for Health and Care Excellence, 2017) but generally ICS should be considered in individuals who use inhaled short-acting beta2-agonists (SABAs) three times a week or more; have symptoms three times a week or more; or wake at least one night a week with asthma, or have any symptoms plus any risk factors for exacerbations (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018). For example, in adults and children 5–12 years, ICS should be considered if they have had an asthma exacerbation

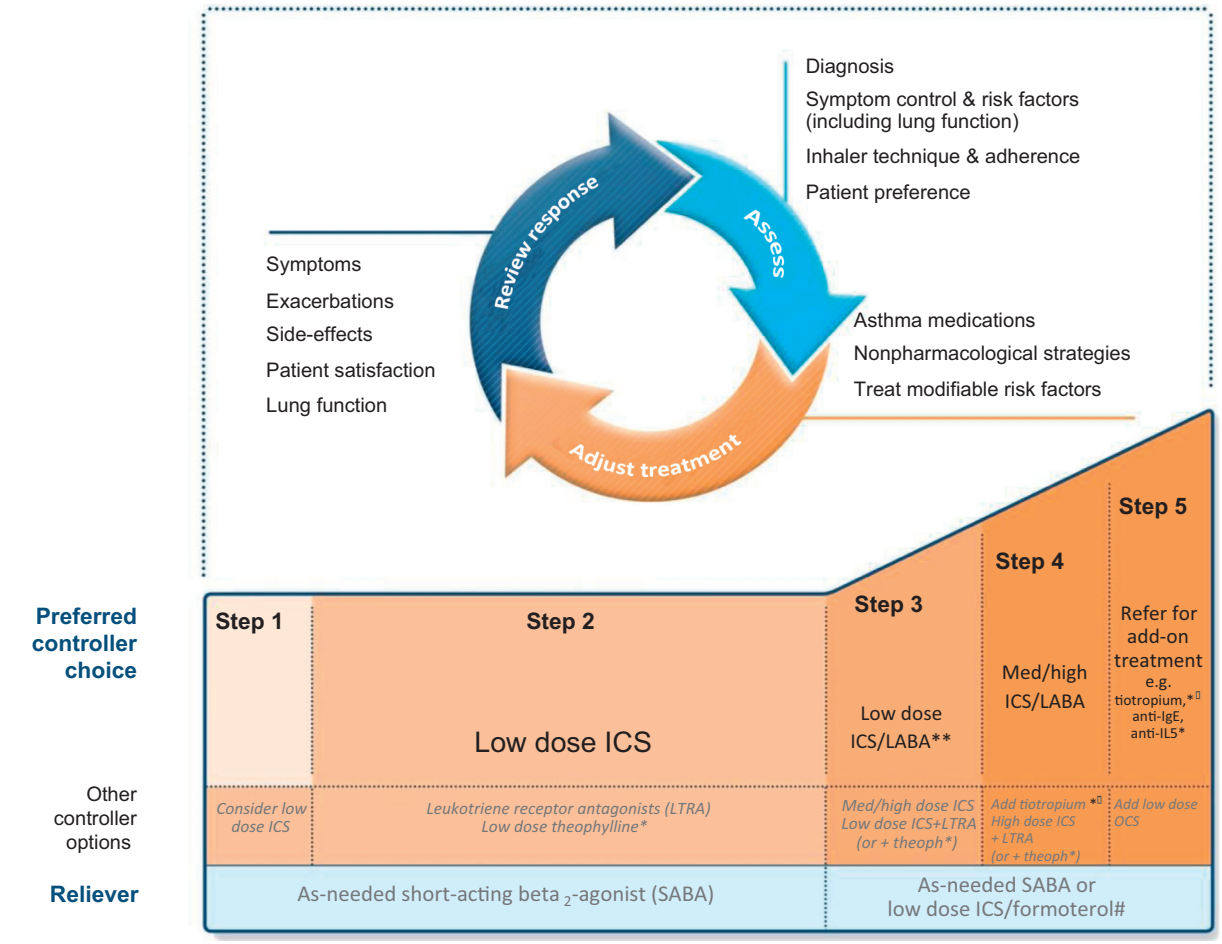

Figure 1 Stepwise approach to control asthma symptoms and minimize future risk. *Source: Reproduced with permission from the Global Initiative for Asthma (Global Initiative for Asthma, 2018).*

or "flare-up" requiring oral corticosteroids in the last two years (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; National Institute for Health and Care Excellence, 2017; O'Byrne et al., 2001; Pauwels et al., 2003; Sorkness et al., 2007; Szefler et al., 2007). ICS should be started at a dose appropriate to the individual's asthma symptoms, and titrated to the lowest effective dose at which asthma control is maintained (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018). Reductions in dose should be slow, with close monitoring for any worsening in asthma control; the individual and/or family/caregiver should be advised about the potential risks and benefits of reducing maintenance treatment. A suggested rate of reduction is 25%–50% reduction in dose, every 3 months (Global Initiative for Asthma, 2018; Hawkins et al., 2003; National Institute for Health and Care Excellence, 2017). In adults who are current or ex-smokers, the dose of ICS required may be higher as the effect of ICS is reduced by current or previous smoking (Tomlinson et al., 2005).

As the adverse effects of ICS are dose-related, there is a need to consider the overall steroid exposure of the individual (i.e., whether the individual is on any other steroid therapies) so that systemic risk can be adequately assessed. This is particularly important in children, as exposure to medium-high doses of ICS can lead to systemic effects such as adrenal suppression, and growth retardation (Sharek and Bergman, 2000). Adrenal suppression can place children at risk of clinical adrenal insufficiency during intercurrent illness or surgery, and therefore this should be considered in any child presenting with shock or reduced consciousness (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018).

In individuals who are not adequately controlled on ICS alone, add-on treatments maybe trialed, following an assessment of adherence, inhaler technique, and review of triggers/risk factors, and comorbidities which may be contributing to symptoms (National Institute for Health and Care Excellence, 2017; Global Initiative for Asthma, 2018). Response to the add-on treatment should be monitored closely, and where there is no response, the add-on treatment should be discontinued (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). The approach to treatment varies depending on the age of the patient (**Figs. 2 and 3**).

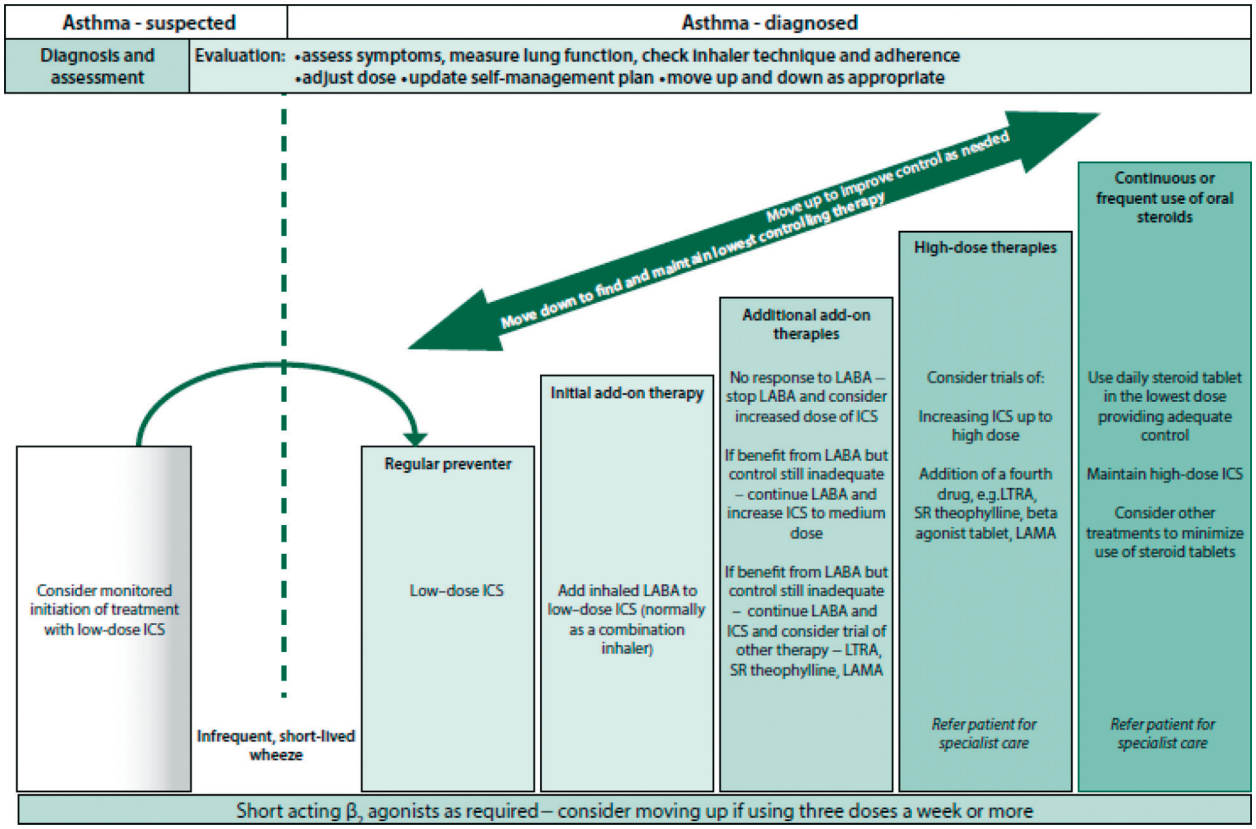

Figure 2 Summary of management in adults (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). *Source: Figure reproduced with permission from BTS/SIGN British Guideline on the management of asthma by kind permission of the British Thoracic Society.*

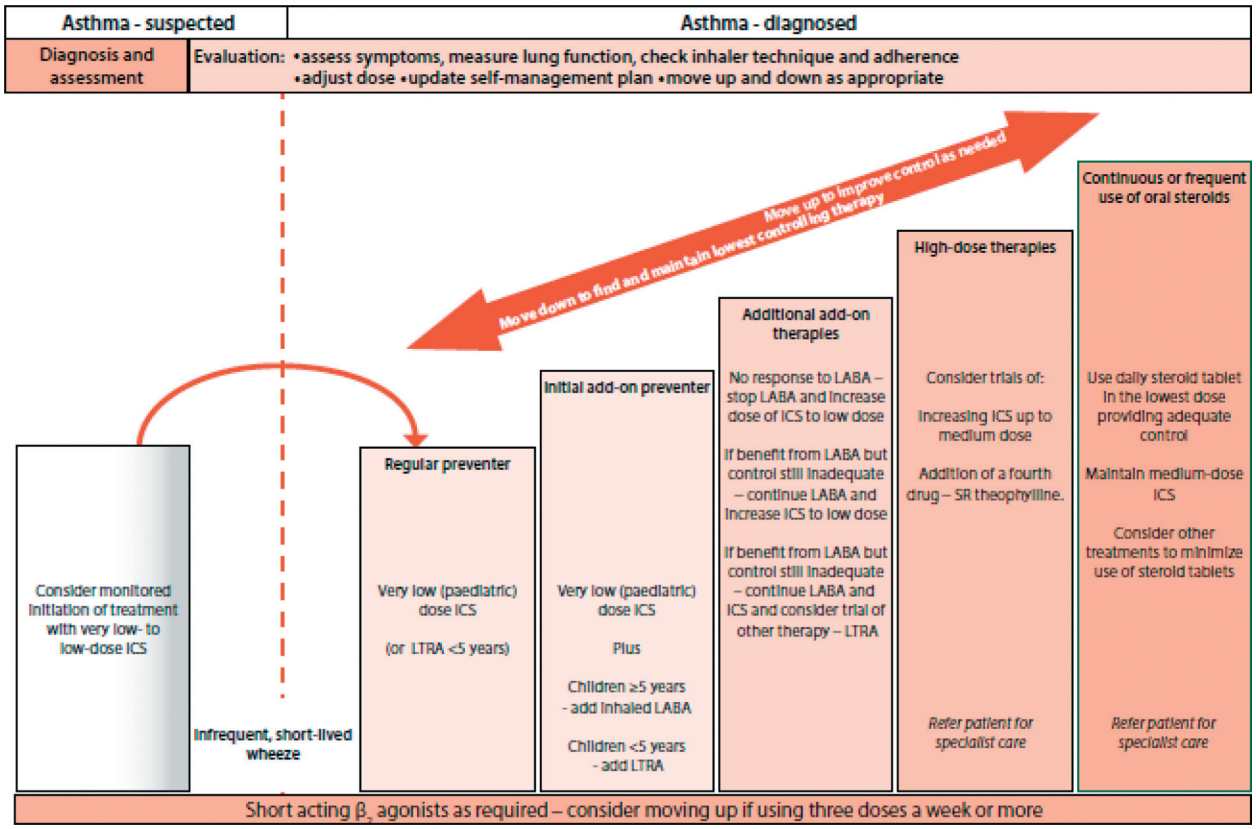

Figure 3 Summary of management in children (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). *Source: Figure reproduced with permission from BTS/SIGN British Guideline on the management of asthma by kind permission of the British Thoracic Society.*

Inhaled Long-Acting Beta Agonists

The addition of inhaled long-acting beta agonists (LABAs) to ICS monotherapy have been shown to improve lung function, and reduce symptoms and asthma exacerbations (De Blic et al., 2009; Ducharme et al., 2011; Kips and Pauwels, 2001; Morice et al., 2008). This evidence is stronger in adults—the use of LABA should be considered one of the first-choice add-on therapy in adults (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). A systematic review comparing LABA as add-on treatment to ICS, compared to leukotriene receptor antagonists (LTRAs) as add-on to ICS in adults, found that adding LABA to ICS was more effective in terms of reducing asthma exacerbations, reducing SABA use, and improving symptoms and quality of life (Chauhan and Ducharme, 2014; Ducharme et al., 2011). In children over 5 years old, add-on therapies can be either LABAs or LTRA, as the evidence supports both with little evidence to demonstrate the benefit of one over the other (Chauhan and Ducharme, 2014; Ducharme et al., 2011). It is worth noting here that the guidance on when LABAs should be added to ICS differs between the current BTS/SIGN and GINA guidelines and the NICE asthma guidelines (White et al., 2018). BTS/SIGN and GINA both recommend a trial of add-on LABA if asthma is uncontrolled on low-dose ICS monotherapy (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016), while NICE recommend trialing LTRAs first, then adding LABA (with or without LTRA, depending on patient response). A key reason for this difference is due to cost—LABAs are more expensive than LTRAs, thus NICE adopts a more cost-effective approach while BTS/SIGN favor LABA as the more effective treatment (White et al., 2018).

LABAs are add-on therapies which should only be used in combination with ICS, either in separate or combination inhalers. LABAs work by keeping the airways open and relaxing the muscles of the airways, but does not treat any underlying inflammation (Johnson, 1995). As such, LABAs should always be used with ICS and never alone as a series of studies and reports showed an increased risk of death and severe asthma exacerbations from use of LABA monotherapy (Drazen and O'Byrne, 2009; Kramer, 2009; Martinez, 2005), potentially through a masking effect of deteriorating asthma (Chowdhury and Dal Pan, 2010). Most current formulations of LABA are combined with ICS in a single inhaler to support adherence, and to ensure that LABAs are not administered without ICS (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

In certain adult individuals who remain poorly controlled with ICS and LABA, or medium-dose ICS monotherapy, a regime using the combination ICS/LABA as both controller and reliever therapy has been shown to be effective. This regimen—called maintenance and reliever therapy (MART)—has been shown in two systematic reviews to reduce the risk of asthma exacerbations in individuals not controlled on ICS monotherapy and who have a history of exacerbations (Cates and Karner, 2013; Kew et al., 2013), compared to ICS/LABA as controller and SABA as reliever (Kew et al., 2013), or ICS monotherapy or ICS with/without LABA (Cates and Karner, 2013). The formulations which are licensed for MART vary between countries—local regulations should be checked prior to prescription.

If control remains inadequate to LABA add-on treatment, despite improvement with LABA, then one of two strategies can be used (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018; National Institute for Health and Care Excellence, 2017). The LABA can be continued and the ICS dose increased; or the LABA and ICS continued, but additional treatment added. Below describe the three add-on treatments that can be considered (LTRAs, long-acting muscarinic antagonists (LAMAs), or theophyllines). If the LABA trial was ineffective, then the LABA should be stopped, and either the dose of ICS increased; or a trial of LTRA or LABA started (as add-on to ICS).

Leukotriene Receptor Antagonists

LTRA work by blocking the effects of cysteinyl leukotrienes in the airways—these leukotrienes are released during asthma flare-ups and cause bronchoconstriction (Jones et al., 1995). LTRAs are licensed for use in both adults and children 5 years and over. In children under five years who are unable to take ICS, LTRAs may be used as an alternative preventer. In those over 5 years of age, LTRAs are usually considered as add-on therapies to ICS or ICS plus LABA, though evidence for use of LTRA is primarily from studies where LTRA were added to ICS monotherapy (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). Addition of LTRA to ICS may lead to improvements in asthma symptoms and lung function in those over 5 years, the evidence is most robust for adolescents and adults (≥12 years) as evidence in children is limited (Joos et al., 2008).

Long-Acting Muscarinic Antagonists

LAMA can be considered as add-on treatment in adults—the evidence primarily relates to tiotropium bromide as add-on treatment to ICS/LABA therapy (rather than ICS alone) (Kew et al., 2015). The use of tiotropium as add-on to ICS/LABA was found to reduce asthma exacerbations, improve lung function, and asthma control compared to ICS/LABA alone (Kew and Dahri, 2016).

Theophyllines

Theophyllines have been used historically for asthma management, however are no longer commonly used to the need for therapeutic drug monitoring, and the increased risk of side effects (Weinberger and Hendeles, 1996). These are primarily used as last-line failing trials of LTRAs or LAMAs as add-on therapy (National Institute for Health and Care Excellence, 2017), and recommended only in adults (Global Initiative for Asthma, 2018).

Slow-Release Beta2-Agonist

These oral formulations of beta2-agonists can be considered as add-on treatment in adults who remain uncontrolled after trials of other add-on therapies. Although these can improve lung function and symptoms, the risk of side effects is higher, so use is generally reserved in latter stages of treatment. Caution is advised in individuals already on LABA treatment (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

Other Controller Therapies

Antihistamines and ketotifen have been investigated as controller asthma therapies, however little evidence remains to support their use (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). In some patients, low-dose maintenance oral corticosteroids may be required but the risks of potential long-term side effects need to be balanced against any benefit (Global Initiative for Asthma, 2018).

Biologics

In individuals with a high steroid burden who continue to have frequent asthma exacerbations, symptoms, and impaired lung function, in whom allergy has been identified as an important cause of the asthma, injectable maintenance treatment with monoclonal antibodies may be considered. Omalizumab is a humanized anti-IgE monoclonal antibody which binds to free circulating IgE, thus reducing free IgE levels (Bousquet et al., 2005). This is given as a subcutaneous injection every 2–4 weeks, dosed according to IgE level and weight (Lanier et al., 2009). Omalizumab has been shown in three systematic reviews to reduce asthma exacerbations in individuals with moderate-severe allergic asthma, compared to placebo, in addition to oral steroids or ICS (Norman et al., 2013; Normansell et al., 2014; Rodrigo et al., 2011). This has been shown to reduce overall steroid burden for the individual.

Anti-interleukin-5 monoclonal antibody injections have been investigated in adults and adolescents (12 years or older) with severe eosinophilic asthma (Powell et al., 2015). Options include intravenous reslizumab (18 years or older) or subcutaneous mepolizumab or benralizumab (12 years or older) and can be considered as add-on failing response to previous therapies (Global Initiative for Asthma, 2018).

Acute Reliever Treatment

Short-Acting Beta-Agonists

These SABAs work on beta2-receptors in the airways to relax the smooth muscle, leading to immediate but short-lived bronchodilation effects (Barnes, 1995). These are useful as intermittent therapy for acute symptom relief in individuals with infrequent, short-lived wheezing episodes. SABA is the preferred treatment in individuals with intermittent symptoms as SABA works quicker with fewer adverse effects than other bronchodilator alternatives. There have been ongoing concerns however around overuse or overreliance on SABA therapy, which have been related to poor asthma control, asthma exacerbations, and increased mortality (Patel et al., 2013; Pavord et al., 2017; Suissa et al., 1994). Individuals identified as frequent users of SABA (e.g., prescriptions of more than one short-acting bronchodilator therapy per month or reported use of SABA more than twice a week) should have their asthma reviewed urgently (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016; Global Initiative for Asthma, 2018). Future advances in therapy are focusing on a move away from SABA monotherapy except in the mildest of cases (Pavord et al., 2017) (see What's coming up in pharmacological management); though current BTS/SIGN asthma guidelines recommend using ICS even in very mild cases (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016), an approach that is more in line with recommendations from the UK National Review of Asthma Deaths (NRAD) (Levy, 2014).

Other Bronchodilators

Falling within this class are the inhaled short-acting muscarinic antagonists (SAMA—e.g., ipratropium bromide), and per oral formulations of beta2-agonists (e.g., tablets or syrup) (see previous sections for details). These are considered not as effective as SABA, and should be viewed as alternatives only if SABA is not indicated or tolerated for use (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

Other Treatments

Vaccinations should be considered in all individuals with asthma, particularly as influenza contributes to acute asthma exacerbations (Global Initiative for Asthma, 2018). A recent systematic review of influenza vaccine efficacy in individuals with asthma found that the live vaccine reduced febrile illness by 72%, and the vaccine prevented 59%–78% of asthma exacerbations leading to emergency visits and/or hospitalizations (Vasileiou et al., 2017).

Nonpharmacological Treatment

Beyond treatment with pharmacotherapy, there are a several nonpharmacological management options which should be considered for all people with asthma. These fall in the categories of supported self-management, trigger minimization and optimization of delivery route (e.g., consideration of inhaler technique or device).

Supported Self-Management

Self-management refers to the tasks that the individual needs to do to live with their long-term condition. In asthma, this primarily relates to the management of symptoms, such as knowing when asthma flares up and how to manage this, and when to seek additional help. Understanding and assessing asthma control is the first step to proactive asthma management; what is crucial is the response to deteriorating asthma control. Patients with poor asthma control need to adjust treatment to improve lung function and restore symptom control.

There is a significant role for education to support self-management. Written asthma action plans have been proven to be highly beneficial to improving asthma health outcomes including reductions in exacerbations and decreases hospitalizations, emergency department, and emergency medical practitioner visits (Gibson and Powell, 2004). Education incorporating the use of written personalized asthma action plans, with regular health professional review, improves outcomes in individuals with asthma, regardless of ethnicity, age, asthma severity, and health care context (Gibson et al., 2003; National Institute for Health and Care Excellence, 2017; Powell and Gibson, 2002). These asthma action plans should include advice about how to recognize when asthma control is deteriorating (e.g., what symptoms and/or signs to look for), and what actions to take and when (e.g., seeking help or starting/changing treatment (Gibson and Powell, 2004). Patients can actively participate in the step-up and step-down adjustments to their treatment (Global Initiative for Asthma, 2018). Of greatest benefit are individualized plans that have two to four action points and used both inhaled corticosteroids (ICS) and oral corticosteroids (OCS) (Gibson and Powell, 2004).

This self-management support can be delivered by health professionals or via technology-based platforms depending on the individual's needs and health care setting (Bussey-Smith and Rossen, 2007; de Jongh et al., 2012). The most effective self-management support is ongoing, personalized to the individual (e.g., consideration of the individual's age and language), and continually reviewed to ensure it meets the changing needs of the person with asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

Self-management support should also encompass issues relating to treatment and monitoring adherence. Adherence to regular monitoring, such as use of peak flow monitoring, is poor with rates as low as 6% reported (Redline et al., 1996). Similarly, adherence to regular controller treatment averages around 33%–50%; this tends to worsen with time (Krishnan et al., 2012). This poor adherence may be unintentional (i.e., when the individual does not adhere to factors not directly within their control such as difficulties with medication-taking or financial barriers to treatment access (Clifford et al., 2008; Horne et al., 2005), or intentional (i.e., the individual chooses not to adhere due to their beliefs about treatment or perceptions of asthma (Clifford et al., 2008). To optimize adherence, the individual's adherence should be regularly assessed (e.g., by asking specific questions about treatment use in a nonjudgmental fashion, exploring their attitudes/beliefs around medication, and/or reviewing their prescription record (Horne et al., 2005); and adherence support tailored to address the individual's unique medication-taking barriers provided (Covvey et al., 2014).

Trigger Minimization

Part of successful asthma management is understanding the warning signs of an asthma flare-up but also recognizing what can trigger an exacerbation. Triggers are substances or events that lead to an acute worsening of asthma symptoms. Patients with asthma may have multiple triggers. Common triggers in asthma include allergens (both indoor and outdoor), environmental pollutants or irritants (Lin et al., 2003), infections, weather, exercise, foods, smells, emotions and stress and even laughing. Occupational asthma can be particularly difficult for patients to manage, due to the wider implications of avoidance.

Each individual will have different triggers—these should be identified and lifestyle changes made to minimize exposure to these, where possible (Global Initiative for Asthma, 2018; National Institute for Health and Care Excellence, 2017). Regardless of the individual's unique triggers, current recommendations supports smoking cessation as part of the nonpharmacological management of asthma, as direct or passive exposure to cigarette smoke can affect lung function, asthma quality of life, and asthma symptoms (Ehrlich et al., 2001; Mannino et al., 2002). Electronic cigarettes have been marketed as safer alternatives to cigarette smoking for individuals who have difficulty quitting smoking. Data on safety are conflicting and e-cigarettes cannot be considered harmless (Pisinger and Døssing, 2014); in individuals with asthma there is even more limited data on safety, however one small retrospective study suggests that use of e-cigarettes to substitute traditional smoking can lead to reduce cigarette consumption and therefore lead to improvements in asthma outcomes (Polosa et al., 2014). E-cigarettes may therefore be a potential option to consider as part of a harm minimization strategy in those who are regular cigarette users; however abstinence from both traditional and electronic cigarettes should be supported where possible.

Optimization of Treatment Delivery

Inhaler technique is an important aspect of asthma management to ensure optimal medication delivery. Inhaler training should be incorporated as part of routine asthma consultations and technique reviewed on a regular basis. In terms of inhaler device choice, this should primarily be based on the individual's preference and their ability to use the device correctly in everyday situations (e.g., many individuals may not wish to carry around a spacer to use with a metered-dose inhaler, in which case a dry powder inhaler may be more appropriate) (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016) (see "Role of the Pharmacist" section for additional details).

Other Nonpharmacological Treatments

There have been several other nonpharmacological treatments studied in the research setting, such as the use of fish oils and probiotics (Helin et al., 2002; Stephensen, 2004). However, current guidelines report that there is generally insufficient evidence to recommend other nonpharmacological treatments in the routine management of asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). The evidence around weight-loss interventions is still in its early stages, but may be considered for overweight or obese adults and children with asthma as this may improve asthma control (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016). Similarly, certain breathing exercises may be useful in people with asthma as an add-on, but not in place of, pharmacological treatment of asthma (O'Connor et al., 2012).

Family therapy may have a place as an adjunct to pharmacological treatment—in a recent Cochrane review, family therapy was found to be useful particularly in difficult childhood asthma, however the small study samples limits the widespread recommendation of this therapy (Yorke and Shuldham, 2005).

Management of Acute Asthma

The management of acute asthma depends on the setting to which the individual presents (e.g., primary care versus hospital), age of the individual, and the individual's severity of acute asthma exacerbation. Acute asthma can present as moderate, severe, or life-threatening. Any individual presenting with features of acute severe or life-threatening asthma requires early hospital referral.

Treatment of Acute Asthma in Adults

Acute asthma is generally managed in the hospital setting. Local guidelines may govern the management of acute asthma so there may be variations in the treatment(s) used, however the mainstay of treatment generally includes: oxygen, SABA, corticosteroids, and SAMA.

Many individuals are hypoxemic, and emergency oxygen should be given as soon as possible (Rebuck and Read, 1971). High-dose SABAs (e.g., salbutamol or terbutaline) should be given via metered-dose inhalers through large volume spacers to quickly relieve bronchospasm, unless asthma is life-threatening in which nebulized or intravenous administration may be required (Cates et al., 2006; Travers et al., 2001).

All individuals should be given corticosteroids as these have been proven to reduce mortality, relapses and re-admission, and requirements for SABA treatment. These should be given early for better outcomes (Rowe et al., 2007). Corticosteroids can be given as tablets or parenterally, and during the course, ICS should be continued as usual. The corticosteroid courses used for acute asthma exacerbations can generally be stopped abruptly without tapering, as the courses tend to be time-limited and less than 3 weeks' duration, and the individual will continue to be on ICS treatment (Hatton et al., 1995).

Nebulized SAMA should be considered in individuals with acute severe or life-threatening asthma, or if the individual has had a poor initial response to the SABA treatment. The addition of SAMA has been shown to lead to greater bronchodilation than SABA alone, and faster recovery with shorter admission time (Rodrigo et al., 1999).

Treatment of Acute Asthma in Children

Like adults, children can present with different levels of severity of asthma exacerbations, ranging from moderate to acute severe or life-threatening. Treatment decisions will depend on the severity of the airways obstruction based on presentation and clinical signs. The mainstay of acute treatment should include oxygen, inhaled SABA, corticosteroids, and SAMA.

Inhaled SABAs are considered first-line treatment for acute asthma in children aged 2 years or older (Schuh et al., 1999). As with adults, these should be given via a pressured metered-dose inhaler with spacer; the nebulized route is associated with a higher risk of side effects such as tachycardia and hypoxia (Cates et al., 2006). Any LABA in children should be discontinued if SABA treatment is needed more frequently than every 4 hours. Oral corticosteroids should be given early on as use can reduce risk of relapse, with benefits seen within 3–4 hours (Rowe et al., 2001). As in adults, there is no need to taper the corticosteroid course, unless treatment duration exceeds 14 days (Hatton et al., 1995). Any usual controller ICS treatment should be continued during an asthma exacerbation.

Nebulized SAMA may be used in addition to SABA treatment in children with severe or life-threatening asthma, if there is a poor response to SABA treatment alone (Plotnick and Ducharme, 2000); this should be started early in the course of treatment for maximal benefit.

Monitoring of Treatment

During acute treatment, close monitoring of the following should be undertaken: PEF, oxygen saturation, blood gases, heart rate, serum potassium, and blood glucose (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2016).

For individuals on prolonged or recurrent courses of oral steroids (e.g., recurrent frequent asthma flare-ups), the overall steroid load should be monitored. Monitoring should include blood pressure, urine or serum blood sugar, cholesterol, bone mineral density (in adults and children >5 years), growth (height/weight in children), cataracts, or glaucoma (adults).

What's Coming Up in Pharmacological Management

Immunotherapy

There have been recent studies investigating the use of subcutaneous and sublingual allergen immunotherapy (SCIT and SLIT). These involving administration of increasing doses of extracts of various allergens (e.g., house dust mite, grass pollen, cat/dog allergen, moulds). These may have benefits in reducing symptoms and bronchial hyperreactivity (Abramson et al., 2010), however few studies have compared immunotherapy with ICS versus immunotherapy as add-on treatment to ICS, so it remains unknown where this may fit in the asthma treatment pathway. Furthermore, reported side effects are frequent with SCIT with a high possibility of a local adverse reaction or systemic reaction such anaphylaxis, asthma, urticaria, rhinitis, or a combination of these. While SLIT is associated with fewer adverse reactions, the benefits in terms of asthma control remain small (Calamita et al., 2006).

Changes in Management of Acute Symptoms (Reliever Treatment)

The recent 2017 Lancet Commission has suggested a move away from use of SABA monotherapy as reliever treatment, and instead to use a combination ICS/SABA inhaler in all but the mildest of asthma cases (Pavord et al., 2017). This represents a significant shift in the treatment of asthma and is a step to reducing the increasing overreliance and overuse of SABA currently seen. How this will be implemented in practice in the coming years remains to be seen.

The Role of the Pharmacist in Asthma Management

Pharmacists are highly accessible health care professionals and are recognized as medicines experts. Within a hospital or other secondary/tertiary care setting, pharmacists play an essential role in the multidisciplinary team to optimize asthma management. In primary care, community pharmacists are highly accessible (Bush et al., 2009; International Pharmaceutical Federation, 2009), and as such are ideally placed to play a significant role in asthma management (Bollmeier and Prosser, 2014; Garcia-Cardenas et al., 2016; Saini et al., 2011a). The accessibility of pharmacists in supporting patients is particularly beneficial due to the intermittent nature of the condition and the high degree of patient self-management required. Quality use of medicines (QUM) is an essential element to controlling symptoms and reducing risk of exacerbations in asthma and pharmacists are critical members of the health care team to ensure access to appropriate pharmacotherapy, misuse and suboptimal use of medications abounds (Murphy et al., 2012; Price et al., 2014; Rabe et al., 2000, 2004).

Evidence for the Role of the Pharmacist in Asthma Management

Research has demonstrated the capacity and potential of pharmacists to improve clinical, humanistic, and economic outcomes for asthma patients (Benavides et al., 2009; Bollmeier and Prosser, 2014; Garcia-Cardenas et al., 2016). Pharmacist-led interventions to improve asthma management have focused on areas such as patient education, drug therapy monitoring, and supporting patient self-management. The benefit of these pharmacist-led interventions have been demonstrated by improvements in measures of asthma severity, asthma symptoms, lung function, quality of life, ED visits, hospitalizations, and direct and indirect cost savings (Benavides et al., 2009). More recent research has investigated the benefit of comprehensive interventions in the form of community pharmacy-based asthma programs (Bollmeier and Prosser, 2014). There has been increasing acknowledgement that pharmacists have an important role to play in chronic disease-state management (DSM) programs, which use a collaborative approach and put the patient at the center of their own care (Saini et al., 2011a). Positive outcomes from DSM asthma programs have included improvements in patient asthma knowledge scores, inhaler device technique, quality of life, asthma control, symptom scores, and lung function (Bollmeier and Prosser, 2014). What is clear, from the research at this point in time, is the immense potential that pharmacists have to influence outcomes (Garcia-Cardenas et al., 2016).

Currently, pharmacists already play an important role in the provision of medications to treat asthma, but there is little evidence about routine clinical practice in the community pharmacy setting (Benavides et al., 2009). While there are examples of excellence and expanded clinical roles in asthma in pharmacy, generally the indications are that current practice is variable, suboptimal and there is a lack of translation of research findings (Kritikos et al., 2010; Royal Pharmaceutical Society, 2013; Schneider et al., 2009, 2011). Research has highlighted deficiencies in pharmacy practice in the areas of patient assessment, medication counseling, demonstration of inhaler technique as well as a lack of pharmacist engagement with patients (Basheti et al., 2009; Schneider et al., 2009; Takemura et al., 2012). Efforts have also been made to examine the underlying reasons for suboptimal asthma management and patient care by pharmacists. Identified barriers to optimal care of asthma patients in the pharmacy setting include lack of knowledge, lack of time, lack of confidence, patient-related factors, and environmental issues (Basheti et al., 2009; Bollmeier and Prosser, 2014; Kritikos et al., 2010; Watkins et al., 2016b). Another issue identified in the literature on pharmacist involvement in asthma management is the lack of participation in collaborative care. Research in asthma management has shown that pharmacists do not routinely communicate with other members of the primary health care team (Cairns and Everleigh, 2000; Emmerton et al., 2012). The advantages to patients of collaborative care are well established (Gums et al., 2014), but have been difficult to foster in the primary health care setting. Jargon, such as "silos," relate not only to medical practitioners but also to pharmacists and patients may also play a role in undermining health professional collaborative care (Cheong et al., 2013). It could be argued that optimal asthma management will only be achieved when collaborative care issues have been addressed.

Encouragingly, research has shown that patients have a high degree of satisfaction with expanded asthma services provided by community pharmacists (beyond the current offering which primarily revolves around medication supply) (Armour et al., 2007; Bereznicki et al., 2008a,b; Kritikos et al., 2007; Naik-Panvelkar et al., 2010; Saini et al., 2004; Smith et al., 2007). This demonstrates patient receptivity and the potential to develop this role in a more consistent and sustainable way, if some of the barriers to practice change can be addressed.

Expanded services that have been identified as opportunities for greater participation by pharmacists in asthma management (George et al., 2010; Mehuys et al., 2008; Saini et al., 2011a) include: patient screening to facilitate early intervention (Armour et al., 2011; Bereznicki et al., 2008b; Fathima et al., 2013; Saini et al., 2011a; van Boven et al., 2013); patient education (Saini et al., 2011b); inhaler technique education and review (Basheti et al., 2005, 2007; Takemura et al., 2012); self-management education and support (Barbanel et al., 2003; Dolovich et al., 2007; Kheir et al., 2001; Smith et al., 2007); improving quality use of medication and adherence (Bereznicki et al., 2008b; Elliott et al., 2008; Herborg et al., 2001); comprehensive disease state management (Armour et al., 2007; Mangiapane et al., 2005); health promotion and servicing rural and remote populations where access to services is limited (Kritikos et al., 2005; Shah et al., 2005). Also relevant are contributions to smoking cessation and management of comorbid conditions (Brown et al., 2012).

To unlock the potential of pharmacists, more effort needs to go into the translation of research through implementation science. It is recognized that medication management and patient health outcomes in asthma are suboptimal. It remains to be seen whether the potential of pharmacists can be realized to affect change in outcomes.

Medication Management by Pharmacists in Asthma

Pharmacists are medication experts (Kehrer et al., 2013), are part of the medication supply chain and participate in health referral pathways. These attributes and functions determine they are integral in asthma management. Medications are the mainstay of treatment and can effectively control the symptomatic manifestations of this chronic, incurable disease, in the majority of patients (Bateman et al., 2004; Global Initiative for Asthma, 2018). Inappropriate use of medication has been found to be a key issue in many of the instances of suboptimal asthma management (Al-Jahdali et al., 2013; Garcia-Cardenas et al., 2016; Reddel et al., 2015). There are several areas where pharmacists can intervene or support patients to ensure QUM in asthma management.

Medication Supply

Chronic conditions such as asthma require that patients have continual and reliable access to high quality medications. However, in many countries and certain socio-economic demographics accessibility to medications continues to be a problem. Access to high quality asthma medications is a multifactorial problem that requires initiatives and funding at a global and national level to be addressed (The Global Asthma Network, 2014). Pharmacists form part of a global workforce that facilitates patient access to medications and health care advice (International Pharmaceutical Federation, 2017). Maintaining a strong global network of pharmacists to equitably and adequately service the ongoing medication needs of patients with asthma is crucial to reducing the individual and societal burden of the disease.

Medication Education

Patient education is crucial due to the combination of medications generally used to manage the condition. Patients can be overwhelmed with information at the time of diagnosis and require repeated educational opportunities to assimilate the required knowledge to be proactive in the management of their health.

Many patients remain unaware of the role and benefits of ICS as controller therapy (Menckeberg et al., 2012) and have detrimental beliefs about their potential for side effects (for example, concerns over effects on growth in children). Overreliance on reliever medications (SABAs) is also well documented and puts patients at risk of severe exacerbations and even death (Levy, 2014; Partridge et al., 2006; Reddel et al., 2015; Sawyer and Fardy, 2003). Similarly use of LABA without ICS is contraindicated and associated with increased mortality and requires intervention (Armour et al., 2011; Levy, 2014; Reddel et al., 2015; Watkins et al., 2016a). Patients need to be provided with the knowledge of how to use medication in an emergency first aid situation, which can be life-saving. Patients also need to be aware of ways to minimize side effects of medications such as rinsing their mouth and use of spacer devices.

The knowledge and belief of patients are intrinsically linked to their health behaviors and pharmacists are in an ideal position to engage with individuals to support appropriate medication self-management. This is particularly relevant to situations where patients may not necessarily be seeking health professional assistance or advice, or in areas where access to health services may be limited. Inappropriate medication management identified by pharmacists requires intervention. It also requires communication and collaboration with other health professionals and the patient.

Medication Dose Monitoring

The characteristic disease variability in asthma requires frequent adjustments to pharmacotherapy using a control-based asthma management cycle that involves assessment, treatment, and review on a continual basis. Medication is stepped up or down depending on the symptom control and assessments of future exacerbation risk (**Fig. 1**) (Global Initiative for Asthma, 2018). Pharmacists can play a role in ensuring that patients maintain good asthma control using the minimal effective doses of medications, thus reducing the potential for unwanted side effects and limiting unnecessary overuse of medication (Watkins et al., 2016a).

Medication Adherence

Pharmacists have the capability to monitor medication adherence, not only due to their regular contact with patients, but also through their access to medication records and data mining (Bereznicki et al., 2008a; van Boven et al., 2013). Poor adherence to prescribed medication regimens is a complex problem and a major cause of poor clinical outcomes in asthma (Bender, 2002; Saini et al., 2011b).

Having uncovered any adherence issues, the challenge is for the pharmacist to resolve what predicates patient behaviors. Lack of medication adherence can be intentional or unintentional. To provide appropriate patient-centered care, and resolve adherence issues that may undermine patient health, the pharmacist needs to appreciate the patient perspective and gain insight into a patient's medication beliefs (Gadkari and McHorney, 2012). The strategies that pharmacists can use to promote patient medication adherence are as many and varied as the reasons for patient nonadherence. Strategies may include suggesting simplified medication regimens. For instance, reducing the types of devices a patient uses, utilizing combined medication formulations or formulations that allow for lower dosing frequencies. Education can be used to address any misconceptions patients may have about the disease and the medications used to treat it. Even so called "unintentional nonadherence" has been shown to relate to patient's perceptions around the necessity and importance of the medication (Gadkari and McHorney, 2012). Patients may also be struggling psychologically with the diagnosis, motivation, and self-efficacy to manage the condition. Pharmacists can directly address such issues or refer patients for appropriate care from other health professionals. Some patient adherence issues may relate to financial considerations. Pharmacists are well placed to suggest cost effective therapeutic solutions (such as generic preparations) or inform patients of medication subsidy systems they can access. Finally, some patients can benefit from pharmacists suggesting or offering organizational strategies which encourage routines that assist medication adherence. Newer digital technologies such as medication reminder texts, electronic adherence monitoring, smart phone applications and online medication ordering, and delivery have the potential to improve medication adherence (Chan et al., 2013; Tran et al., 2014).

Inhaler Technique Assessment and Education

In terms of QUM, one of the major roles for pharmacists is to assess and educate patients with respiratory diseases (such as asthma) on correct inhaler device use. The majority of medications used to treat asthma are inhaled medications and incorrect use is detrimental to patient health and results in increased health care costs (Inhaler Error Steering Committee et al., 2013; Levy et al., 2016). It is important that patients are provided a suitable device and educated to use the device correctly maximizes the therapeutic benefits obtained from pharmacotherapy. There are startling statistics demonstrating the urgent need to address the issue of poor inhaler technique. Research indicates that up to 90% of patients use their inhalers incorrectly (Levy et al., 2016). Given their role in medication supply, pharmacists may be the last health professional to have access to a patient before they commence using a medication. Ensuring inhaler technique is correct is therefore a key responsibility of the pharmacist and an area where they can play a significant role in improving patient outcomes. However, it is incumbent on pharmacists to have the ability to demonstrate correct inhaler use. Across all health professional disciplines involved in inhaler training there is evidence that between 15% and 69% do not have the skills or training to correctly demonstrate inhaler devices (Levy et al., 2016). Furthermore, these skills can decline over time. An effective way for pharmacists to maintain skills is to be routinely involved in counseling patients on inhaler technique (Basheti et al., 2009).

An important aspect of assisting with inhaler technique is ensuring patients' therapy is maximized through the selection of an appropriate device. Pharmacists are required to understand the various strengths and limitations associated with different devices. For instance, a dry powder device may be a poor choice for a patient with an exacerbation of asthma and low inspiratory flow rate. A metered dose inhaler may be inappropriate for a patient with arthritis and dexterity issues or cognitive impairment. The appropriateness of devices may change over time and pharmacists are appropriately placed to make interventions when necessary. Pharmacists can also encourage patients to use spacer devices to improve lung drug deposition and efficacy. Advice on how to appropriately care for devices such as spacers is another role for pharmacists.

Disease Management by Pharmacists in Asthma

Patients require a holistic understanding of asthma to self-manage the condition appropriately. Pharmacists can play a significant role in, not only educating patients, but by facilitating "patient activation." Education can provide patients with "technical know-how." However, assisting patients to actively and effectively self-manage their condition requires imparting the motivation, courage, skills, ability to problem solve, make decisions, and troubleshoot the condition (Saini et al., 2011b). There is evidence to suggest that patients display asthma acceptance and the limitations asthma puts on their lives rather than managing the condition fully (National Asthma Council Australia et al., 2010). Pharmacists can play a role in solving the problem.

Assessing Asthma Control

The goals of treating asthma include managing symptoms and improving quality of life. Essential to achieving these goals is maintaining good asthma control. Pharmacists have the ability to assess patient asthma control at every encounter which allows for early referral of patients whose condition may be deteriorating. Overuse of SABA is a significant indicator of poor control that pharmacists can identify when patients present with medication requests. The importance of this was highlighted by the National Review of Asthma Deaths (NRAD) in the UK undertaken in 2014. There was evidence of overprescribing of relievers in the preceding year in approximately 40% of the deaths reviewed. In 4% of cases this overuse was extreme and involved prescription of more than 50 reliever inhalers in a 12-month period (Levy, 2014).

Along with considering reliever use, there are a variety of easy to administer tools that pharmacists can use to assist in the assessment of patient asthma control, such as the asthma control test (ACT) (Thomas et al., 2009). Pharmacists can also educate patients on the importance and how to monitor their own asthma control. Symptom recognition is an important way that patients can learn to respond to their asthma.

Supporting Proactive Self-Management and Use of Written Asthma Action Plans

Written asthma action plans are generally written by medical practitioners and the role of the pharmacist is to encourage regular medical review, ownership and appropriate use of a written asthma action plan. However, it is feasible in the future that pharmacists could expand their role and be involved in the development of asthma action plans in collaboration or consultation with medical practitioners (Watkins et al., 2016a).

Assessing Trigger Factors

Pharmacists can play an active role in increasing patient awareness of asthma triggers and, where possible and appropriate, provide advice on how to reduce exposure and mitigate risk. Respiratory infections are a common trigger for asthma and difficult for patients to avoid. However, pharmacists can recommend and/or administer influenza and pneumonia vaccinations and encourage hygiene to reduce viral or bacterial transmission. Advice to patients to avoid cigarette smoke and passive smoking can confer health benefits beyond those related to asthma management.

Assessing Lung Function

Lung function testing is not diagnostic in asthma and does not correlate well with asthma symptoms in either adults or children. However, spirometry (which is the gold standard in lung function testing) can be both a useful diagnostic tool and mechanism for evaluating future exacerbation risk in asthma (see "Diagnosis" section for further detail). Patients with a low forced expiratory volume in 1 second (FEV_1) are more at risk of exacerbations. The recommendation in asthma guidelines is that lung function should be assessed at diagnosis of asthma, once treatment has been initiated, and 3–6 months after the initiation of a controller medication to ascertain a measure of patient "best lung function." Periodic testing at intervals of every one or two years is recommended thereafter (Global Initiative for Asthma, 2018). Historically lung spirometry has been performed in hospitals by specialist technicians. However, technological advances have seen the development of more cost effective and portable equipment and it is now offered in medical practices and usually undertaken by nurses or medical assistants. This also makes it a service that is well suited to community pharmacy practice. There is evidence that pharmacists with specialized training are capable of offering quality spirometry testing and this is likely to be an area of expanded practice is the near future (Cawley and Warning, 2015).

Another form of lung function testing that patients can undertake as part of asthma self-management is PEF monitoring. PEF can be especially beneficial for patients who have trouble gauging asthma control based on symptoms, experience intermittent asthma or need to monitor response to changed treatment. Pharmacists have a role to play in assisting patients to effectively use PEF in conjunction with symptom monitoring and written asthma management plans as part of proactive self-management.

Managing Complex Patients

The medication and disease management skills of pharmacists are at their most valuable when assisting patients with complex health needs. These complexities may relate to certain patient populations (e.g., asthma phenotypes, pregnancy, exercise-induced asthma), multiple chronic conditions, multiple care providers, polypharmacy, frequent exacerbations of asthma, and limitations to daily functioning. There is increasing recognition that asthma is a heterogeneous disease and that different phenotypes exist (see "Etiology and Clinical Presentation" sections) (Global Initiative for Asthma, 2018). Some phenotypes may be resistant to standard therapies making management challenging and the input of pharmacists invaluable, especially in collaborative patient management.

Asthma is often considered to be a disease of childhood, however there is a high prevalence of older adults (aged over 65 years) that have asthma (Yawn and Han, 2017). Many of these patients have comorbid conditions that can directly impact on asthma symptom management and therapeutic choices due to drug-disease or drug-drug interactions. Lung function declines with age and patients may confuse asthma symptoms with aging or other comorbidities. Pharmacists can play a role in the management of conditions such as rhinosinusitis, obesity, psychiatric disorders, and gastro-esophageal reflux disease, all of which can worsen asthma symptoms. Drugs including aspirin (and other nonsteroidal anti-inflammatory drugs), beta-adrenoceptor antagonists (beta blockers), and angiotensin converting enzyme (ACE) inhibitors can be problematic or contraindicated in some patients with asthma. It has even been demonstrated that nonselective beta-antagonist eye drops can impact on lung function (Morales et al., 2016). Elderly patients with asthma may be more susceptible from adverse drug reactions from asthma treatments, especially the cardio-toxic effects of beta-2-agonists and systemic effects from corticosteroids (Global Initiative for Asthma, 2018).

Management of patients who have mixed respiratory diseases can be particularly difficult. It is possible for patients to present with chronic respiratory symptoms and features characteristic of both asthma and COPD. This is particularly true in smokers and the elderly. Patients with mixed etiology disease tend to have more exacerbations, a reduced quality of life and represent a greater burden on health care resources (Global Initiative for Asthma, 2018). Given the detrimental effect smoking has on lung function another crucial role for pharmacists in asthma management is supporting smoking cessation, both through psychological support and provision of nicotine replacement therapy.

Asthma control in pregnancy can often change for the better or worse and throughout pregnancy. Exacerbations can have consequences for the baby (preterm delivery, low birth weight, increased perinatal mortality) and mother (preeclampsia) and need to be avoided through vigilant supported management (Global Initiative for Asthma, 2018).

It is important to encourage exercise in patients with asthma, but many will develop asthma symptom during physical activity. Exercise-induced asthma can be successfully managed with appropriate pharmacotherapy. Pharmacists can play a role in supporting patients to participate in exercise.

Pharmacists can play a significant role in the management of complex patients through extended consultations, pharmaceutical care and disease management programs. In many countries pharmacists are now routinely involved in higher level clinical services such as medication use reviews and DSM programs which support this form of practice (International Pharmaceutical Federation, 2017) (**Fig. 4**).

Health Promotion Activities by Pharmacists

Pharmacists are uniquely placed to play a significant role in health promotion. This is because they have regular contact with a large proportion of the population on a regular basis. They see sick and healthy people and encounter people not necessarily actively seeking health care advice. Pharmacists are highly trusted health care professionals and this also enhances their ability to reinforce health messages (Anderson, 2000).

While promoting health is part of the accepted role of pharmacists in their daily interactions with patients they also participate in more structured health promotional events. Pharmacists may participate as agents for governments and not for profit health agencies or even self-direct health promotion activities. For instance, the first Tuesday in May has been designated as World Asthma Day. It is an annual event to raise awareness about asthma globally and was established by the Global Initiative for Asthma (GINA) in 1998. Pharmacists will often use such events to focus their health promotional activities. However, one of the barriers to expanding the health promotion role of pharmacists is the limited opportunities for remuneration.

Remuneration and Funding for Service Delivery

The potential scope of practice for pharmacists in asthma management is significant and could have a profound impact on patient health outcomes and the societal burden associated with asthma. The role of the pharmacist and pharmacies are essential to the

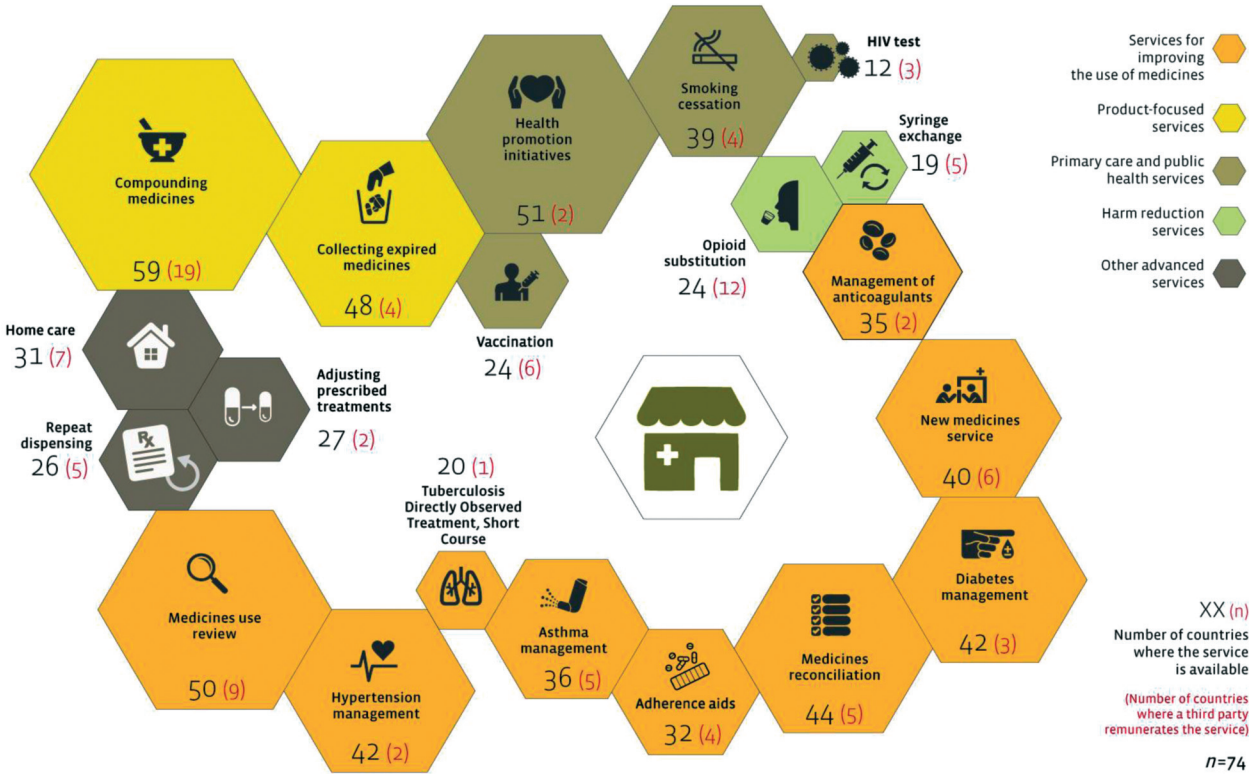

Figure 4 Services community pharmacies are providing and being remunerated for beyond dispensing. *Source: Reproduced with permission from the International Pharmacy Federation.*

health system framework of every country. However, a report by the International Pharmacy Federation from 2015 identified that there is worldwide concern over the long-term financial viability of the community pharmacy sector. The report also noted that despite the shift to a more service-focused clinical practice model, remuneration has remained predominately product-focused. Income still largely depends on dispensing-related activities with funding from third party payers. The issue is that these income sources are decreasing. There is an urgent need to identify other revenue sources to maintain high quality, comprehensive pharmacy services in a sustainable way (International Pharmaceutical Federation, 2015).

At this point in time there is limited financial recognition for many of the clinical services provided by pharmacists for asthma management. This results in ad hoc, inconsistent service provision and impedes the involvement of pharmacists in expanded clinical practices where they could potentially improve patient health and health service utilization. Fig. 4 gives a global picture of service provision and remuneration for clinical services by pharmacists. For instance, pharmacists in 36 countries undertake asthma management services, but remuneration for that service only occurs in five countries (International Pharmaceutical Federation, 2017). The picture is similar across the breadth of clinical services outlined in Fig. 4.

Without a more effective remuneration model it is unlikely that pharmacists will realize their potential in playing a role in improving asthma, and indeed any health outcomes. There are few financial incentives for pharmacists to develop and use higher level clinical skills. It is a testimony to the commitment and dedication of pharmacists that they have pursued clinical service provision and play the important role that they already do in patient health with so few financial incentives.

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Management of Respiratory Disorders and the Pharmacist's Role: COPD

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Foreword

This chapter draws information from the international Global Initiative of Obstructive Lung Disease (GOLD) guidelines—a widely distributed report updated on a yearly basis to incorporate new evidence for COPD prevention, diagnosis, and management (Global Initiative for Obstructive Lung Disease, 2018). In addition, many regional guidelines on COPD management have been developed by various thoracic societies and professional organizations, which inform practice in that region or a particular country.

Learning Outcomes

On completion of this chapter you should be able to:

- Define COPD and outline its pathophysiology, including risk factors, and the changes in airways and other systems;
- Characterize the symptoms of COPD (undiagnosed and/or poorly controlled) and recognize when to make referrals to doctors for diagnosis, and further assessment/management;
- Compare and contrast the pathophysiology, diagnosis, and management of COPD and asthma;
- Understand asthma-COPD overlap (ACO) and when to make referrals to specialist physicians;
- Understand the pharmacological and non-pharmacological management of both stable COPD and COPD exacerbations, including preventive measures to slow the progression of the disease, management of symptoms, and reversal of the underlying pathophysiology; and
- Apply the knowledge in optimizing the management of patients at risk and/or with COPD through education, feedback, follow-up, and promotion of self-management.

Case Study 1

Mr. Trafalgar is a 40-year-old construction worker who visits Meadow Inn Pharmacy occasionally to buy an over-the-counter (OTC) cough suppressant. Mr. Trafalgar came to the pharmacy this morning complaining of occasional shortness of breath (SOB) and an annoying cough, which occurs most commonly on cold mornings and when he walks around the construction site. In addition to the cough medicine, Mr. Trafalgar wanted something for his breathlessness. The pharmacy assistant suggested that Mr. Trafalgar talks to the pharmacist on duty. Mr. Trafalgar told the pharmacist that he becomes breathless after climbing even a single flight of stairs. He is unable to lift anything heavy either, due to lack of breath. He had two chest infections during last winter, both of which required a course of antibiotics.

Mr. Trafalgar has smoked heavily for 25 years (on average 25 cigarettes per day), but has cut down to 10 per day in the last six months. He experiences frequent bouts of cough which he often treats using OTC cough-and-cold preparations. He believes he has "smoker's cough," which is further aggravated by dust inhalation at the construction site, but has never considered quitting smoking even though he knows that smoking may cause cancer. Based on the history, the pharmacist wants to check whether Mr. Trafalgar has already developed COPD.

Chronic Obstructive Pulmonary Disease

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*" (Global Initiative for Obstructive Lung Disease, 2018). COPD is a heterogeneous condition, with multiple clinical features and comorbidities, which are known to increase its morbidity and mortality. COPD is sometimes referred to as chronic obstructive airways disease (COAD) or chronic obstructive

lung disease (COLD). Some definitions of COPD in the past have incorrectly used the terms "*emphysema*" and "*chronic bronchitis*"; however, the GOLD reports (first report in 2001) have not used those terms in defining COPD. Emphysema, characterized by alveolar dilatation and destruction, is a pathological diagnosis and describes only one of the several structural abnormalities present in patients with COPD (Global Initiative for Obstructive Lung Disease, 2018). Chronic bronchitis refers to the presence of daily cough and sputum production for at least 3 months each year in two or more consecutive years, but is present in only a minority of subjects with an existing diagnosis of COPD when this definition is used (Global Initiative for Obstructive Lung Disease, 2018; Kim et al., 2015).

Burden of COPD

COPD causes approximately three million deaths annually (5.6% of all deaths) globally and is the fourth leading cause of global mortality, behind ischemic heart disease, stroke, and lower respiratory infections (Lozano et al., 2012). In 2015, deaths from COPD (3.2 million globally) were eight times more common than deaths from asthma. Globally, COPD affected 104.7 million males and 69.7 million females in 2015 and was ranked eighth (2.6% of global disability adjusted life years [DALYs]) among the 315 global burden of disease causes (GBD Chronic Respiratory Disease Collaborators, 2017). COPD also imposes significant social and economic burden on health systems and society. In 2010, the cost of COPD in the United States of America was approximately $50 billion, which included $20 billion in indirect costs and $30 billion in direct health care expenditures (Guarascio et al., 2013). Burden data and prevalence rates of COPD vary across countries due to differences in survey methods, diagnostic criteria, and analytical approaches used. Prevalence of COPD is known to be higher in smokers and ex-smokers compared to nonsmokers, in those ≥40 years of age compared to those <40 years, and in men compared to women (GBD Chronic Respiratory Disease Collaborators, 2017). Deaths due to COPD are projected to increase to 4.5 million per year (6.5% of all deaths) by 2030 (World Health Organization, 2012).

Causes of COPD

Globally, chronic exposure to tobacco smoke is the most important, preventable risk factor in the development of COPD (Fletcher and Peto, 1977). In high-income countries, smoking and second-hand smoke are the most important risk factors for COPD, whereas environmental risks and occupational risks contribute to significant amount of the burden in lower-income countries. In susceptible people, smoking causes irreversible obstructive changes in the respiratory system, earlier disability and death (Fletcher and Peto, 1977). Smoking increases the rate of decline of lung function and causes airflow obstruction. The Framingham Offspring cohort study of those who had two or more valid spirometry measurements during follow-up (n = 4391; baseline age ranged from 13 to 71 years, with a median follow-up time of 23 years), found that 33.0% of continuous-smoker males and 24.2% of continuous-smoker females developed airflow obstruction during follow-up, compared to 7.4% of men and 5.6% of women, who were never-smokers (Kohansal et al., 2009). Among continuous smokers, lung function (forced expiratory volume in 1 second—FEV_1; measured using spirometry) declined both in males (from 8 to 63 mL/year) and females (from 14 to 49 mL/year) (Kohansal et al., 2009).

Other common etiologies of COPD include exposure to biomass fuel, air pollutants, or occupational dusts and fumes; chronic asthma; impaired lung growth; and genetic predisposition (Omland et al., 2014; Stoller and Aboussouan, 2005). An international cohort study of more than 4000 young adults without asthma who participated in the European Community Respiratory Health Survey found that smoking accounted for 29%–39% of the new cases of COPD (incidence rate of 2.88 cases/1000/year during follow-up) (de Marco et al., 2011). Airway hyperresponsiveness was the second strongest risk factor (15%–17% of new cases); other determinants were respiratory infections in childhood and a family history of asthma (de Marco et al., 2011).

In many middle-low income countries, biomass and coal are used as the main sources of energy for cooking, heating, and other household needs (Assad et al., 2015). Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly ventilated dwellings can lead to very high levels of indoor air pollution (Assad et al., 2015; Orozco-Levi et al., 2006). Outdoor air pollution can also have a significant impact on lung health. The inverse relationship between risk of developing COPD and socio-economic status may be a confounding effect of exposures to indoor and outdoor air pollutants, poor nutrition, infections, or other factors related to low socioeconomic status (Gershon et al., 2011).

Airway hyperresponsiveness is a major risk factor for COPD and an indicator of risk of excess decline in lung function in those with COPD (de Marco et al., 2011). In a cohort of more than 3000 adult subjects from Arizona (USA), those with physician-diagnosed asthma were found to have a 12-fold higher risk of acquiring COPD compared to those without asthma, after adjusting for smoking (Silva et al., 2004). Despite distinct differences present in the pathology of airflow limitation, inflammatory cells and mediators involved in asthma and COPD, distinguishing the two can be challenging in adults with a history of exposure to smoking, and a personal and/or family history of atopy. A subset of patients with airways disease may have features of both asthma and COPD (Leung and Sin, 2017).

Alpha-1 antitrypsin deficiency is a genetic disorder (SERPINA1 gene mutation is frequently implicated) that affects about one in 2000–5000 individuals (Stoller and Aboussouan, 2005). Alpha-1 antitrypsin is mainly produced in the liver and has a protective effect in the lungs by preventing proteolytic damage from neutrophil elastase (Stoller and Aboussouan, 2005). Serum levels less than 11 micromol/L (i.e., the serum protective threshold) increase the risk for emphysema in individuals (Stoller and Aboussouan, 2005).

Pathology of COPD

Lung inflammation occurs after inhalation of irritants such as smoke from combustible tobacco and biomass fuels. The chronic inflammatory response in patients with COPD causes pathological changes including parenchymal tissue destruction (from emphysema), and modifications to normal repair and defense mechanisms (from small airway fibrosis) (Hogg and Timens, 2009). Changes in the airways, lung parenchyma, and pulmonary vasculature lead to gas trapping and progressive airflow limitation.

Pathogenesis

The normal inflammatory response to inhalation of noxious particles appears to be modified in patients with COPD. It is not well understood what the mechanisms are for this amplified inflammation. Genetic factors may be involved in those with no history of smoking (e.g., those with alpha-1 antitrypsin deficiency). Oxidative stress, protease imbalance in the lungs, increased inflammatory cells and inflammatory mediators, autoantigens and changes in lung microbiome may play roles in the lung inflammation and the pathological changes characteristic of COPD (Global Initiative for Obstructive Lung Disease, 2018).

Pathophysiology

Decreased FEV_1 results from the chronic inflammation and narrowing of peripheral airways. Parenchymal tissue destruction (from emphysema) also contributes to airflow limitation and leads to reduced gas transfer. There may also be a loss of small airways, which may play a part in airflow limitation.

Characteristics of COPD include the following:

- Airflow limitation and gas trapping
  - Reduction in FEV_1 and FEV_1/FVC ratio dependent on extent of inflammation, fibrosis, and luminal exudates
  - Peripheral airway limitation progressively traps gas during expiration, ultimately leading to hyperinflation
  - Static hyperinflation reduces inspiratory capacity and is commonly associated with dynamic hyperinflation during episodes of exercise
- Gas exchange abnormalities
  - Abnormalities in gas exchange processes result in hypoxemia and hypercapnia
  - Gas transfer for oxygen and carbon dioxide worsens as disease progresses
  - Reduced ventilation may be due to reduced ventilator drive or increased dead space ventilation
  - Carbon dioxide retention can result when combined with reduced ventilation, due to increased effort to breathe because of severe limitation and hyperinflation coupled with ventilator muscle impairment
  - Abnormalities in alveolar ventilation and reduced pulmonary vascular bed worsen ventilation perfusion ratio (VA/Q)
- Mucous hypersecretion
  - Results in chronic productive cough
  - Chronic productive cough is characteristic of chronic bronchitis but is not always associated with airflow limitation; however, not all patients with COPD have symptomatic mucus hypersecretion
  - Chronic exposure to irritants causes increased goblet cell numbers and enlarged submucosal glands
- Pulmonary hypertension
  - Develops late in disease, mainly due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes in these arteries
  - Significant abnormalities in pulmonary microvascular blood flow are already seen in mild COPD and smokers susceptible to emphysema
  - An inflammatory response, similar to that in the airways, and endothelial cell dysfunction seen in vessels
  - Loss of pulmonary capillary bed in emphysema increases pressure in pulmonary circulation
  - Progressive pulmonary hypertension can lead to right ventricular hypertrophy and eventually right-sided cardiac failure
- Exacerbations
  - Are acute episodes of worsening symptoms
  - Triggered by respiratory infections due to bacteria or viruses (these may coexist), environmental pollutants, or unknown factors
  - Increased dyspnea due to increased hyperinflation and gas trapping with reduced expiratory flow; worsening of VA/Q abnormalities resulting in hypoxemia; increased airways inflammation
  - Conditions such as pneumonia, thromboembolism, and acute cardiac failure mimic or aggravate COPD exacerbations

Table 1 Key indicators for considering a diagnosis of COPD (Global Initiative for Obstructive Lung Disease, 2018)

Consider COPD and perform spirometry to confirm COPD diagnosis, if any of these indicators (especially multiple indicators) are present in an individual over 40 years.	
Dyspnea that is	Progressive over time
	Characteristically worse with exercise
	Persistent
Chronic cough	May be intermittent and may be unproductive
	Recurrent wheeze
Chronic sputum production	Any pattern of chronic sputum production
Recurrent lower respiratory tract infections	
History of risk factors	Genetics factors, congenital/developmental abnormalities
	Tobacco smoke
	Smoke from home cooking and heating fuels
	Occupational dusts, vapors, fumes, gases, and other chemicals
Family history of COPD and/or childhood factors	e.g., low birth weight, childhood respiratory infections

- Systemic features
  - Most patients with COPD have multiple comorbidities
  - Airflow limitation and hyperinflation affect cardiac function and gas exchange
  - Systemic circulation of inflammatory mediators may initiate or worsen conditions such as skeletal muscle wasting, cachexia, ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, and metabolic syndrome.

For more detailed explanation of pathological changes in COPD please refer to GOLD Report, Chapter 1: Definition and Overview, https://goldcopd.org/.

Diagnosis of COPD

Investigations for COPD should be considered in patients presenting with dyspnea, chronic cough (productive or unproductive), sputum production, and/or history of exposure to risk factors (**Table 1**). It is important to note that not all patients with airflow limitation present with symptoms. Likewise, not all patients with symptoms display airflow limitations. Patients usually seek health advice because of chronic respiratory symptoms or an acute respiratory episode.

Symptoms

Symptoms in COPD can vary from day-to-day. Dyspnea is a key symptom, and is usually the major cause of disability and anxiety associated with COPD. Dyspnea may be described differently by individuals. Some patients experience wheezing and chest tightness which can also vary between days. Chronic cough is usually the first and most disregarded symptom. Coughing may start as intermittent and progress, to being present every day and throughout the day. Chronic sputum production is hard to assess as not all patients expectorate it. Fatigue, weight loss, and anorexia are common in more severe cases of COPD.

Spirometry and Other Investigations

A detailed medical history (risk factor exposures, past medical history, family history, comorbidities, etc.), physical examination, and spirometry testing are necessary in new and already diagnosed patients. Spirometry is the "gold standard" for diagnosing airflow obstruction present in COPD.

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are important measures. COPD is confirmed by the presence of persistent airflow limitation (post-bronchodilator FEV_1/FVC ratio < 0.7).

Patients with COPD often have reductions in both FEV_1 and FVC (**Fig. 1**). Increase in FEV_1 greater than 400 mL following bronchodilator, may be suggestive of asthma, or coexisting asthma and COPD. However, degree of reversibility after administration of a short-acting bronchodilator or corticosteroids (i.e., volume of FEV_1 change or % change in FEV_1) is no longer recommended as it does not inform therapeutic decisions or differentiate an asthma diagnosis (Albert et al., 2012). If the post-bronchodilator FEV_1/FVC ratio is between 0.6 and 0.8, the result should be confirmed by repeat spirometry on a separate occasion (Schermer et al., 2016).

Two different criteria are used in practice for interpreting spirometry. The fixed cut-off ($FEV_1/FVC < 0.7$) method is relatively simple and is independent of reference values (i.e., comparisons with population values based on age, height, gender, and race). The lower limit of normal (LLN) method uses reference values for FEV_1/FVC based on the normal distribution of the healthy population; the bottom 5% is classified as abnormal. The fixed cut-off method may result in overdiagnosis of COPD in the elderly, and underdiagnosis in adults <45 years, especially in mild COPD.

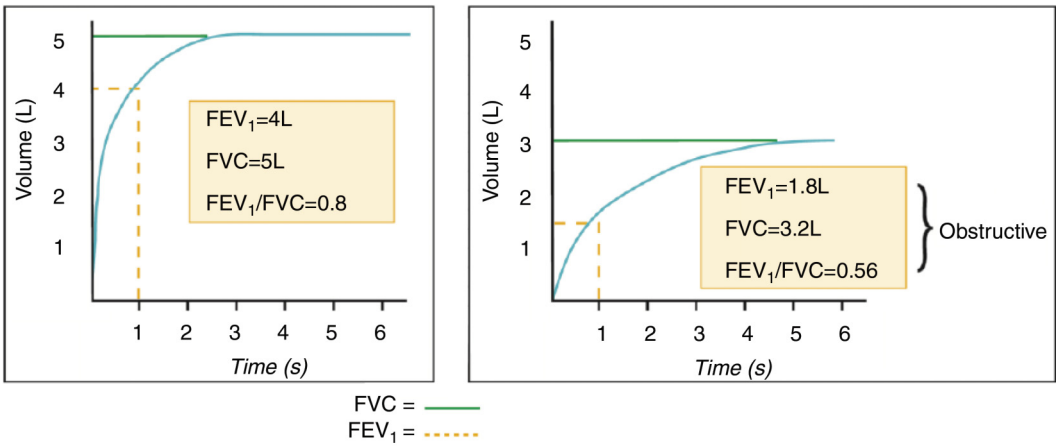

Figure 1 Normal vs. obstructive spirometry traces (Global Initiative for Obstructive Lung Disease, 2018).

Do you:	**Yes**	**No**
Have a new, persistent, or changed **cough**?		
Cough up **mucus, phlegm, or blood**?		
Get **breathless** more easily than others your age?		
Experience **chest tightness or wheeze**?		
Have frequent **chest infections**?		
Experience **chest pain, fatigue, or sudden weight loss**?		
If you answered yes to any of the above questions, your lung health could be at risk... particularly if you:		
Smoke or have ever smoked?		
Work or worked in a job that **exposed** you **to dust, gas, or fumes**?		

Figure 2 Lung Health Checklist (Lung Foundation Australia, 2018).

Correct performance of spirometry and careful interpretation of results are key to avoiding misdiagnosis. Regular calibration of the spirometer and periodical retraining in the technique and interpretation are essential for maintaining performance standards (Miller et al., 2005). Trained pharmacists can perform spirometry with acceptable repeatability based upon standards set by the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al., 2005).

Case-Finding

Screening spirometry in the general population is not currently recommended (Siu et al., 2016). However active case finding (i.e., spirometry testing in patients with symptoms and/or risk factors) is advocated. Community pharmacists are in an ideal position to be involved in case finding of COPD utilizing a combination of risk assessment/symptom questionnaires (e.g., Lung Health Checklist [from Lung Foundation Australia—Fig. 2], modified Medical Research Council [mMRC] questionnaire, COPD Assessment Test [CAT]) and microspirometry (Fathima et al., 2017).

It should be noted that these questionnaires identify symptoms of lung disease and not just specifically COPD. These questionnaires may also identify other respiratory conditions such as asthma, pulmonary hypertension, lung cancer, etc.; hence it is important to refer those with symptoms to a doctor/specialist for further investigation. Further investigations, including chest X-ray, hematology and biochemistry, complex lung function tests, exercise stress testing, and electrocardiography and echocardiography, may be necessary to confirm or exclude other conditions with a similar presentation to COPD (e.g., bronchiectasis, lung cancer, heart failure, and anemia).

The PiKo-6 and COPD-6 devices have been used to screen for airway obstruction (Fig. 3). These devices are good for targeted case finding to identify individuals for further investigative spirometry. Different FEV_1/FEV_6 cut-off values have been trialed in the clinical

(A) (B)

Figure 3 (A) COPD-6. (B) Piko-6.

setting. A FEV_1/FEV_6 <0.75 has been associated with an 86%–90% probability that a patient has abnormal lung function (Frith et al., 2011). It is advisable to then order spirometry to confirm the diagnosis.

Case Study 1

Let us revisit our patient, Mr. Trafalgar. The pharmacist used the Lung Health Checklist to gauge symptoms Mr. Trafalgar has been experiencing. The pharmacist also asked Mr. Trafalgar to blow into a microspirometer.

Based on the reading (FEV_1/FEV_6 = 0.69) and responses to the questionnaire (coughing, breathlessness), the pharmacist recommended that Mr. Trafalgar makes an appointment with the general practitioner (GP) to review his symptoms and lung health. The following week, the GP assessed Mr. Trafalgar's lung function by having him blow into a spirometer. His spirometry readings were:

FEV_1—pre-bronchodilator: 1.95 L (58%); post-bronchodilator: 1.98 L (59%)
FEV_1/FVC—pre-bronchodilator: 0.61; post-bronchodilator: 0.62

The GP told Mr. Trafalgar that his lungs were damaged from smoking and he had moderate COPD. The GP started Mr. Trafalgar on a once daily inhaler for his COPD, and a "when-required" inhaler for his acute SOB. The GP also asked Mr. Trafalgar to contact Quitline and the community pharmacist for some advice on quitting smoking.

Assessment of Severity

Assessment involves determining the degree of airflow limitation, impact of disease on health status, risk of future events (exacerbations, hospital admission, or death), to guide therapy. Disease severity should be regularly assessed after diagnosis to determine any necessary changes to medication regimens.

Assessment of the following areas is recommended:

- Presence and severity of airflow limitation after spirometry
- Nature and magnitude of symptoms
- Exacerbation history and future risk
- Comorbidities

Severity of Airflow Limitation

Airflow limitation can be classified into categories depending on severity (Table 2). There is weak correlation between FEV_1, symptoms and patient health status; so it is important that assessment of symptoms is undertaken in all patients.

Symptom Assessment

The mMRC (Celli et al., 2004, Mahler and Wells, 1988) dyspnea grade questionnaire is commonly used for measuring breathlessness as it predicts mortality risk and correlates well with other health status measures. It is a scale consisting of five statements describing levels of dyspnea based on the extent to which various physical activities precipitate breathlessness. Each statement corresponds to a grade; grade 0 indicates no dyspnea and grade 4 indicates severe dyspnea to the point of almost incapacity.

Other disease-specific questionnaires such as the Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and COPD Control Questionnaire (CCQ) are used for comprehensive symptom assessment in practice, but more in research. Details of these questionnaires are beyond the scope of this chapter.

Table 2 Classification of airflow limitation severity in COPD (based on post-bronchodilator spirometry) (Global Initiative for Obstructive Lung Disease, 2018)

In those with $FEV_1/FVC < 0.7$		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Table 3 Differences in asthma and COPD (Global Initiative for Obstructive Lung Disease, 2018)

Asthma	*COPD*
Onset early in life (often childhood)	Onset in mid-life
Symptoms vary from day-to-day	Symptoms slowly progressive
Symptoms worse at night/early morning	Long smoking history
Allergy, rhinitis, and/or eczema also present	
Family history of asthma	

Exacerbation Risk

A history of exacerbations is the best predictor of having frequent exacerbations (two or more exacerbations per year) (Hurst et al., 2010). More severe airflow limitation and higher blood eosinophil counts may also be associated with higher exacerbation rates.

Comorbidities

Patients with COPD usually present with multiple comorbidities. Having COPD may increase the risk for developing other diseases. Comorbidities such as cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancers need to be considered (may still be undiagnosed) and should be managed appropriately. Suboptimal management of comorbidities may affect mortality and hospitalizations (Global Initiative for Obstructive Lung Disease, 2018).

Combined Assessment—ABCD Assessment Tool

The GOLD recommends the use of the ABCD assessment tool (Vogelmeier et al., 2017, Global Initiative for Obstructive Lung Disease, 2018) which takes into account spirometry-based classifications, exacerbation history, patient reported symptom severity, and risk of exacerbations (CAT and mMRC) to understand the impact of COPD on an individual patient. This tool acknowledges that severity of COPD may differ between two patients despite having the same FEV_1 % predicted value.

Other Investigations

The World Health Organization recommends alpha-1 antitrypsin deficiency screening to all patients with a diagnosis of COPD (World Health Organisation, 1997). Chest X-ray, lung volumes and diffusing capacity, oximetry and arterial blood gas measurement, exercise/physical activity testing, and investigations to exclude differential diagnoses (e.g., bronchiectasis, pulmonary fibrosis, tuberculosis) may be considered during work-up of a patient.

Asthma-COPD Overlap

Both asthma and COPD are associated with chronic inflammation of the airways, which may manifest similar symptoms. However, the pathology of airflow limitation and inflammatory cells and mediators involved are different in the two conditions (**Table 3**).

There is a subset of adults with features of both asthma and COPD, which has been controversially termed asthma-COPD overlap (ACO). ACO is not a single, well-defined entity, but includes a range of airway disease phenotypes with different causal mechanisms (see https://assets.nationalasthma.org.au/resources/Asthma-COPD-overlap-info-paper-HP.pdf). It can develop in any smoker, ex-smoker, or nonsmoker, and tends to be worse in the elderly. Patients with ACO have more symptoms, more flare-ups/exacerbations of greater severity, worse quality of life, worse lung function despite lower tobacco exposure, more rapid decline in lung function, a greater need for health care use, and higher mortality rates (Reddel, 2015).

ACO should be considered in adults when they have:

- a history of asthma or have asthma-like symptoms, and
- spirometry before and after bronchodilator shows expiratory airflow limitation that is not completely reversible.

Diagnosis of ACO is based on the probability of asthma or COPD, and the presence of the clinical features of either condition. In-depth evaluation, encompassing complete medical history, physical examination, pulmonary function tests, and imaging is usually

required to diagnose correctly and properly classify patients. Blood eosinophil counts provide an estimate of airway eosinophilia (present in ACO) and testing can be performed easily in routine practice.

Management of ACO should be different in this patient group compared to patients with either condition alone. Previous research has not extensively investigated the ACO patient group specifically, so clear guidelines on the management of these patients are limited. Referral to specialist physician is usually required for definitive diagnosis and ongoing management.

Long-term inhaled corticosteroid (ICS) treatment (at the lowest effective dose) is recommended to reduce the risk of serious flare-ups, even if asthma symptoms appear to be mild or infrequent. For more details on ACO please refer to the "*Further Reading*" section.

Case Study 2

Ms. Nancy Cloti is a 51 year-old female who presents to GP with a complaint of dyspnea while doing heavy housework (e.g., vacuuming) and when climbing stairs. Twelve months ago, she was much better, but the symptoms have become progressively worse in the last 6 months. Nancy admits smoking half a packet of cigarettes per day. She had wheeziness as a child and used to get eczematous patches on her face and around her elbow. She used to use a puffer (salbutamol) when her wheeze was really bad; however, the symptoms improved when she started high school and then she stopped using the puffer. During spring, she gets hay fever for which she uses a corticosteroid nasal spray.

Her FEV_1 is 66% of predicted, FVC is 82% of predicted, and FEV_1/FVC is 0.64. When post-bronchodilator measurements were taken, the FEV_1 is 74% of predicted, FVC is 87% of predicted, and the FEV_1/FVC is 0.69.

What Assessments are Needed for Confirming ACO in Ms. Cloti?

Spirometry should be conducted to establish irreversible airflow limitation in Ms. Cloti. It is also important to evaluate Ms. Cloti for eosinophilia, as this can influence treatment choice and outcomes. Based on demographics, social/medical history and spirometry (≥35 years of age, a smoking history, potential history of asthma, post-bronchodilator FEV_1/FVC <70%; a marked response to a bronchodilator and differential eosinophil count [≥3% of total leukocytes or ≥300 cells/μL eosinophil concentration]), the GP's diagnosis is ACO. The GP refers Ms. Cloti to see a respiratory physician.

What are the Management/Treatment Options for Ms. Cloti?

Preventative measures, including lifestyle modifications should be discussed with and recommended to Ms. Cloti, along with management of symptoms using a short acting beta2-agonist inhaler. A regular ICS is prescribed for Ms. Cloti.

Ms. Cloti should be provided a written action plan (self-management plan). An asthma action plan or a COPD action plan template should be chosen, depending on her dominant clinical features.

Challenges in COPD Management and the Pharmacist's Role

Under-recognition and underdiagnosis of COPD often delay the initiation of appropriate management in many patients with COPD. Furthermore, COPD is a disease characterized by multiple comorbidities (e.g., cardiovascular diseases, osteoporosis, anxiety, depression), which also require ongoing management and monitoring of therapy. Optimal COPD management relies on choosing the right combination of pharmacological and non-pharmacological measures according to a confirmed diagnosis and severity, as well as ongoing monitoring and modifications in treatment, as required. Team efforts of various health professionals (including pharmacists), carers and patients are essential for optimal COPD management.

In the management of COPD, combination therapy has been demonstrated to be clinically beneficial and cost effective. No existing COPD medications have been shown to modify the long-term decline in lung function; medications and modifications to lifestyle can only slow the decline of disease. Reduction of therapy is not normally possible once symptom control has been achieved—it is often necessary to progressively introduce additional pharmacological and non-pharmacological treatments to cope with the deteriorating lung function in many patients. Moreover, patients often need to tailor their drug regimen depending on disease severity, respiratory tract infections and seasonal changes. Patients with COPD are likely to be on complex medication regimens comprising regular and "when required" inhaled respiratory medications and other medications, all of which are major barriers to treatment adherence. Depression, a common comorbidity in patients with COPD, is a known risk factor for nonadherence.

Pharmacists have a major role to play in all areas of COPD prevention, diagnosis, treatment, and monitoring (van der Molen et al., 2017). Some key actions and interventions pharmacists can consider at each stage of the disease include (but are not limited to) the following:

- Prevention—smoking status of patients (both with and without COPD diagnosis) should be screened, assessed, and appropriate smoking cessation therapy should be initiated or referrals made to appropriate health professionals or organizations;

- Case finding/Diagnosis—patients who have any characteristic COPD symptoms could be identified and referred to GPs for spirometry. Case-finding and spirometry programs have previously been implemented in pharmacy settings and evaluated with positive results (Castillo et al., 2009; Cawley and Warning, 2015; Fathima et al., 2017);
- Treatment—assessment of pharmacological treatment appropriateness, medication adherence, and inhaler technique should be performed on a regular basis; influenza (Arabyat et al., 2018) and pneumococcal vaccination; patient education (on the disease and proper inhaler technique); make recommendations for non-pharmacological therapies; and
- Monitoring—assessment of treatment effectiveness and proposing recommendations for subsequent changes in inhaler therapy according to disease stage and severity. When stepping up of pharmacotherapy is necessary, consider combination therapies in single inhalers and minimize the types of inhalers used. Ensure that patients have an up-to-date self-management plan with clear instructions on changes to be made in therapy when symptoms get worse.

Support Patients to Quit Smoking

Smoking cessation is the most important and cost-effective intervention to slow decline in lung function. When a smoker stops smoking, the lost lung function cannot be recovered, but the average rates of further decline will revert to that of a nonsmoker (Fletcher and Peto, 1977).

Smoking cessation advice from multiple health professionals motivates smokers to have quit attempts, which in turn increase long-term abstinence rates. Hospital admission provides an ideal opportunity to initiate smoking cessation as the smoker is in a setting where there are smoking restrictions, absence of usual environmental cues, and most likely in a state of perceived vulnerability and hence more receptive to advice and cessation interventions. However, motivation and post-discharge support are critical for achieving long-term abstinence. A comprehensive approach to supporting smoking cessation involves behavioral support and pharmacological treatment of nicotine dependence. The 5-As framework (Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff, 2008) is recommended to aid in providing support to smokers:

- **Ask** and identify smokers at every health care visit;
- **Assess** nicotine dependence and the motivation to quit;
- **Advise** about the risks of smoking and benefits of quitting;
- **Assist** cessation; and
- **Arrange** follow-up contact with smoker

First line treatments for nicotine dependence include nicotine replacement therapy (NRT), varenicline, and bupropion. The most effective forms of pharmacotherapy are either combination NRT (e.g., a patch combined with a rapid-acting form of NRT such as mouth spray) or varenicline. Longer courses of treatment (>12 weeks) may reduce relapse.

Advice on quitting should be clear and unambiguous, and provided in a supportive and nonconfrontational manner. Even a brief assessment, as little as three minutes, along with advice to quit has been shown to measurably effect quit rates. Relapse following a quit attempt is very common among smokers, and should not be considered as failure of the health professional or patient. Health professional follow up, either face-to-face or via telephone, has been shown to increase the likelihood of long-term smoking abstinence.

Mr. Trafalgar (Case study 1) should be actively supported by the pharmacist to quit smoking, given that he still smokes 10 cigarettes per day. The pharmacist can recommend OTC NRT (e.g., patch) along with behavioral support. Elements of motivational interviewing can be employed when counseling Mr. Trafalgar on smoking cessation. If Mr. Trafalgar is interested, he should be referred to the GP for initiation of a prescription medication (e.g., NRT patch, varenicline, or bupropion). Referral could also be made to support groups for smokers interested in quitting (e.g., Quitline). Whatever recommendation that is made, the GP should follow-up with Mr. Trafalgar to evaluate his progress.

Non-Pharmacological Therapy

Advice on non-pharmacological strategies should be considered along with pharmacological therapies.

Pulmonary Rehabilitation

There is strong evidence for the benefits of pulmonary rehabilitation that involves supervised (usually by a physiotherapist) exercise training alone or in conjunction with patient education or other non-pharmacological interventions (e.g., behavior change, nutritional intervention, and psychosocial support) (Spruit et al., 2013). Programs can be delivered in hospital outpatient departments or in the community setting.

Benefits are evident not only in those with stable COPD but also following an acute exacerbation of COPD. However, research shows that only a small proportion of patients who would benefit from pulmonary rehabilitation actually access these programs. Pharmacists can facilitate in making patients become aware of pulmonary rehabilitation programs and assist in the referral process.

In the absence of specialist exercise professional (e.g., physiotherapist or exercise physiologist) consultation, individuals with COPD should be encouraged to be physically active as inactivity is associated with increased mortality and exacerbations. Some support groups provide opportunities for patients with COPD to perform group exercise activities, after completion of a rehabilitation program.

Mr. Trafalgar (Case study 1) will benefit from pulmonary rehabilitation. He may be referred to a hospital-based program for at least six weeks and then continue exercising at home. Joining a support group, where Trafalgar is likely to meet other people with the same condition and take part in group exercise programs, will ensure that he continues to have regular physical activity, in turn achieving better quality of life.

Pharmacological Therapy

Pharmacological therapies aim to reduce symptoms, prevent exacerbations, and improve health status, by targeting the pathophysiology of COPD (Global Initiative for Obstructive Lung Disease, 2018). Medications can only slow disease progression and manage symptoms; they do not modify long-term decline in lung function. The choice of agent within each therapeutic class depends on availability, cost, clinical response, and side-effect profile.

Inhalation route is primarily used for delivery of medications directly to the lungs. It is common for patients to have issues with inhaler technique, with studies reporting operating errors in 50%–100% of patients. Poor technique may lead to worse outcomes and symptom control in patients with COPD. Moreover, inhaler device polypharmacy is an increasing problem, and with the introduction of many new combinations of medications and inhaler devices onto the market, there are greater chances for errors in their use. The array of agents available as monotherapy and combination therapy, may cause confusion in both patients and prescribers, resulting in duplication of therapy and increased adverse effects.

Key considerations when choosing an inhaler device include cost, access, inspiratory flow rate required for the device, patient dexterity and preference. With any inhaler prescription, education and training in the proper use of devices is imperative. Available inhalation devices are numerous and include: nebulizers, metered-dose inhalers (MDIs) with or without spacers, soft-mist inhalers, and breath-actuated devices (e.g., breath-actuated MDIs and single/multidose dry powder inhalers [DPIs]). Inhaler technique should be regularly assessed while on long-term therapy, and considered when presented with signs of treatment failure. Pharmacists play crucial roles in ensuring optimal inhaler technique education on initial and subsequent supply to patients. Resources, including demonstration videos and checklists for assessment of inhaler technique are available from asthma/lung foundations and thoracic societies.

Note: The GOLD guidelines provide detailed explanations of each drug class and recommendations for initiation and subsequent drug therapy (and have been used for the preparation of this chapter) (**Table 4**), however specific guidelines/formularies are available for COPD management in many countries.

Bronchodilators

Bronchodilators are used to increase FEV_1. They act by altering airway smooth muscle tone, widening the airways to improve symptoms and exercise capacity. Short-acting bronchodilators (i.e., beta 2-agonists or muscarinic antagonists) are used on a "when required" basis for short term symptom relief. Cardiac rhythm disturbances and tremor may occur with high doses in susceptible patients. Long-acting bronchodilators are usually given on a regular basis to prevent or reduce symptoms. Combining bronchodilators of different classes may improve efficacy, without the associated side effects from increasing the dose of a single bronchodilator too high.

Beta-2 Agonists

Beta2-agonists relax airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic AMP and antagonizes mechanisms of bronchoconstriction. There are short-acting beta2-agonists (SABA) and long-acting beta2-agonists (LABA). SABAs improve FEV_1 and symptoms; doses usually last 4–6 hours. LABAs can last for 12 hours or more and do not preclude additional benefit from "when required" SABA dosing. Twice daily LABAs (formoterol and salmeterol) and once daily LABAs (indacaterol, olodaterol, and vilanterol) can improve dyspnea, health status, and reduce exacerbation rate. Some patients may experience cough following indacaterol inhalation.

Muscarinic Antagonists

Muscarinic receptor antagonists relax smooth muscle by blocking M3 muscarinic receptors expressed in airways smooth muscle that cause bronchoconstriction. There are short-acting muscarinic antagonists (SAMAs) and long-acting muscarinic antagonists (LAMAs). SAMAs include ipratropium and oxitropium. LAMAs can be administered once daily (tiotropium and umeclidinium), or twice daily (aclidinium and glycopyrronium). LAMA treatments have been shown to improve symptoms, health status, effectiveness of pulmonary rehabilitation, reduce exacerbations and related hospitalizations.

Inhaled antimuscarinic drugs have poor systemic absorption—wide dose ranges have been safely used across various clinical settings, with the main side effect being dry mouth. Some patients using ipratropium report a bitter, metallic taste. Nebulizer treatments may cause acute glaucoma due to contact with the eyes; hence eye protection is recommended.

Table 4 Commonly used medications in COPD

Generic	*Brand*	*Form*	*Usual dosage*
Bronchodilators			
Long-Acting Beta$_2$-Agonists (LABAs)			
Arformoterol	Brovana	soln	Adults: Inhale 15 μg twice daily (AM & PM) by nebulization (max: 30 μg/day). Use standard jet nebulizer with air compressor (see literature). Children: Not recommended.
Formoterol	Perforomist	soln	Adults: One 20 μg vial twice daily (AM & PM) by oral inhalation via nebulizer (max: 40 μg/day). Children: Not recommended.
Indacaterol	Arcapta Neohaler	caps	Adults: 1 inh of one 75 μg caps once daily, using Neohaler device. Do not swallow caps. Children: Not recommended.
Olodaterol	Striverdi Respimat	MDI	Adults: 2 inh daily; max 2 inh/day. Children: Not established.
Salmeterol	Serevent Diskus	DPI	Adults: 1 inh (50 μg) twice daily (AM & PM) every 12 hrs. Children: Not recommended.
Short-Acting Anticholinergics			
Ipratropium bromide		soln	Adults: 500 μg by oral nebulization 3–4 times daily every 6–8 hrs. Children: Not recommended.
	Atrovent HFA	MDI	Adults: 2 inh 4 times daily (max: 12 actuations/day (408 mcg/day). Children: Not recommended.
Long-Acting Anticholinergics			
Aclidinium bromide	Tudorza Pressair	DPI	Adults: 1 inh (400 μg) twice daily. Children: Not established.
Glycopyrrolate	Seebri Neohaler	caps	Adults: 1 oral inhalation of one 15.6 μg caps twice daily (AM & PM). Do not swallow caps. Children: Not established.
Tiotropium bromide	Spiriva HandiHaler	caps	Adults: 2 oral inhalations of one 18 μg caps once daily, using HandiHaler device. Do not swallow caps. Children: Not recommended.
Umeclidinium	Incruse Ellipta	DPI	Adults: 1 inhalation every 24 hrs. Children: Not established.
Anticholinergic + Beta$_2$-Agonist			
Ipratropium bromide + albuterol		soln	≥18 yrs: 1 vial (3 mL) 4–6 times daily via nebulizer. <18 yrs: Not recommended.
	Combivent Respimat	MDI	Adults: 1 inh 4 times daily (max: 6 inh/day). Children: Not recommended.
Anticholinergic + Long-Acting Beta$_2$-Agonist (LABA)			
Glycopyrrolate + formoterol	Bevespi Aerosphere	MDI	Adults: 2 inh twice daily (in the AM + PM) (max: 2 inh twice daily). Children: Not established.
Glycopyrrolate + indacaterol	Utibron Neohaler	caps	Adults: 1 oral inhalation of one 27.5 μg/15.6 μg caps twice daily (AM & PM), using Neohaler device. Do not swallow caps. Children: Not established.
Tiotropium + olodaterol	Stiolto Respimat	MDI	Adults: 2 inh once daily (max: 2 inh/day). Children: Not established.
Umeclidinium + vilanterol	Anoro Ellipta	DPI	Adults: 1 inh once daily. Children: Not established.
Corticosteroids			
Corticosteroid + Long-Acting Beta$_2$-Agonist (LABA)			
Budesonide + formoterol	Symbicort 160/4.5	MDI	Adults: 2 inh of 160/4.5 μg twice daily. Children: Not indicated.
Fluticasone + salmeterol	Advair 250/50 Diskus	DPI	Adults: 1 inh of 250/50 μg twice daily. Children: Not recommended.
Fluticasone + vilanterol	Breo Ellipta	DPI	Adults: 1 inh of 100/25 μg once daily (max). Children: ≤17 yrs: Not established.
Corticosteroid + Anticholinergic + Long-Acting Beta$_2$-Agonist (LABA)			
Fluticasone + umeclidinium + vilanterol	Trelegy Ellipta	DPI	Adults: 1 inh once daily (max). Children: Not established.
Other			
PDE4-Inhibitor			
Roflumilast	Daliresp	tabs	Adults: One 500 μg tab once daily. Children: Not recommended.

(Source: https://www.empr.com/clinical-charts/chronic-obstructive-pulmonary-disease-treatments/article/216550/; Global Initiative for Obstructive Lung Disease, 2018. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Lung Foundation Australia, 2018. Lung Health Checklist.)

Methylxanthines

The exact mechanism and duration of action of xanthine derivatives is not well established. They may act as nonselective phosphodiesterase inhibitors but other non-bronchodilator actions have also been reported. Theophylline is the most commonly used methylxanthine, but not as first line. Theophylline has a narrow therapeutic index, and is beneficial only at near-toxic doses—this poses a great risk as clearance of the drug declines with age, and many physiological variables and drugs/diet/social habits affect theophylline metabolism (significant interactions with many common medications, smoking and caffeine consumption). Extensive monitoring is required to avoid toxicity when methylxanthines are prescribed.

Antiinflammatory Agents

Inhaled Corticosteroids

Combination of ICS and LABA is more effective at improving lung function, health status, and reducing exacerbations in moderate-very severe COPD than monotherapy. ICS use is associated with pneumonia, oral candidiasis (oral thrush), voice hoarseness, and bruising of the skin. Smoking, age ≥55 years, history of exacerbation or pneumonia, body mass index $<25 kg/m^2$, low mMRC dyspnea grade, and/or severe airflow limitation, are risk factors in developing pneumonia while on ICS therapy.

Oral Glucocorticoids

Long-term oral glucocorticoid therapy is associated with many side effects without evidence of benefits in stable COPD. Side effects such as steroid myopathy contribute to muscle weakness, reduced functionality, and respiratory failure are important considerations before initiating long-term oral glucocorticoid therapy. However, in acute COPD exacerbation, oral glucocorticoid therapy has been shown to reduce treatment failure and rate of relapse, and improve lung function and breathlessness. Prednisolone is commonly used in the management of COPD exacerbations.

Phosphodiesterase-4 (PDE-4) Inhibitors

PDE-4 inhibitors primarily reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast is a once daily oral PDE-4 inhibitor which may improve lung function and reduce exacerbations when used alone or with LABA/ICS combinations, in severe to very severe COPD. Common side effects include diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects usually occur early in treatment, but are reversible, and diminish over time with continued treatment. Roflumilast should be used with caution in underweight patients and those with depression.

Antibiotics

COPD exacerbations with signs and symptoms of infection benefit from antibiotics. First-line agents include oral amoxicillin or doxycycline for five days. In patients requiring admission to hospital or when pneumonia is suspected, a chest X-ray should be performed and pneumonia treatment should be initiated according to local treatment guidelines. Long-term azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) therapy over one year may reduce exacerbations. Bacterial resistance and hearing impairments have been reported with azithromycin treatment.

Mucolytics and Antioxidant Agents

Mucolytics such as N-acetylcysteine (NAC), ambroxol, sobrerol, and carbocysteine may reduce sputum viscosity, and have antioxidant, antiinflammatory, or antibacterial activity. Regular use of NAC and carbocysteine may reduce the risk of exacerbations in certain patient groups. A high dose (≥1200 mg/day) of NAC should be considered as an effective therapy for reducing exacerbations (Cazzola et al., 2015). In patients with chronic bronchitis but without airflow limitation, a dose of 600 mg/day leads to reduced exacerbations (Cazzola et al., 2015).

Other Antiinflammatory Agents

Some observational studies suggest that statins (e.g., simvastatin) may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications. Immunoregulators, nedocromil, and leukotriene modifiers, anti-TNF-alpha antibody (infliximab), and vitamin D supplementation have been trialed, however their place in COPD therapy is unclear.

Combination Inhaler Therapy

Combination Bronchodilator Therapy

Combinations of SABA and SAMA are superior compared to either medication alone at improving FEV_1 and symptoms. LAMA/LABA combinations increase FEV_1, improve symptoms, and reduce exacerbations compared to monotherapy or ICS/LABA combinations.

Triple Therapy

The use of an ICS/LABA inhaler together with a LAMA inhaler remains an option for patients with moderate to severe COPD who require additional treatment. Triple therapy (ICS/LAMA/LABA) improves lung function, symptoms and health status, and reduces

exacerbations compared to ICS/LABA or LAMA monotherapy. For the initiation of triple therapy (LABA/LAMA/ICS) the patient must have a post-bronchodilator FEV_1 <50% predicted prior to therapy, a history of frequent exacerbations (two or more) with significant symptoms despite regular bronchodilator therapy with a LAMA/LABA or an ICS/LABA or the patient must have been stabilized on a combination of a LAMA, LABA, and an ICS for COPD.

Pharmacological Treatment Algorithm

The ABCD grading systems allows the clinician to determine initiation of therapies and subsequent escalation/de-escalation regimens (more details are available in the GOLD strategy document—https://goldcopd.org/).

Briefly, the recommendations for pharmacological regimes of patients in each group are as follows:

Group A

- should be initiated on a short or long-acting bronchodilator based on response on breathlessness
- should be continued if breathlessness is controlled

Group B

- should be initiated on a LABA or LAMA (dependent on patient's self-reported symptom relief)—if symptoms persist, combine LABA and LAMA
  - if addition of additional bronchodilator does not relieve symptoms, can revert to single bronchodilator again
- if patient has severe breathlessness, initial therapy using dual bronchodilators can be considered
- investigate comorbidities that may be contributing to symptoms

Group C

- should be initiated on a long acting bronchodilator—LAMA is recommended over LABA
- if persistent exacerbations occur, step-up to LABA/LAMA combination or LABA/ICS combination
  - consider risk of pneumonia with ICS introduction, step up to LABA/LAMA combination is preferred for this reason

Group D

- Preferred initial therapy is LABA/LAMA
  - LABA/ICS combination is associated with higher risk of pneumonia, however ICS may be beneficial in ACO patients
- **If further exacerbations develop while on LABA/LAMA:**
  - Escalate to triple therapy (LABA/LAMA/ICS) or
  - Switch to LABA/ICS
- **If further exacerbations develop while on triple therapy, consider the following:**
  - Add roflumilast (if FEV_1 < 50% predicted, has chronic bronchitis and experienced at least one hospitalization in previous year)
  - Add macrolide—best evidence for azithromycin
  - Stop ICS

Vaccination

Influenza vaccination is recommended for all patients with COPD as it reduces exacerbations, serious illness, and death in patients with COPD. Adverse effects are mild, localized, and transient. Community pharmacists are trained and can offer vaccination in many countries.

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients >65 years. The PPSV23 is also recommended for younger COPD patients with significant comorbid conditions including chronic heart or lung disease. Pneumococcal immunization has additive beneficial effect on COPD exacerbations, when added to annual influenza immunization.

It is important to commence Mr. Trafalgar (Case study 1) on one or more long-acting bronchodilators (depending on symptoms and response). He should also be recommended influenza and pneumococcal vaccination.

COPD Self-Management and Action Plans

Self-management interventions in COPD are defined as *"structured but personalised and often multi-component, with goals of motivation, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease"* (Effing

et al., 2016). Education and supportive interventions are provided by health care professionals with the aim of increasing patients' skills and confidence in managing their own health problems. Programs are not limited to emotional support, problem solving, and decision-making, but also include development of therapeutic partnerships, goal setting, and action planning. A multidisciplinary team is usually in-charge of the delivery of such programs; the doctor, specialist physician, respiratory and primary care nurses, physiotherapists, psychologists, nutritionists, occupational therapists, social workers, and pharmacists are professionals commonly involved in the care of patients with COPD.

COPD action plans are recommended as part of self-management. They provide agreed instructions (between the clinician and patient) on action required when experiencing symptoms of an exacerbation. COPD exacerbation action plans that are prescribed and delivered within a single short educational program, with ongoing support surrounding use of the action plan, reduce in-hospital health care use and increase the initiation of corticosteroids and antibiotics for exacerbation episodes. Templates for COPD actions plans are available; an example from the Lung Foundation Australia is available here: https://lungfoundation.com.au/health-professionals/clinical-resources/copd/copd-action-plan/.

Self-management interventions, which include written negotiated actions plans between the patient and health care professional for worsening symptoms, may reduce risk of respiratory-related and all-cause hospitalizations, and may improve health status.

COPD Exacerbations—Prevention and Management

COPD exacerbations are episodes of acute worsening of symptoms that result in additional therapy. It is usually associated with increased airway inflammation, increased mucous production, and significant gas trapping, which ultimately results in increased dyspnea, cough, and sputum. A history of exacerbations is the best predictor of future exacerbations.

Triggers for exacerbations include:

- Viral (most common is human rhinovirus) or bacterial respiratory infection
- Exposure to fine particulate matter
- Left ventricular failure
- Psychosocial stressors, and
- Environmental factors (e.g., air pollution, ambient temperature)

COPD exacerbations can be classified based on severity:

- Mild (treated with short acting bronchodilators only)
- Moderate (treated with short acting bronchodilators and/or oral corticosteroids), or
- Severe (require hospitalization/emergency departments visits, may be associated with acute respiratory failure)

Exacerbation episodes usually last 7–10 days. Exacerbations contribute to disease progression, especially if recovery from these episodes is slow. Early recognition and management of exacerbations improve recovery and quality of life, reduce hospitalization and may prevent progressive functional deterioration. Educating patients on signs and symptoms of a COPD exacerbation is important. A COPD action plan may help patients and carers to recognize and respond to early signs of exacerbations and prevent unnecessary hospitalization.

The main aims of COPD exacerbation treatment are to reduce the negative impact of the current exacerbation episode and to prevent subsequent events. Exacerbations can be managed in the outpatient setting or in hospitals, depending on severity. Majority of exacerbations are managed in the outpatient setting with pharmacological therapies. Indicators for hospitalizing patients with exacerbation include insufficient home support, other serious comorbidities (especially cardiac related issues), onset of new physical signs (e.g., cyanosis, peripheral edema, acute respiratory failure), severe symptoms (e.g., increased respiratory rates, decreased oxygen saturation, confusion, drowsiness, sudden worsening of resting dyspnea), and initial treatment failure.

Upon presentation to hospital, patients are assessed to determine if the exacerbation is life threatening and if noninvasive ventilation is required to help breathing. Hospitalized patients can be classified, depending on clinical signs, into: (1) no respiratory failure; (2) acute respiratory failure—nonlife threatening; and (3) acute respiratory failure—life threatening.

Supplemental oxygen is administered and noninvasive ventilation is considered if necessary. Initiation of bronchodilator therapy, oral corticosteroids, and antibiotic therapy (if there are signs of bacterial infection such as purulent sputum or fever) is considered. Fluid balance monitoring, venous thromboembolism prophylaxis, and treatment of comorbidities are important.

Pharmacological Treatment of Exacerbation

Bronchodilators

SABAs, with or without short-acting anticholinergics, are recommended as initial bronchodilators in treating an acute exacerbation. Nebulizers are commonly used to deliver agents, despite no significant difference compared to MDI with or without spacer, when treating inpatients. Inhaled long-acting bronchodilators, regardless of ICS therapy, should be used during exacerbation episodes.

Glucocorticoids

Short courses (no longer than five to seven days) of systemic corticosteroids can improve lung function (FEV_1), shorten recovery time and length of hospitalization. Prednisolone 40 mg daily for five days is usually recommended. If oral route cannot be used, intravenous methylprednisolone 0.5 mg/kg/6 hrs may be given.

Antibiotics

Antibiotics may be used in patients who show signs of bacterial infection (e.g., sputum purulence), although the evidence behind the use of antiinfectives in exacerbations is still unclear. Short courses (no longer than five to seven days) of antibiotics may shorten recovery time, reduce early relapse, treatment failure, and hospitalization duration. The antibiotic to be prescribed depends on local guidelines/formulary restrictions, but initial empirical treatment usually involves an aminopenicillin with clavulanic acid, macrolide, or tetracycline.

Other Adjunct Therapy

Use of diuretics (for fluid balance), anticoagulant treatment (for other comorbidities), nutritional considerations, smoking cessation support, and deep vein thrombosis prophylaxis should be considered in all hospitalized patients.

Respiratory Support

Oxygen is imperative in patients to improve hypoxemia; the target oxygen saturation is 88%–92%. Administration of oxygen is via nasal cannula at a rate of 0.5–2 L/min (Yang et al., 2017). Arterial blood gases should be monitored. Noninvasive (nasal or facial mask) or invasive (orotracheal tube or tracheostomy) ventilation are instigated to manage acute respiratory failure.

Hospital Discharge and Follow-up

Although, evidence behind formalized care programs posthospital discharge is insufficient, it is good practice to focus on areas such as education, optimization of medication, inhaler technique corrections, optimizing comorbidity management, smoking cessation, early rehabilitation, telemonitoring, and continued patient contact to improve outcomes. Follow-up with patients after discharge is important to review progress. Pharmacists can play a major role in ensuring liaison with primary care professionals with regard to pharmacological treatments and smooth transition from acute care to chronic community-based care.

Advanced Stages of COPD

Long-term continuous oxygen therapy (ideally at least 18 hours a day) may be appropriate for patients who meet criterion for blood gas levels (Yang et al., 2017). Extensive assessment of suitability for oxygen is performed before initiating therapy. Surgical interventions such as bullectomy and lung transplantation are options in advanced stages.

Patients with advanced COPD experience many distressing symptoms including breathlessness, fatigue, depression, anxiety, and insomnia. Palliative care is aimed at improving the quality of life of patients and their families when facing life-threatening illness, by preventing and relieving suffering through controlling symptoms and addressing physical, psychosocial, and spiritual issues. Early access to and discussions about palliative care is recommended for patients with COPD and persisting symptoms.

Relevant Websites

- Global Initiative for Chronic Obstructive Lung Disease—https://goldcopd.org/
- National Institute for Health and Clinical Excellence—Chronic obstructive pulmonary disease in over 16s: diagnosis and management—https://www.nice.org.uk/guidance/CG101
- The COPD-X Plan—Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease—https://copdx.org.au/
- British Thoracic Society—https://www.brit-thoracic.org.uk/
- American Thoracic Society—http://www.thoracic.org/statements/copd.php
- European Respiratory Society—https://www.ersnet.org/
- Thoracic Society of Australia and New Zealand—https://www.thoracic.org.au/
- Lung Foundation Australia—https://lungfoundation.com.au/

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Nomenclature

ACO asthma COPD overlap
DALY disability adjusted life years
FEV_1 forced expiratory volume in 1 second; the volume of air exhaled during the first second of the forced expiratory maneuver
FEV_6 forced expiratory volume in 6 seconds; the volume of air exhaled during the first six second of the forced expiratory maneuver
FVC forced vital capacity; the volume of air forcibly exhaled from the point of maximal inspiration
FEV_1/FEV_6 forced expiratory volume in 1 second/forced expiratory volume in 6 seconds
FEV_1/FVC forced expiratory volume in 1 second/forced vital capacity
GOLD Global Initiative for Chronic Obstructive Lung Disease
GP general practitioner
ICS inhaled corticosteroid
LABA long acting beta2 agonist
LAMA long acting muscarinic antagonist
OTC over-the-counter
SABA short acting beta2 agonist
SAMA short acting muscarinic antagonist
SOB shortness of breath

Glossary

Dyspnea Breathlessness; shortness of breath; patients typically describe dyspnea as a sense of increased effort to breathe, chest heaviness, air hunger, or gasping.
Exacerbation of COPD An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations, that is acute in onset and may warrant a change in regular medication in a patient with underlying COPD.
Forced expiratory volume in 1 second This is the volume of air expelled in the first second of maximal forced expiration from a position of full inspiration.
Forced vital capacity This is the volume of air expelled by a forced maximal expiration from a position of full inspiration. It is usually 3–6 liters, varying with age, gender, and height. In normal subjects the fraction of the FVC which can be expelled in 1 second is >80% of the predicted value.
Rehabilitation A branch of medicine that aims to enhance and restore functional ability.
Spirometry A common test used to assess how well someone's lungs work by measuring how much air they can inhale, how much they can exhale, and how quickly they can exhale. It can measure how effectively air can be moved in and out of the lungs.

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Further Reading

ATS/ERS Guidelines on Performing Spirometry Testing

Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P., Gustafsson, P., Jensen, R., Johnson, D.C., Macintyre, N., Mckay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J., 2005. Standardisation of spirometry. Eur. Respir. J. 26, 319–338.

Recommendations for Treatment of ACO

Reddel, H.K., 2015. Treatment of overlapping asthma-chronic obstructive pulmonary disease: can guidelines contribute in an evidence-free zone? J. Allergy Clin. Immunol. 136, 546–552.

Management of Respiratory Disorders and the Pharmacist's Role: Cough, Colds, and Sore Throats and Allergies (Including Eyes)

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Background

Complaints relating to the upper airways are arguably one of the most common reasons for presentation to community pharmacies and other primary care providers, and contribute to a substantial loss of productivity and absence from work and school (Deckx et al., 2016; Sclar et al., 1996). The common cold, influenza, and allergies affect a large proportion of the population every year. Infections of the upper respiratory tract (URTI) show a seasonal trend, with cases peaking in the winter months. Allergies may be either seasonal or perennial depending on allergen sensitivity. It is necessary to elicit a sufficient history from patients to reach a differential diagnosis and manage symptoms appropriately (May and Dolen, 2017).

The respiratory tract serves the vital functions of bringing oxygen into the body for distribution throughout the body via the vascular system and expelling toxic carbon dioxide. The respiratory tract is divided into two sections: the upper and lower respiratory

tract. The upper airways, also referred to as the upper respiratory tract, consist of the nose, the nasal passages, the paranasal sinuses, the pharynx (throat), and the larynx (voice box). The lower airways consist of the trachea, bronchi, and lungs. The purpose of the upper airways is to take in, filter, and humidify the air, as well as expel carbon dioxide during respiration.

Common Cold, Influenza, Sore Throats, and Cough

The Common Cold

The common cold is the most common infection of the upper respiratory tract. The common cold is caused by over 200 virus strains, which are predominantly rhinoviruses, but also human coronaviruses and adenoviruses (Heikkinen and Järvinen, 2003; Mäkelä et al., 1998). A successful vaccine for the common cold has not yet been developed (Heikkinen and Järvinen, 2003). The common cold primarily affects the nose, pharynx, and sinuses, presenting symptoms often include a blocked or runny nose, fever, headaches, coughing, a sore throat, and sneezing. The common cold is transmitted through air droplets from infected individuals, which are then breathed in or, more commonly, enter the body through the eyes or mouth via the hands after coming into contact with a contaminated surface (Arroll and Kenealy, 2018). Unlike influenza, there is no antiviral therapy available to eradicate the causative virus (Jefferson and Tyrrell, 2001). The common cold is usually mild and self-limiting in nature with an average duration of 7–10 days (Arroll and Kenealy, 2018). The virus penetrates the tissues of the airways, resulting in local inflammation which presents as nasal discharge, sneezing, sore throat, and cough. Children experience between 5 and 7 colds each year, and adults have 2–4 infections each year. Infections may be more severe in the young or elderly or those who are immunocompromised (Arroll and Kenealy, 2018).

Influenza

Unlike the common cold, influenza, colloquially referred to as "the flu," is a more serious infection that tends to present with an abrupt onset of symptoms and may include systemic symptoms that are not restricted to the upper airways such as lethargy, diarrhea, nausea, and muscular aches. There are a number of strains of the influenza virus, and those known to infect humans are broadly divided into Type A, Type B, and Type C influenza. The influenza virus is transmitted similarly to the common cold, via air droplets from infected individuals (Radojicic, 2018). Individuals will often say that they are experiencing influenza when they are presenting with the common cold, it is important for pharmacists to differentiate between the two and educate patients on the difference. Although seasonal influenza infection may prove fatal to the young or elderly or those who are immunocompromised, epidemic strains such as the recent "swine flu" A/H1N1 strain also have the potential to kill otherwise fit and healthy individuals (Donaldson et al., 2009). Unlike the common cold, influenza can be treated with antiviral therapy such as the neuraminidase inhibitors oseltamivir and zanamivir, which stop the virus from replicating (Jefferson et al., 2006b). Seasonal attenuated live influenza vaccines are produced annually and are recommended as routine vaccinations for certain populations such as those who are immunocompromised and pregnant women (Radojicic, 2018). Pharmacists may be able to administer these vaccines in certain jurisdictions. It is worthy to note that these vaccines are produced using chicken eggs, and people with a known allergy to eggs should not receive the vaccine (Radojicic, 2018).

Pharmacological Management

Pharmacological management of upper respiratory tract infections in the community pharmacy consists primarily of symptomatic relief for the presenting symptoms. Choice of product should be based on patient preference, presenting symptoms, and clinical considerations such as contraindications and potential drug–drug interactions.

Cough

In patients presenting with an upper respiratory tract infection, coughs can be classified as productive (chesty) or nonproductive (dry). Nonproductive coughs may be the result of increased throat irritation due to sensitization from the virus, whereas productive cough results from increased mucosal secretions (Fuller and Jackson, 1990). Opioid derivatives are commonly sold as cough suppressants (antitussives) to suppress the cough reflux from the medulla in the brain stem to provide relief from frequent coughing. Common drugs include dextromethorphan, pholcodine, dihydrocodeine, and codeine. These may be sold as syrups, medicated lozenges, or as tablets or capsules. There is limited quality evidence for the benefit of these agents (Smith et al., 2014); however, consumer demand for these products may be high. Caution should be taken with preparations that may cause drowsiness such as codeine and dihydrocodeine. Dextromethorphan has been implicated in serotonin toxicity and should not be given to patients taking other drugs known to contribute to serotonin toxicity. Patients presenting with a nonproductive cough who are known to have asthma should not be supplied cough suppressants as these may contribute to respiratory depression or mask signs and symptoms of asthma flareups. Narcotic cough suppressants may be subject to misuse and abuse and this must be considered when supplying. In order to combat misuse and abuse, some formulations contain laxatives such as sorbitol to discourage consumption of supratherapeutic doses.

Productive coughs present as a cough where mucus is expectorated when coughing. Drugs licensed for the management of productive coughs fall into two categories: expectorants (protussives) and mucolytics. Like antitussives, these drugs come as syrups, medicated lozenges, and tablets or capsules. Expectorants, such as guaifenesin, stimulate the secretion of mucus in the airways and

reduce adhesion to improve the efficacy of coughing in clearing mucus. Mucolytics, for example, bromhexine, act to thin the mucus to facilitate easier clearance. Mucolytics and expectorants are sometimes sold in combination products to provide a synergistic effect in aiding cough management. Similar to antitussives, quality evidence for the clinical efficacy of expectorants and mucolytics is limited (Rubin, 2007; Smith et al., 2014).

In 2008, the United States Food and Drug Administration advised that cold and flu products should be avoided in children under 2 years of age due to the risk of serious adverse effects. Following this announcement, manufacturers in the United States changed the packaging of cold and flu products to state they should not be used in children under 4 years of age (Fashner et al., 2012; U. S. Food and Drug Administration, 2018). In response to this withdrawal from market, products containing complementary medicines such as ivy leaf (Hedera helix) have entered the market as a treatment option in children. Although individual studies suggest some efficacy of these preparations, quality data from randomized controlled trials are lacking (Holzinger and Chenot, 2011).

A nonmedicated alternative for cough syrups is demulcents such as simple syrup or honey. These ingredients are included in many cough syrups and are thought to be responsible for some of the reported symptom relief from the use of these syrups. It has been proposed that these may increase salivation and the secretion of pulmonary mucus (Eccles, 2002; Fuller and Jackson, 1990). These are safe to use in children and other populations where medicated syrups or lozenges are contraindicated.

Sore Throat

Sore throats manifest during an infection with the common cold or influenza due to an increase in inflammation in the throat. Sore throats may be either viral or bacterial in nature, with the vast majority (up to 90%) of cases caused by a virus. Sore throats attributed to a bacterial infection are most often caused by *Streptococcus pyogenes*, resulting in the term "strep throat." Pustules on the throat and tonsils do not necessarily indicate a bacterial infection, and the causative organism of a sore throat can only be determined through culturing a throat swab and considering associated symptoms. Sore throat lozenges, gargles, and sprays may contain a combination of antiinflammatory agents (such as flurbiprofen and benzydamine hydrochloride), antiseptic agents (such as dichlorobenzyl alcohol), and local anesthetics (such as lidocaine). Povidone-iodine throat gargles are also used with the notion that the use of these gargles reduces viral load in the throat (Satomura et al., 2005) as povidone–iodine has been shown to exert antibacterial, antifungal, and antiviral activity. In addition to throat-specific products, patients experiencing a sore throat may also benefit from simple analgesia such as acetaminophen (paracetamol) or ibuprofen. Regular dosing of simple analgesia has been shown to improve sore throat symptoms for patients (Schachtel et al., 1988).

Pain and Fever

Pain and fever are common symptoms during an infection with the common cold or influenza as the body's immune system responds to the invading virus. Simple analgesics such as acetaminophen (paracetamol) or ibuprofen also exert antipyretic effects and can be used to manage both pain and fever. Nonsteroidal antiinflammatory drugs (NSAIDs) have been shown to be effective in improving pain symptoms associated with the common cold (Kim et al., 2015). Aspirin should not be used in children as there is an increased risk of Reye's syndrome, and caution may be required with the use of the ibuprofen and other NSAIDs in patients with asthma, hypertension, electrolyte disturbances, and renal impairment. Fever in children is of particular concern to parents and may be managed overaggressively (Crocetti et al., 2001), the pharmacist has a role to educate parents on fever and reduce "fever phobia." Routine monitoring of body temperature is not necessary in uncomplicated cases of upper respiratory tract infections.

Nasal Congestion

As mucous production increases in the nose and sinus cavities, patients may experience a blocked nose, which results in difficulty breathing through the nose and discomfort. Patients may also describe thick, purulent discharge from the nose. Sympathomimetics are most commonly used for blocked noses and may be systemic (oral) or topical (as a nasal spray or drops). Sympathomimetics used in these preparations include pseudoephedrine, phenylephrine, and oxymetazoline. Although the quality of the evidence available is poor, decongestants may improve the subjective measures of symptoms. There is insufficient evidence to suggest whether systemic or topical agents provide superior relief (Deckx et al., 2016). Topical preparations of sympathomimetics should not be used for more than three-to-five consecutive days due to the risk of "rebound congestion" (rhinitis medicamentosa), this does not seem to occur with oral decongestants. Topical decongestants are preferred in pregnancy and in people with poorly controlled hypertension due to the low level of systemic exposure. Sympathomimetics (including topical) should be avoided in patients using monoamine oxidase inhibitors (e.g., moclobemide, phenelzine) due to the risk of hypertensive crisis. Systemic sympathomimetics can be used in children over 12 years of age, whereas most topical agents are appropriate from 6 years and above. In some jurisdictions, the sale of pseudoephedrine may be controlled or prohibited due to its use as a precursor for methamphetamine, leaving phenylephrine as the only remaining systemic option. The efficacy of oral phenylephrine compared to both placebo and oral pseudoephedrine has been questioned (Eccles, 2006). In addition to medicated nasal sprays, saline douches, drops, and sprays may also be used to clear mucus from a blocked nose. These saline preparations present a viable option in patients who cannot use sympathomimetics, and limited evidence suggests that saline irrigation may help relieve symptoms associated with an URTI, although this may not be clinically significant (King et al., 2015).

Rhinorrhea

Rhinorrhea may occur in an upper respiratory tract infection, or as a result of allergic rhinitis (allergies). In the case of rhinorrhea as a result of an upper respiratory tract infection, symptomatic management can be achieved with muscarinic antagonists, such as

atropine, in a nasal spray formulation (AlBalawi et al., 2013). Antihistamine (H_1 antagonist) monotherapy (both sedating and less sedating) appears to have a limited effect on rhinorrhea of an infectious origin or any symptoms of the common cold (Sutter et al., 2003). There is currently insufficient quality evidence for or against the use of intranasal corticosteroids to relieve the symptoms associated with a common cold (Hayward et al., 2015). For the management of allergic rhinorrhea, see the Section "Allergic Rhinitis."

Diarrhea and Vomiting

Gastrointestinal syptoms, such as diarrhea and vomiting, may present in some patients infected with influenza, in particular, pediatric patients (Dilantika et al., 2010). The mainstay of therapy for patients experiencing diarrhea and/or vomiting is ensuring adequate hydration. This can be achieved through the use of oral rehydration solutions, available in a number of brands and formulations worldwide. Oral rehydration solutions replace essential electrolytes lost from diarrhea and vomiting, glucose aids sodium absorption, and citrate counters acidosis that results from dehydration. The revised WHO reduced-osmalarity formula contains 75 mmol/L glucose and sodium, 20 mmol/L potassium, 65 mmol/L chloride, and 10 mmol/L citrate. Preparations may be sold as powders or effervescent tablets, which require reconstitution in clean water or ready-to-drink formulations. Patients should be discouraged from reconstituting oral rehydration solutions using, or rehydrating with, caffeinated drinks, soft drinks (soda), milk, or fruit juice. Opioid antidiarrheal agents such as loperamide and diphenoxylate (often supplied in combination with atropine to reduce abuse potential) are available in some jurisdictions and may be considered in adult patients in combination with rehydration therapy as a short-term management of symptoms for social convenience.

Antiviral Medicines

In some jurisdictions, antiviral medicines may be available from a pharmacist under certain circumstances without the prescription of a physician. There are two main classes of antiviral medicines that are available to manage infection with influenza: neuraminidase inhibitors and M2 ion channel inhibitors. Pharmacists should follow local guidelines on the supply of these medicines with regard to time since onset of symptoms and seasonal supply restrictions. Reviews of evidence state poor quality trials are a barrier to evaluating the role of these agents as prophylaxis and treatment in both seasonal and pandemic influenza (Jefferson et al., 2006b); however, one review stated that the use of M2 ion channel inhibitors in influenza infection should be discouraged (Jefferson et al., 2006a). Patient demand for antibiotics in upper respiratory tract infections may be high and this may be further driven by patient beliefs that antibiotics help them get better faster and prevent mores serious illness when they are experiencing a common cold (Gualano et al., 2014). Current evidence suggests that antibiotics have no benefit in the management of the common cold and place users at risk of adverse effects (Kenealy and Arroll, 2013). As such, patients should be reminded that antibiotics do not play a role in the management of the common cold or influenza as the causative organism is viral and not bacterial in nature.

Combination Products

Products containing various combinations of active ingredients are available on the market. Combinations may include ingredients to manage more than one symptom, such as analgesia and a decongestant. Combination products may be more convenient for patients, but may also contain subtherapeutic doses, irrational combinations (such as an antitussive and an expectorant), or may increase the risk of duplication of therapy. Evidence suggests that combination products are effective, convenient for patients, and not inherently more dangerous than single ingredient preparations (Eccles et al., 2014). Pharmacists should ensure patients are aware of the ingredients in combination products and that only ingredients to manage symptoms that are present are used.

Complementary Medicines

Complementary medicines may be often sought by consumers in upper respiratory tract infections to either reduce symptom severity or decrease the duration of symptoms. Preparations may commonly include ingredients such as vitamin C (ascorbic acid), zinc, garlic, propolis, Echinacea, ivy leaf (Hedera helix), and Andrographis paniculata (Fashner et al., 2012). Evidence supporting the use of these preparations is of mixed quality and individual patient circumstances, the potential for adverse effects and drug interactions, and patient expectations must be considered when complementary medicines are used for the common cold. Precaution must be taken in certain patient groups with some common complementary preparations, for example, the use of Echinacea in patients with asthma and Andrographis in pregnant women.

A Cochrane Review on the use of regular vitamin C in prevention and treatment of the common cold suggests that there is a mixed evidence regarding its efficacy for prevention but may have a role in those who undertake extreme exercise or are placed under cold stress. Some efficacy was demonstrated in reducing the duration of cold symptoms; however, current evidence is not sufficient to recommend routine supplementation (Hemilä and Chalker, 2013). Given the limited risk of adverse effects from using vitamin C and its low cost, some patients may wish to trial vitamin C supplementation. Similarly to vitamin C, there is some evidence to suggest that zinc, in particular zinc lozenges, may be beneficial in reducing the duration of cold symptoms if taken close to onset of symptoms (within 24 h), although the use of zinc in prophylaxis has not been established (Singh and Das, 2013).

Echinacea is another complementary medicine commonly marketed in tablets and lozenges with claims of benefits in preventing and treating the common cold. The most recent Cochrane Review to examine the effects of Echinacea was unable to establish a

recommendation based on the included trials, although it did acknowledge some preparations may have a benefit (although the clinical significance is questionable) (Karsch-Völk et al., 2014).

Nonpharmacological Management

Patients presenting with the common cold are often told to rest and drink plenty of fluids. Increasing fluid intake is recommended with the notion that dehydration may occur in episodes of upper respiratory tract infections and may also assist with reducing the viscosity of mucus. A review article was unable to establish the benefit of this advice in a primary care setting due to the majority of studies being observational in nature and in an in-patient setting (Guppy et al., 2011).

In addition to rest and increasing fluid intake, steam inhalation is also commonly recommended to patients with upper respiratory tract infections. It is believed that inhaling heated and humidified air helps to relieve congestion associated with the common cold, and it is also hypothesized by some that the increased temperature may limit the ability for rhinoviruses to replicate. Current evidence does not demonstrate significant benefits or harms from using steam inhalation, with the exception of some nasal irritation, lightheadedness, and worsening of congestive symptoms (Singh et al., 2017).

Topical preparations containing camphor, menthol, and eucalyptus oil (vapor rubs) are used by adults and children alike to alleviate common cold symptoms and are commonly applied to the chest area or above the upper lip. A recent randomized trial compared the effects of vapor rub, white petroleum jelly, and no treatment on parents' perceptions of their child's symptoms found that vapor rub was superior to petroleum jelly and no treatment, although irritation was reported in those using the vapor rub (Paul et al., 2010).

When to Refer

Pharmacists in the community setting should be able to reach a diagnosis of a common cold with relative ease. In the event a clear diagnosis cannot be reached, or a more serious infection is suspected, for example, influenza or involvement of the lower airways, then patients should be referred to a medical practitioner for further assessment.

Referral is also warranted in the event of prolonged or recurrent symptoms (especially cough), infections resulting in exacerbation of chronic respiratory conditions (asthma or chronic obstructive pulmonary disease), suspected dehydration, high-grade fever, neck stiffness, young infants, and the elderly. A cough that persists for greater than 3 weeks, or is concomitant with breathing difficulties, wheezing, pain on inspiration, or blood in the sputum or a persistent nocturnal cough (particularly in children) also requires referral.

Allergies

Allergic Rhinitis

Allergies affecting the nose (allergic rhinitis) are common among the population, and it is estimated that approximately 23% of the European population and up to 40% of the world's population experiences allergic rhinitis (Bauchau and Durham, 2004; May and Dolen, 2017). Allergic rhinitis is characterized by inflammation of the nasal passages, congestion, itching, sneezing, and rhinorrhea. These symptoms are a result of the inflammatory chemical mediators released (histamine, leukotrienes, and prostaglandins) due to the activation of immunoglobulin type E (IgE) on the surface of mast cells in the nasal passages in response to the presence of triggering allergens. This immune response tends to result in sneezing and bilateral watery rhinorrhea at first, which may progress to nasal congestion. In addition to nasal symptoms, ocular symptoms may also be present. After the initial activation of the immune response, extra inflammatory cells, such as eosinophils and T-lymphocytes, are attracted to the site resulting in chronic inflammation. The presence of these cells also results in "priming" of the immune response, resulting in increased sensitivity to the offending allergen as well as other allergens (Greiner, 2018).

Formal diagnosis is not common, and patients often (correctly) self-diagnose and self-manage their symptoms (May and Dolen, 2017). Allergic rhinitis can be classified several ways, including whether it is seasonal or perennial (intermittent or persistent), and mild or moderate–severe. As the name suggests, seasonal allergic rhinitis (hay fever) is triggered by seasonal allergens such as high pollen counts during spring. The presence of allergens implicated in seasonal rhinitis and the duration of the presence of allergens, can differ depending on both the time of year and geographical location. Unlike seasonal allergic rhinitis, those who experience perennial allergic rhinitis may experience symptoms at any time when exposed to allergens such as animal dander, dust mites, or mold spores. Although individuals experiencing allergic rhinitis symptoms have a high degree of presenteeism at work and school, productivity may be reduced when symptoms are present, quality of life is impacted, and the economic burden of allergic rhinitis is estimated to be billions of dollars each year in the United States alone (Crystal-Peters et al., 2000).

Individuals may present to the pharmacy with symptoms they attribute to the common cold, when they may in fact be experiencing allergies. To reach a differential diagnosis, the pharmacist should consider associated symptoms, timeline of symptoms, recent social history, and personal and familial medical history. Unlike an upper respiratory tract infection, fever, headache, cough, thick nasal discharge, and cough are not common with allergic rhinitis. Symptoms are bilateral in nature (i.e., both nostrils are affected), cases where symptoms are unilateral require referral for further investigation. If the symptoms suggest allergic rhinitis, it may be worthwhile taking a recent social history to identify if any possible triggers can be identified, for example, the patient may

have been exposed to a friend's cat or a moldy room. A personal and familial medical history may assist in confirmation of differential diagnosis as a personal of familial history of atopy such as allergic rhinitis, asthma, and/or atopic dermatitis (the "atopic triad") is often present. Up to 85% of patients with asthma may have comorbid allergic rhinitis. Poorly controlled allergic rhinitis in those who are comorbid with asthma results in poorer asthma control and increased asthma medication use.

Pharmacological Management

Management of symptoms is not specific to the offending allergen, and so identification of causative allergens is not necessary to commence therapy. Treatment should aim to reduce the severity of symptoms and their subsequent impact on quality of life, and in some cases reduce the likelihood of future flare ups or complications. There are a number of preparations for the management of allergic rhinitis symptoms available both over-the-counter and on prescription. Classes of medicines used in these preparations include H_1 antihistamines (oral and intranasal), intranasal corticosteroids (INCS), mast cell stabilizers, anticholinergic agents, decongestants (oral and intranasal), and intranasal leukotriene receptor antagonists. Choice of treatment should be based on frequency and severity of the symptoms and patient preference (including the cost of treatment). There are regional variations in guidelines for the management of allergic rhinitis and these must be considered when making therapeutic recommendations.

Intranasal Corticosteroids (INCS)

Intranasal corticosteroids are considered first-line therapy for patients with moderate to severe allergic rhinitis as they are the most effective in controlling symptoms resulting from the inflammatory response (May and Dolen, 2017). INCS exert their effects by decreasing the release of cytokines and other chemicals implicated in the inflammatory mechanism of allergic rhinitis from cells in the nasal mucosa by exerting immunosuppressive effects via glucocorticoid receptors. Many agents are available on the market including budesonide, fluticasone, and mometasone. Each has been shown to be effective in the management of allergic rhinitis, and so patient preference in terms of device, dosing frequency, and cost must be considered in order to choose between them. When supplying INCS, patients should be counseled on the correct use of the device to ensure therapy is successful. Patients should also be informed that some benefit should be seen within 24 h; however, it can take 7 days or more before the full benefit of treatment is seen. Some patients may wish to use an oral or topical antihistamine during initiation of INCS therapy due to their faster onset of effects, although Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines state there is limited evidence supporting the need for routine recommendation of an oral antihistamine in conjunction with INCS (Brożek et al., 2017). For convenience of those who use both INCS and an intranasal antihistamine, combination products are available. Much like the use of inhaled corticosteroids in asthma, adverse effects typically associated with systemic corticosteroids (e.g., adrenal suppression) are unlikely with the use of INCS, with adverse effects restricted to local irritation in the nose and throat.

Antihistamines (H_1)

H_1 antihistamines act by blocking the actions of the histamine-1 receptor, thereby reducing the inflammatory effects of the receptors. These antihistamines can be categorized as either sedating ("first generation") or less-sedating ("second generation"). Sedating antihistamines include promethazine and dexchlorpheniramine. Examples of oral less-sedating antihistamines are cetirizine (most likely to cause sedation), fexofenadine, and loratadine. Oral antihistamines may be preferred by some patients due to ease of use and cost and may be particularly useful in patients with both nasal and ocular symptoms due to their systemic effects. The systemic use of antihistamines, in particular sedating antihistamines, may result in undesirable adverse effects such as sedation, dry mouth, and constipation. There is no evidence to suggest that either sedating or less-sedating antihistamines are more efficacious.

In addition to oral preparations, intranasal antihistamines, such as azelastine, are also available (with or without an INCS). Intranasal antihistamines have been shown to be at least as effective as oral antihistamines and work faster, and may be preferred by some patients. Combination therapy of intranasal antihistamines and INCS may have some benefit over INCS alone; however, ARIA guidelines place emphasis on INCS as the preferred choice for therapy over antihistamines alone (Brożek et al., 2017).

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists, such as monteleukast, block the effects of leukotrienes at leukotriene receptors, thus reducing nasal inflammation and subsequent nasal congestion. Leukotriene receptor antagonists are only available with a physician's prescription in many jurisdictions. These agents may be more expensive than antihistamines and there is limited evidence to suggest using them over antihistamines; however, some evidence suggests they may be useful in patients with comorbid asthma (Brożek et al., 2017).

Decongestants

Much like in the management of cold symptoms, decongestants (either topical or oral) may be used in allergic rhinitis to alleviate congestive symptoms. As these medicines have no effect on the inflammatory response and simply constrict blood vessels to reduce mucus production, they may not be useful in monotherapy for the management of allergic rhinitis. In some markets, oral decongestants may be sold in combination with antihistamines. Topical agents (e.g., oxymetazoline and phenylephrine) should not be used for extended periods due to the risk of rhinitis medicamentosa ("rebound congestion"). Adverse effects of systemic agents, such as pseudoephedrine, include tachycardia, insomnia, and reduced appetite. The sale of pseudoephedrine is restricted in some markets due to its use as a precursor to methamphetamine.

Anticholinergics

Much like decongestants, the anticholinergic ipratropium may be used in allergic rhinitis as it is in the common cold to alleviate rhinorrhea by reducing mucus secretion in the nasal passages. Again, this has no effect on the underlying inflammatory processes implicated in allergic rhinitis and may be of little use in monotherapy.

Mast Cell Stabilizers

Mast cell stabilizers, such as sodium cromoglycate, are available as intranasal preparations and reduce the secretion of inflammatory mediators such as histamine from mast cells in the nasal mucosa, thus reducing inflammation. Intranasal preparations are generally well-tolerated with adverse effects restricted to local irritation. Sodium cromoglycate is less efficacious than INCS and so may not be a preferred option.

Nonpharmacological Management

Where possible, people who experience allergic rhinitis should attempt to avoid allergens that are known to trigger their allergies (although causative allergens may not always be known). In the case of pollen, windows should be kept shut, outdoor time restricted (particularly if pollen counts are high), and clothes and bedding should be dried in a clothes dryer rather than on an outdoor washing line. Air filters either inside the home, or on air conditioning units may also prove useful. In the instance of allergic rhinitis from mold spores or dust mites, regular cleaning may help reduce exposure to these allergens. In some cases, physicians may decide that the patient is a candidate for skin prick allergy testing in an effort to determine any allergens that may be responsible for allergic rhinitis.

Saline irrigation (nasal douching, wash) is another practice that is sometimes recommended for patients with allergic rhinitis. This is achieved through using either isotonic (0.9% sodium chloride), hypotonic, or hypertonic saline preparations, which are administered into the nose and sinus cavities through either a spray or a squeeze bottle or similar device. The proposed mechanism of action for this procedure is the mechanical "flushing out" of mucus, allergens, and inflammatory mediators. A recent Cochrane Review found that there is limited quality evidence investigating the use of saline irrigation in allergic rhinitis, but that it may have a role in its management (Head et al., 2018). Given the favorable adverse effect profile (uncommonly local irritation, a feeling of ear fullness, and nose bleeds), and the low cost of treatment, saline irrigation may be considered in the management of allergic rhinitis.

Allergic Conjunctivitis

Allergic conjunctivitis (allergies affecting the conjunctiva of the eyes) is characterized by red, itchy eyes with a watery discharge. It is estimated that approximately 25% of the American population experiences allergic conjunctivitis in their lifetime. As with allergic rhinitis, allergic conjunctivitis is the result of an IgE-mediated allergy in response to the presence of allergens in the eye. Allergic conjunctivitis may be classified as seasonal (occurring at particular times during the year according to pollen counts, for example) or perennial (occurring at any time of the year in response to allergens such as dust mites, mold, and animal dander). Allergic conjunctivitis is highly comorbid with allergic rhinitis, and a personal or familial history of atopy (atopic dermatitis, asthma, and/or allergic rhinitis) should be confirmed during history-taking.

Table 1 outlines the distinguishing characteristics of the three primary classifications of conjunctivitis. Individuals with red eye symptoms may come to the community pharmacy seeking advice and treatment with what they may misdiagnose as infectious (bacterial) conjunctivitis. The pharmacist should be able to reach a differential diagnosis with relative ease with adequate history-taking. The presence of itch is a key differentiating factor for the diagnosis of allergic conjunctivitis, along with a personal or familial history of atopy. Watery discharge may be present both in viral conjunctivitis and dry eye syndrome, the presence of itch and consideration of associated symptoms will help in distinguishing allergic conjunctivitis from these conditions. The management of bacterial and viral conjunctivitis and dry eye syndrome is covered elsewhere in this book.

Table 1 Characteristics of different types of conjunctivitis

Characteristic	*Bacterial conjunctivitis*	*Viral conjunctivitis*	*Allergic conjunctivitis*
Discharge	Thick, purulent, yellow	Watery	Watery
Sensation	Gritty	Gritty	Itchy
Affected eyes	One at first, commonly spreads to other after initial infection of first eye	One at first, commonly spreads to other after initial infection of first eye	Both eyes
Associated symptoms	Nil	Recent signs and symptoms of an upper respiratory tract infection	May be associated with a personal or family history of allergic rhinitis or atopy (eczema, asthma)
Pathology	Infection with bacterial organism (commonly *Staphylococcus aureus*, *Streptococcus pneumoniae*)	Infection with a virus such as adenovirus (most common) or herpes simplex	Exposure to allergens such as animal dander, dust mites, pollen
Contagious	Highly	Highly (if adenovirus infection)	No

Management

The goals of management for conjunctivitis are to reduce the severity of symptoms and, in some cases, reduce the chance of reoccurrence. If eye drops are recommended as part of therapy, patients should be reminded of correct eyedrop administration technique, the importance of hygiene when using eye drops, and the appropriate discard date after opening dropper bottles (if not supplied as single dose units). Single-dose units (preservative-free preparations) may preferred in those with known sensitivity to commonly used preservatives such as benzalkonium chloride. Users of contact lenses should be advised to remove their lenses for administration of eye drops and replace them no earlier than 15 min after administration.

Antihistamines (H_1)

Both oral and topical antihistamines may be considered for use in patients presenting with allergic conjunctivitis. Oral antihistamines may be preferred in patients who are also experiencing nasal symptoms so both nasal and ocular symptoms can be managed. Oral antihistamines, in particular sedating antihistamines such as promethazine, may contribute to drying of the eyes, and hence less-sedating antihistamines should be recommended over these agents. Topical antihistamines include levocabastine, ketotifen, and pheniramine and are administered as eye drops. This local delivery results in a faster onset of action than oral agents. Adverse effects of topical antihistamines are limited to local irritation of the eye and bad taste. A recent review found that topical antihistamines are beneficial for controlling signs and symptoms in allergic conjunctivitis in short-term use, but was unable to make a recommendation between the available agents (Castillo et al., 2015).

Mast Cell Stabilizers

Mast cells stabilizers, including nedocromil sodium and sodium cromoglicate, are sold in eye drop preparations for the management of allergic conjunctivitis. Adverse effects are mild and limited to the eye and nose. A recent review found that mast cell stabilizers may be useful in controlling signs and symptoms of ocular allergy, but could not make a recommendation between the available agents (Castillo et al., 2015).

Ocular Decongestants

Ocular decongestants, for example, naphazoline, are available in single-ingredient eye drops and in combined preparations with topical antihistamines. Their role in allergic conjunctivitis is limited to superficial reduction in redness of the eye as they have no effect on the underlying pathology of the allergic response. As with topical agents used in nasal congestion, extended use of ocular decongestants may result in conjunctivitis medicamentosa (rebound hyperemia), as such patients should be advised to avoid using these preparations for extended periods of time. Due to the risk of systemic absorption with poor administration technique, caution should be taken when recommending ocular decongestants in patient groups who would be excluded from taking oral decongestants (e.g., uncontrolled hypertension, concomitant use of phenelzine) as well as those at risk of angle-closure glaucoma.

Lubricating Drops and Saline

Lubricating eye drops (artificial tears) or normal saline (0.9% sodium chloride) may be useful in conjunction with other therapies to relieve discomfort in the eye and dilute both allergens and inflammatory mediators released during the allergic response. Lubricating eye drops contain lubricants such as carmellose and may be used as often as required. If insufficient lubrication is achieved with an eye drop, a gel or ointment applied before sleep may be considered.

Nonpharmacological Management

Prevention of allergic conjunctivitis is achieved through allergen avoidance. Where the causative allergen(s) are known patients should take necessary measures to avoid or minimize exposure to these. Practical measures may include limiting time outdoors during high pollen counts, keeping windows and doors shut, using air filters in air conditioning units, and undertaking strict cleaning routines to reduce animal dander and dust mites. If a specific allergen cannot be identified a physician may refer patients for further investigation such as a skin prick test.

When to Refer

Community pharmacists should be able to reach a differential diagnosis when it comes to allergies and conditions that present similarly. In the event, a clear differential diagnosis cannot be reached, and patients should be referred to either a medical practitioner or optometrist for further assessment. In nasal allergies obstruction or rhinorrhea from just one nostril may indicate the presence of a foreign object in the nose and this should be particularly considered in pediatric patients. Rhinitis symptoms persisting despite over-the-counter treatment should be assessed for the possibility of prescription therapy by a medical practitioner, as should rhinitis that is associated with pain or suspected to be the result of medication use (either prolonged use of topical decongestants or other drugs known to cause rhinitis medicamentosa). Due to the association between poorly managed allergic rhinitis and worsening asthma, patients who are comorbid should have their asthma control assessed by the pharmacist (e.g., frequency of "reliever" use) and referred if worsening of asthma symptoms occurs.

In the case of ocular allergies, in addition to nonspecific referral points such as over-the-counter treatment failure, specific referral points include if there is a change in vision, a foreign body present, eye pain, or photophobia then the patient should be referred.

Some eye conditions (including allergic conditions) may result in scaling or other changes to the eye lids and surrounding tissue, these conditions are beyond the scope of community pharmacy practice and should also be reviewed by a medical practitioner.

The Role of the Pharmacist

Similar to many other common minor ailments, the community pharmacy (among other primary health-care providers) is often the first port of call for people experiencing allergies and signs and symptoms of upper respiratory tract infections. Pharmacists have a unique opportunity, due to their accessibility and expertise in medicines, to make a differential diagnosis, educate patients on the management of these common conditions, and provide appropriate therapy and advice.

Consumer expectations of over-the-counter products for management of the common cold and associated symptoms may be high, and pharmacists can educate patients on the expected effects of any over-the-counter medicines (including complementary and alternatives medicines) and comment on the limited evidence supporting their use. Patients should be reminded that there is no cure for the common cold or influenza and that antibiotics do not play a role in the management of infections of viral origin, this is of particular importance in jurisdictions where antibiotics are available over-the-counter without a physician's prescription and consumer demand may be high. As always, pharmacists should promote safe, judicious, and appropriate use of medicines. Consumers may have misconceptions about the common cold and influenza, including the need to seek medical attention for a common cold, in this case the pharmacist can dispel myths surrounding these common infections and act as a "triage" for those who truly need referral for medical assessment based on their presenting symptoms, thereby reducing burden on the health system for ailments that can be easily managed in the scope of the community pharmacy. Where local laws permit, pharmacists should also offer (and administer) vaccination against seasonal influenza or other infectious diseases to patients who are eligible.

Literature has demonstrated that people living with allergic rhinitis do not frequently speak to health-care professionals about their condition, and instead make a (correct) self-diagnosis and self-select over-the-counter treatments, which are readily available. Several reasons have been proposed for this, including the self-perception that allergic rhinitis is relatively less severe than asthma (given that the two are frequently comorbid). Given that consumers may not be discussing their allergic rhinitis with a physician, pharmacists can take the opportunity to engage with consumers requesting medicines such as antihistamines or intranasal corticosteroids to elicit a history and make a differential diagnosis. Pharmacists can assist these patients in optimizing therapy, explain the correct use of devices, and educate patients about allergic rhinitis, for example, emphasizing the benefit on comorbid asthma if allergic rhinitis is managed appropriately. Finally, pharmacists can identify patients who require referral to another health-care provider (medical practitioner, optometrist).

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Management of Respiratory Disorders and the Pharmacist's Role: Cystic Fibrosis

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Learning Objectives

After completion of the chapter, the reader will be able to:

- Describe the epidemiology, etiology, and pathophysiology of cystic fibrosis (CF) and its multiple organ system involvement.
- Describe the genetic modifications and the genotypic classification of CF transmembrane regulator gene defect.
- Explain the clinical presentations and diagnosis of CF and its associated complications.
- Recommend appropriate pharmacologic therapies for the management of CF and its multi-organ system complications.
- Identify appropriate nonpharmacologic therapies for the management of CF and its complications.
- Design monitoring plans for acute and chronic CF pharmacotherapy.
- Recognize the pharmacist's traditional and emerging roles of in the management of CF.

Take-Home Messages

- Cystic fibrosis (CF) is a genetic disorder that occurs as a result of a defect in the cystic fibrosis transmembrane conductance regulator protein—a chloride channel responsible for regulating fluid and electrolyte transport within secretory epithelial cells in the entire body.
- The primary manifestation of CF encompasses pancreatic insufficiency and pulmonary dysfunction associated with chronic airway obstruction, infection, and inflammation whereas, the secondary manifestation includes malnutrition.
- CF is diagnosed through screening of newborn, appearance of typical signs and symptoms of the disease, or through documented abnormalities in ion transport or presence of two CF genetic mutations.
- Malabsorption, vitamin deficiencies, and poor nutritional status associated with CF are managed by using pancreatic enzymes and fat-soluble vitamins.
- The mainstay of therapy for managing CF includes inhaled dornase alfa and hypertonic saline along with mechanical airway clearance techniques for combating obstruction of airway.
- Inhaled antibiotics are administered to manage airway infections, and oral azithromycin is used to treat inflammation of the airways.
- Patients with CF may periodically experience acute pulmonary exacerbations along with increased pulmonary symptoms, acute loss of lung function, and weight loss, thus requiring the intensification of airway clearance and administration of systemic antibiotics and nutritional supplements.
- Key monitoring parameters in CF include observing trends in pulmonary function tests for determining response to therapies and identification of possible acute pulmonary exacerbations.
- Special consideration must be given to the disease-associated complications such as CF-related diabetes mellitus, osteoporosis, and depression.
- Pharmacists can play an important role in the management of patients with CF due to their expertise in pharmacotherapy, pharmacokinetics, pharmacodynamics, and drug interactions.
- Pharmacist's care of patients with CF can improve medication nonadherence, decrease incidence of readmission, and improve quality of life.

Introduction

Cystic fibrosis (CF) is a genetic disorder, which occurs due to a defect in the CF transmembrane conductance regulator protein—a chloride channel responsible for regulating fluid and electrolyte transport within secretory epithelial cells in the entire body. This affects many organ systems including respiratory system (lungs and sinus), liver, sweat glands, pancreas, intestine, and reproductive system (Cutting, 2015). The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) classified CF as category E84. On the basis of manifestations, this genetic defect is categorized as CF with pulmonary manifestation (E84.0), CF with intestinal manifestation (E84.1), CF with other manifestations (E84.8), unspecified CF (E84.9), CF with meconium ileus (E84.11), and CF with other intestinal manifestations (E84.19) (World Health Organization, 2016).

CF transmembrane regulator (CFTR) gene shows expression in multiple organs like pancreas, lungs, bile system, and sweat glands. The mutation causes defect in the gene, leading to this hereditary autosomal disease. Another name for CF is mucoviscidosis because rise in sodium and chloride level causes exocrine glands to produce excessively thick mucus, and cause obstruction in pancreas, intestine, bile duct, and bronchi. It is also accompanied by lower body temperature and difficulty in breathing and digestion (World Health Organization, 2018). The symptoms of CF vary from person to person. In most of the patients, symptoms appear in early childhood (e.g., poor growth rate despite good appetite, meconium ileus, foul bulky stools, malabsorption, recurrence of pneumonia, chronic bronchitis with cough, emphysema, bronchiectasis, salt depletion in hot weather, and clubbing of the fingers). However, some patients suffer from mild form of the disease and remain asymptomatic until adulthood. Although it is an incurable disease, the advancements in medical and pharmaceutical sciences have increased the average life expectancy of CF patients up to an average of 37 years of age (Health, 2018).

Epidemiology

CF is a genetic disorder affecting more than 70,000 people globally (CF Foundation, 2017). This life-shortening disease is predominantly found in Caucasians, because most of them (1 in 29 individuals) are carriers of the CF gene (O'Sullivan and Freedman, 2009). According to the World Health Organization (WHO), CF is prevalent in Europe (1 in 2000–3000 live births), North America (1 in 3500 live births), the United Kingdom (1 in 10,000 individuals), Latin America (1 in 3900–8900 neonates), Middle East (1 in 2560–15,876 people), Japan (1 in 100,000–350,000 live births), and India (1 in 40,000–100,000 live births), irrespective of the particular race and ethnicity (Cuppens et al., 2004; Farrell et al., 2008; World Health Organization, 2004). The apparently low incidence rate of CF in Asia, Latin America, and Africa may be due to the fact that CF remains underdiagnosed (World Health Organization, 2002). The progression and diagnosis of CF are markedly influenced by the age and gender of the patients because factors such as social, cultural, behavioral, and physiological dissimilarities have an impact on it (Demko et al., 1995). Among children, females are less commonly diagnosed with CF as compared to male patients (MacKenzie et al., 2014) while among adult patients, CF is more prevalent in women with shorter life expectancies than men (Nick et al., 2010). Biological mechanisms like female sex hormones have been identified as the root cause of this disparity. It is believed that estrogen increases the viscosity of mucus by modulating the ion channels on respiratory epithelium and reducing the air surface liquid on bronchial epithelial cells (Harness-Brumley et al., 2014). The advancement in treatment has decreased the morbidity among children and it is now predominantly found in adult population. The number of adults with CF is predicted to increase by 70% by 2025 (Burgel et al., 2015). The median life expectancy can be improved with better provision of care (e.g., mucociliary clearance) in multidisciplinary CF centers and the use of efficacious drugs in the treatment and control of infections (Burgel et al., 2015).

Etiology

Genetic Basis of Cystic Fibrosis

CF is the result of mutation of a gene on chromosome number 7 (Knowlton et al., 1985). This gene encodes the CFTR protein. The extent and severity of CF-associated illness depend on the insertion, deletion, and duplication of the CFTR gene. To date, approximately 2000 mutations of CFTR gene have been reported. On the basis of genotype, these mutations are grouped into six major classes (**Table 1**). These defects are not mutually exclusive, because a given mutation can demonstrate abnormalities across more than one mutation class (Hudock and Clancy, 2017).

CF shows an autosomal recessive pattern of inheritance. It means that patients suffering from CF have two copies of mutant CFTR gene, while carriers have only one copy. If both the parents are carriers, then there will be 25% chances that either next generation will be CF sufferer or disease free, while 50% chances that child will be careers but not sufferers. But when one parent is a carrier and other is a sufferer, then the chances of next generation to become sufferers and carriers will be 50% (C. F. Foundation, 2017).

Table 1 Classification of mutations of cystic fibrosis transmembrane regulator gene

Class	*Defect*	*Mechanism*	*Outcome*	*Example of gene mutation*
I	Biosynthetic defects	Frameshift mutations and large deletions lead to PTC	Absence of CFTR expression	G542X, W1282X
II	Defect in trafficking and protein folding	Missense mutations and in-frame deletions cause folding defect of CFTR	CFTR is not transported to the surface or only transported in residual amount	N1303K, F508del
III	Gated defect	CFTR channel does not open in response to agonist due to disrupting regulation	Absence or decreased opening of CFTR ion gated channel	G551S, G551D
IV	Conductance defect	Some mutations cause changes in structure of protein	The abnormal shape of CFTR pore of the channel restricts the movement of chloride ions	R347P, R117H
V	Splice abnormalities	Some mutations result in alternative splicing that disrupts mRNA processing and lesser number of normal CFTR protein synthesized	Less number of normal CFTR protein at the surface	A455E
VI	Defect in channel	Different types of mutations lead to increased turnover of CFTR protein at cell surface	Functional CFTR protein is unstable at cell surface and is quickly removed and degraded by cell machinery	F508del, 120del23

CFTR, CF transmembrane regulator; *PTC*, premature termination codons.
(Cystic Fibrosis Foundation, 2017c; Fanen et al., 2014; Marson et al., 2016; Tsui, 1995)

Consequences of Cystic Fibrosis Transmembrane Regulator Gene Mutation

Normally, the CFTR protein is responsible for the ion conduction and is regulated by cyclic adenosine monophosphate (cAMP). Primarily, it controls the movement of chloride ions in the luminal side of epithelium. It also hinders the activity of amiloride-sensitive epithelial sodium channel (ENaC) and causes reduction in reabsorption of sodium ions in the lung. The inability of CFTR protein to function normally in CF results in altered ionic concentration and volume of airway surface liquid in the lungs of individuals with CF (McKone and Aitken, 2004). Since CFTR gene is located in various organs like lungs, sinus, pancreas, intestine, liver, and sweat glands, ionic conduction in these organs is disturbed due to defective gene.

Clinical Presentations

Since CF involves abnormal functioning of multi-organ systems, several phenotypic features of pulmonary and gastrointestinal diseases are consistent with its diagnosis (Rosenstein and Cutting, 1998).

Pancreatic Involvement

CF affects both the exocrine and endocrine functions of the pancreas. Normally, the pancreatic enzymes are secreted into bicarbonate-rich fluid from the pancreatic duct. The dysfunctioning of CFTR inhibits the secretion of digestive enzymes and bicarbonate into the duodenum, leading to ductal obstruction. As time progresses, these enzymes (lipase, protease, and amylase) accumulate and start digesting the pancreatic tissue (Li and Somerset, 2014). The term "cystic fibrosis" refers to the fibrotic scar tissue, which replaces the destroyed pancreas. The absence of these enzymes leads to poor digestion of fats, proteins, and carbohydrates. Consequently, almost 90% of patients experience pancreatic insufficiency (PI), which in turn is characterized by steatorrhea (fatty stools), decreased absorption of the fat-soluble vitamins (A, D, E, and K), malnutrition, and deterioration of the normal function of pancreas (Hackert et al., 2014; Peretti et al., 2005). In early life, the concentration of amylase and lipase rises secondary to pancreatic autodigestion. This may lead to either painful or asymptomatic chronic pancreatitis. Subsequently, the destruction of the pancreas leads to glucose intolerance in about 17% of children and 75% of adults (Koda-Kimble, 2012; Sterescu et al., 2010). Almost 40%–50% of adult sufferers of CF also develop diabetes mellitus (Kayani et al., 2018). This complication is associated with increased morbidity and mortality. Decreased insulin sensitivity is linked with pulmonary exacerbations. Initial aggressive insulin therapy may result in improved clinical outcomes (Moran et al., 2010).

Pulmonary Involvement

The following are common pulmonary presentations in patients with CF:

- Persistent colonization/infection with typical CF pathogens, including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*.
- Chronic cough and sputum production.
- Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation).
- Airway obstruction, manifested by wheezing and air trapping.
- Nasal polyps; radiographic or CT abnormalities of the paranasal sinuses.
- Digital clubbing.

Gastrointestinal Involvement

The following are common gastrointestinal abnormalities in patients with CF:

- Intestinal—Meconium ileus, distal intestinal obstruction syndrome, rectal prolapse.
- Pancreatic—PI, recurrent acute pancreatitis, chronic pancreatitis, pancreatic abnormalities on imaging.
- Hepatic—Prolonged neonatal jaundice, chronic hepatic disease manifested by clinical or histological evidence of focal biliary cirrhosis or multilobular cirrhosis.

Nutritional Abnormalities

Failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, and complications secondary to fat-soluble vitamin deficiencies are typical nutritional abnormalities found in CF.

Other Abnormalities

Other abnormalities commonly encountered in CF include:

- Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis.
- Genital abnormalities in males, resulting in obstructive azoospermia.

Diagnosis

In individuals presenting with clinical signs and symptoms of CF or a positive family history, the following diagnostic tests are recommended:

Sweat Test

1. A patient is said to have CF if the sweat chloride value is ≥60 mmol/L. If the mutation analysis finds that there is a mutation in two CF genes, then the sweat chloride test is recommended for confirmation. Such patients are more likely to develop this disorder irrespective of their age.
2. If a patient aged ≥6 month is presented with a sweat chloride value ≤39 mmol/L, then he/she cannot be categorized as CF. Such patient should be referred to a CF care center for follow up if he/she is identified with mutation in two CF genes (Farrell et al., 2008; Stern, 1997).
3. If the sweat chloride value ranges between 30 and 59 mmol/L in patients aged <6 months and 40–59 mmol/L among patients aged >6 months, then the extensive CFTR mutation analysis (e.g., gene sequencing, expanded panel of CFTR mutations and evaluation of deletions) is recommended for confirmation (LeGrys et al., 2007).

    a. If the individual is found to have mutation in two CF genes, then he/she must be treated as a CF patient.
    b. If the individual is found to have no or mutation in one CF gene, then he/she can be either categorized as a CF patient or high-risk patient on the basis of family history and the clinical presentation of CFTR dysfunctioning (i.e., bronchiectasis, obstructive azoospermia and acute, chronic or recurrent pancreatitis). Patients aged 6 months to 2 years must undergo repeated sweat chloride test. If the sweat chloride values are found to be intermediate on repeat testing, then the patient must be referred to a CF center and confirmation should be made on the basis of ancillary testing, which may include signs and symptoms, expanded gene testing, respiratory tract culture testing for the identification of causative microorganism (e.g., *P. aeruginosa*), and exocrine pancreatic function tests (Elborn and Bradley, 2006).

Ancillary Test

On the basis of signs and symptoms, patients may be prescribed several ancillary tests, including pancreatic imaging, high-resolution computed tomography (HRCT) for chest, bronchoalveolar lavage, assessment of reproductive system, respiratory function tests (not routinely recommended for infants), nasal potential difference (NPD) test, assessment for presence of immune deficiency, and ciliary dyskinesia.

An individual is said to be suffering from CF, if it is confirmed by clinical presentation, laboratory biomarkers, and microbial culture test. If an individual does not show any signs and/or symptoms related to CF, but has sweat chloride values in intermediate ranges, then he/she must be regularly monitored for the appearance of CF-related signs and symptoms.

Management of Cystic Fibrosis

CF is an incurable disease, but there are several therapeutic agents available to reduce or prevent its complications, control its symptoms, and improve the quality-adjusted life years (QALY) of patients with CF (Klimova et al., 2017). The treatment of the CF encompasses the use of medications and techniques for mobilizing pulmonary secretions, antibiotics for treating infections, and anti-inflammatory agents for reducing the inflammation of airways (National Health Services, 2018). Early diagnosis, close monitoring, multidisciplinary collaborative care approach, and referral to a regional CF center are highly recommended strategies for improving chances of survival (Mayo Clinic Staff, 2016). In 2007, the Pulmonary Therapies Committee, founded by the Cystic Fibrosis Foundation (CFF) of America, had established guidelines on the basis of safety and efficacy of therapeutic agents (Flume et al., 2007). With the approval of novel medicines for treating CF patients, these guidelines were revised by the committee in 2013 (Mogayzel et al., 2013). Various therapeutic options have been summarized in **Table 2**.

Cystic Fibrosis-Associated Pulmonary Exacerbations

Pharmacological Management

Cystic fibrosis transmembrane regulator modulators

Novel therapeutic agents that target the aforementioned classes of mutation are developed (Sawczak et al., 2015). CFTR modulators are classified into three groups of drugs: potentiator, corrector, and read-through agents. If the CFTR channel is correctly located, then the potentiator enhances its activity. The defect in trafficking and protein folding is corrected by the correctors, while read-through agents produce full-length protein by allowing the ribosome to ignore the premature codon (Edmondson and Davies, 2016).

Table 2 Treatment options for patients with cystic fibrosis

Pharmacological therapies	
CFTR modulators	*Potentiator*: Ivacaftor
	Corrector: Lumacaftor, Tezacaftor
	Combination therapy: Ivacaftor/Lumacaftor; Ivacaftor/Tezacaftor
	Read-through agents: Ataluren
Antibiotics	Flucloxacillin; Amoxicillin and clavulanic acid; Tobramycin; Azithromycin; Clarithromycin; Rifampicin; Fusidic acid; Tetracyclines
Bronchodilators	β_2-Receptor agonists
Mucolytic and mucoactive agents	*N*-acetylcysteine; Dornase alpha
Anti-inflammatory agents	*NSAIDS*: Ibuprofen
	Corticosteroids: Leukotriene β_4-receptor antagonist
Nutritional therapies	Pancreatic enzymes replacement therapy; Multivitamin supplements
Anti-hyperglycemic agents	Insulin
Anti-osteoporosis agents	Bisphosphonates
Non-pharmacological therapies	
Oxygen therapy	
Chest physiotherapy	
Lung transplantation	
Gene therapy	
Preventive measures to control infections	
Vaccination	Influenza vaccine; prevnar vaccine
Monoclonal antibody	Palivizumab

CFTR, CF transmembrane regulator.
(Cystic Fibrosis Foundation, 2017a; Döring et al., 2012; Flume et al., 2007; Stenekes et al., 2009)

Potentiator The role of potentiator is to restore CFTR activity and function in CF patients. These agents cause the CFTR channel to remain open and functional for prolonged period of time. In this way, the defects related to gating and conductance can be improved (**Fig. 1**) (Sloane and Rowe, 2010; Van Goor et al., 2014).

Ivacaftor Ivacaftor 150 mg (VX-770) is a potentiator of CFTR chloride channel that improves the lung function of patients with CF by 10%, and reduces the pulmonary exacerbation by 55% and sweat chloride concentration within indeterminate range (Davies et al., 2013). The most common adverse drug reactions (ADRs) associated with its use include nausea, headache, upper respiratory tract infections, abdominal pain, nasal congestion, nasopharyngitis, oropharyngeal pain, dizziness, diarrhea, and rash whereas, serious ADRs may include elevation in liver transaminases. There is little evidence suggesting ocular toxicity, so regular eye examination is recommended for patients. As Ivacaftor is administered orally, patient's adherence affects treatment outcomes. It has been found in phase II clinical trials that withdrawal of Ivacaftor caused diminished therapeutic outcomes (Accurso et al., 2010).

Corrector These are the small molecules that increase gating, conduction, and improve the cell-surface expression by making F508del to leave the endoplasmic reticulum (ER). They work either as "pharmacological chaperones" (i.e., to improve folding of CFTR protein by direct binding) or as "proteases regulators" (Mijnders et al., 2017). This class mainly includes Lumacaftor (VX-809), and Tezacaftor (VX-661) (**Fig. 1**).

Lumacaftor Lumacaftor (VX-809) improves CF symptoms by acting as protease regulators (i.e., show an improvement in CFTR folding by adapting protein homeostasis—proteostasis), aiding the conformational stability of F508del-mutated CFTR proteins and thus causing an increased processing and trafficking of mature protein to the cell surface. In phase IIa of clinical trial, Lumacaftor showed a dose response change in sweat chloride (Clancy et al., 2012).

Tezacaftor Tezacaftor (VX-661) is a novel drug that improves processing and trafficking of CFTR to the cell membrane among CF patients with F508del mutation. Cough, nausea, increased sputum, and fatigue are the most commonly reported ADRs with Tezacaftor monotherapy. Unlike Lumacaftor, it neither induces CYP3A enzyme nor shows any drug interaction with Ivacaftor during metabolism (Donaldson et al., 2018).

Combination therapy A combination of tezacaftor (100 mg) and ivacaftor (150 mg), also known as VX-440, has been approved by FDA in February 2018 under the brand name Symdeko™ (Vertex Pharmaceuticals, 2018). The common ADRs include headache, nausea, sinus congestion, and dizziness. This combination also alters the level of hepatic enzymes and patient can show various symptoms like yellowing of skin or sclera of the eye, dark amber color urine, nausea, vomiting, and

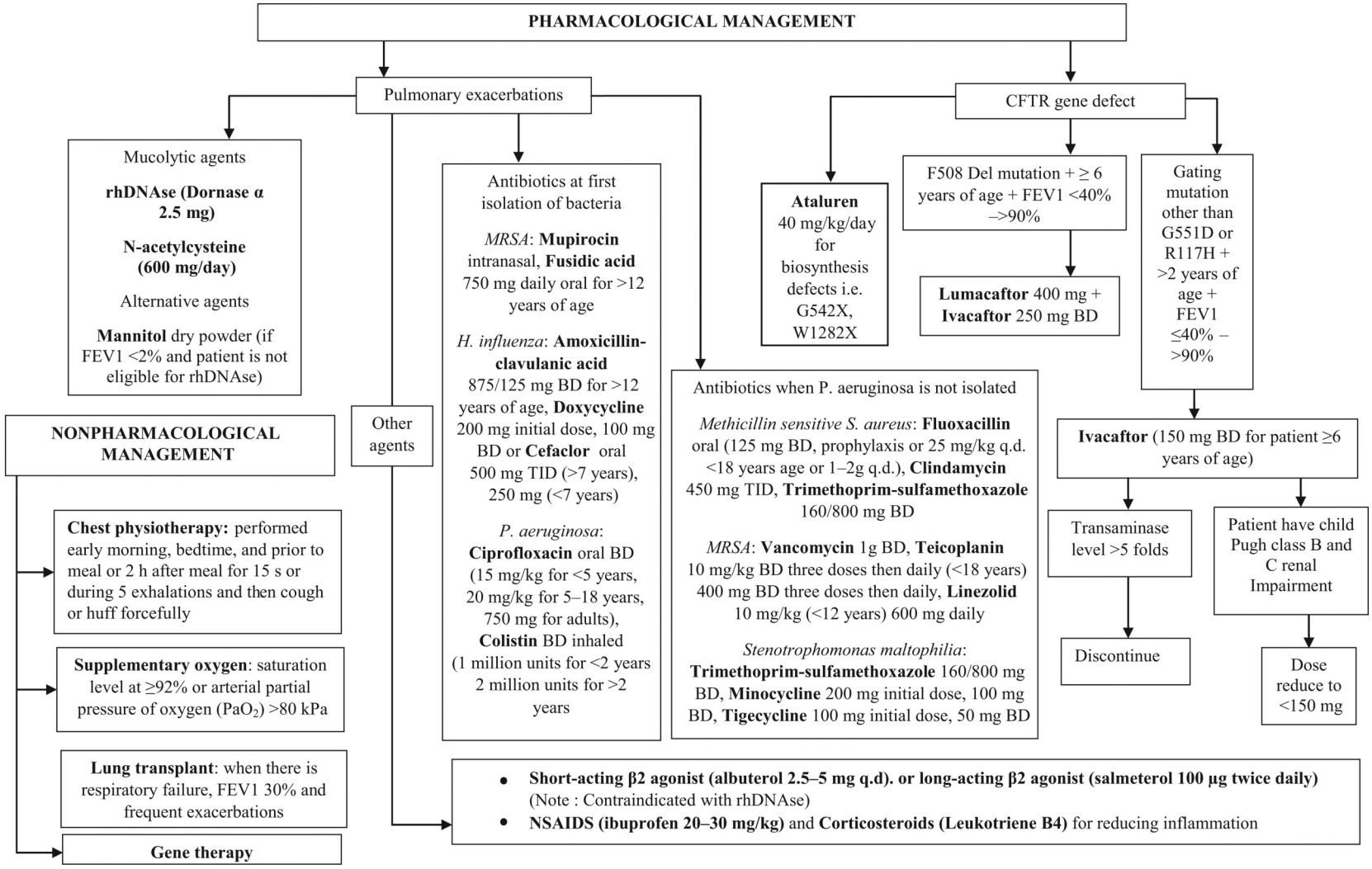

Figure 1 Algorithm of management of CF and associated pulmonary exacerbations.

loss of appetite. As a precautionary measure, an eye examination is mandatory during or after treatment with this combination therapy to check patient for cataract. In phase II studies, this combination shows a reduction in sweat chloride level, improvement in forced expiratory volume (FEV_1) for patients' homozygous for Phe508del. In 2015, FDA approved this combination under the brand name Orkambi™ (lumacaftor 200mg/ivacaftor 125 mg) for CF patients aged ≥12 years who are homozygous for Phe508del mutation (Zhang et al., 2016).

Read-through agents Almost 10% of the CF patients have class I mutation in CFTR gene (Pettit and Fellner, 2014; Rowe et al., 2005; Van Goor et al., 2011). Ataluren 40 mg/kg/day (PTC124) is effective against class I mutations in which premature stop codons (UAA, UAG, or UGA) inhibit the formation of full-length protein (Du et al., 2008). Although it is structurally similar to aminoglycoside antibiotics, Ataluren does not show any similarity with respect to toxicity profile or antibiotics characteristics (Ratjen, 2009).

Antibiotics

In comparison to healthy population, CF patients are more prone to bacterial infections, which mainly include *S. aureus*, *P. aeruginosa*, *B. cepacia* complex, *S. maltophilia*, *Achromobacter* species, and other Gram-negative microorganisms (Coutinho et al., 2008). *S. aureus* is a significant pathogen that is commonly found in respiratory cultures. Sometimes, it shows asymptomatic infections, but it can also initiate immunological responses that may cause lung damage. For symptomatic relief, anti-staphylococcal antibiotics are recommended especially during the first 2 years of life (Hewer and Smyth, 2017). A child must be administered a narrow spectrum anti-staphylococcal antibiotic such as flucloxacillin until 5 years of age. This therapy must be discontinued if there are less than three isolates of *S. aureus* in the preceding year (Gibson et al., 2003). There is no significant evidence that suggests the role of *H. influenza* in the pathogenesis of CF-associated lung diseases (Agrawal and Murphy, 2011). If there are two or more isolates of *H. influenza* in 1 year, then patient should be administered amoxicillin and clavulanic acid prophylactically (Cuthbert, 2011). Oral cephalosporins are not recommended in both *S. aureus* and *H. influenza* infections (Döring et al., 2004). If the patient is chronically infected with *P. aeruginosa*, nebulized colistin or nebulized tobramycin can be given on alternative months. Moreover, azithromycin can be given prophylactically owing to its anti-inflammatory actions and activity against formation of biofilms (G. Davies and Wilson, 2004).

However, there is a need to administer antibiotics in 1–10 pediatric patients despite antibiotic prophylaxis every year (Hewer and Smyth, 2017). Bacterial exacerbation is triggered by viral infections; therefore, the use of antibiotics can be justified. In case of upper respiratory tract infections (URTIs), CF patients should be administered with double dose of flucloxacillin. If there is no relief within 2 days of treatment, then the therapy should be switched to co-amoxiclav (Ciofu et al., 2015; Grimaldi-Bensouda et al., 2014). The antibiotic doses for CF are provided in **Table 3**.

Table 3 Antibiotics for the treatment of bacterial infection in cystic fibrosis

Sl. no.	*Drug*	*Spectrum*	*Dose*	*Frequency*	*Route*	*Age (years)*
1.	Flucloxacillin	*Staphylococcus aureus*	25 mg/kg	6 h	Oral	<18
			1–2 g			>18
2.	Fusidic acid	*Staphylococcus aureus*	500 mg	8 h	Oral	<12
			750 mg			>12
3.	Rifampicin	*Staphylococcus aureus*	10 mg/kg	12 h	Oral	<18
			600 mg			>18
		Mycobacterium avium complex	10 mg/kg	24 h	IV	<12
			450 mg			>12
4.	Clindamycin	*Staphylococcus aureus*	5–7 mg/kg	6 h	Oral	<18
			600 mg			>18
5.	Vancomycin	*Staphylococcus aureus*	15 mg/kg	8 h	IV	<18
			1 g			>18
			4 mg/kg	12 h	Inhaled	<18
			250 mg	6–12 h		>18
6.	Teicoplanin	*Staphylococcus aureus*	10 mg/kg	12 h	IV	<18
			400 mg			>18
7.	Linezolid	*Staphylococcus aureus*	10 mg/kg	8 h	Oral/IV	<12
			600 mg	12 h		>12
8.	Amoxicillin	*Haemophilus influenza*	250 mg	8 h	Oral	<7
			500 mg			>7
9.	Co-amoxiclav (amoxicillin and clavulanic acid)	*Haemophilus influenza*	250 mg	8 h	Oral	All age groups
10.	Doxycycline	*Haemophilus influenza* *Burkholderia cepacia*	200 mg	24 h	Oral	>12
11.	Cefaclor	*Haemophilus influenza*	250 mg	8 h	Oral	<7
			500 mg		Oral	>7

Table 3 Antibiotics for the treatment of bacterial infection in cystic fibrosis (*cont.*)

Sl. no.	*Drug*	*Spectrum*	*Dose*	*Frequency*	*Route*	*Age (years)*
12.	Cefixime	*Haemophilus influenza*	200 mg	24 h	Oral	<10
			400 mg			>10
13.	Chloramphenicol	*Haemophilus influenza*	12.5–25 mg/kg	6 h	Oral	All age groups
14.	Cefuroxime	*Haemophilus influenza*	50 mg	6–8 h	IV	<18
			750 mg			>18
15.	Cefotaxime	*Haemophilus influenza*	50 mg/kg	6–8 h	IV	<18
			2 g			>18
16.	Clarithromycin	*Mycobacterium avium complex*	7.5 mg/kg	12 h	Oral/IV	<12
			500 mg			>12
17.	Azithromycin	*Mycobacterium avium complex*	10 mg/kg	24 h	Oral	<18
			500 mg			>18
		Pseudomonas aeruginosa	250 mg	8 h	Oral	All age groups
			500 mg			
18.	Ethambutol	*Mycobacterium avium complex*	15 mg/kg	24 h	IV	All age groups
19.	Cefoxitin	*Mycobacterium avium complex*	40 mg/kg	6 h	IV	<12
			2–3 g			>18
20.	Amikacin	*Mycobacterium avium complex*	250 mg	12 h	IV	<12
			500 mg			>18
		Pseudomonas aeruginosa	10 mg/kg	8 h	IV	<18
			7.5 mg/kg	12 h		>18
21.	Ciprofloxacin	*Mycobacterium avium complex*	20 mg/kg	12 h	Oral	<18
			750 mg			>18
22.	Piperacillin—Tazobactam	*Pseudomonas aeruginosa*	90 mg/kg	6–8 h	IV	<18
			4.5 g			>18
23.	Ticarcillin—Clavulanic acid	*Pseudomonas aeruginosa*	80–100 mg/kg	6–8 h	IV	<18
			3.2 g			>18
24.	Ceftazidime	*Pseudomonas aeruginosa*	50 mg/kg	8 h	IV	<18
			2–3 g			>18
		Burkholderia cepacia	1 g	12 h	Inhaled	All age groups
25.	Aztreonam	*Pseudomonas aeruginosa*	50 mg/kg	6–8 h	IV	<12
			2 g			>12
26.	Imipenem	*Pseudomonas aeruginosa*	22.5 mg/kg	6 h	IV	<18
27.	Meropenem	*Pseudomonas aeruginosa*	25–40 mg/kg	8 h	IV	<18
			1–2 g			>18
28.	Colistin	*Pseudomonas aeruginosa*	25,000 units/kg	8 h	IV	<18
			2 million units	8 h	IV	>18
29.	Tobramycin	*Pseudomonas aeruginosa*	10 mg/kg	24 h	IV	All age groups
			3.3 mg/kg	8 h		
30.	Fosfomycin	*Pseudomonas aeruginosa*	100 mg/kg	8 h	IV	<12
			5 g	8–12 h		>12
31.	Co-trimoxazole	*Burkholderia cepacia*	480 mg	12 h	Oral	<12
			960 mg			>18
32.	Trimethoprim	*Burkholderia cepacia*	4 mg/kg	12 h	Oral	<12
			200 mg			>12
33.	Temocillin	*Burkholderia cepacia*	1–2 g	12 h	IV	>12
34.	Taurolidine	*Burkholderia cepacia*	4 mL of 2% solution	12 h	Inhaled	>18

(Cystic Fibrosis Foundation, 2009; Edward DeSimone, 2018; Sarath Ranganathan, 2006)

Bronchodilators

Bronchodilators (long- and short-acting β2 agonist) are the most frequently used therapeutic agents among patients with CF (Konstan et al., 1999). These drugs are used to treat the obstruction and hyper-responsiveness of the airways. They also improve mucus clearance (Brand, 2000).

Mucolytic and mucoactive agents

These agents decrease the elasticity and viscosity of mucus by breaking its gel structure. However, they have negative effect on physiological clearance of mucus by ciliary transport, which can efficiently remove thick mucus as compared to viscous mucus (Dulfano and Adler, 1975; Gelman and Meyer, 1979). These secretions are aspired via suction catheters especially in hospitalized patients. Two mucoactive agents, namely N-acetylcysteine (NAC) (600 mg/day) and dornase alpha (2.5 mg), have been administered in CF patients through aerosols to treat abnormal pulmonary secretions (Henke and Ratjen, 2007). NAC is not widely

recommended because of its potential ADR (i.e., bronchospasm). Dornase alpha is not only safe in CF patients having forced ventilatory capacity (FVC) < 40% of predicted value, but is also associated with side effects such as laryngitis, pharyngitis, hypersensitivity reactions, chest pain, rhinitis, sinusitis, dyspnea, pneumothorax, hemoptysis, and conjunctivitis (Fuchs et al., 1994; McCoy et al., 1996).

Anti-inflammatory and antioxidants agents

As CF progresses, pulmonary function declines due to inflammatory response and subsequent tissue damage (Rowe et al., 2005). Thus, therapy with nonsteroidal anti-inflammatory agents (NSAIDs) and corticosteroid gives beneficial outcomes. NSAIDS like propionic acid derivatives (e.g., ibuprofen 20–30 mg/kg twice daily) have been shown to improve disease condition of CF patients with mild type of the disease (Konstan et al., 1995). Ibuprofen gives proinflammatory response at low doses, but is associated with ADRs (e.g., decrease in lung function and kidney injuries) at high doses and consequently increases the lengths of hospital stay (Lahiri et al., 2014; Lands and Stanojevic, 2013). Topical use of corticosteroids (e.g., Leukotriene B4 (LTB4) receptor antagonists) seems to be more beneficial as compared to those formulations, which are designed for systemic use. However, phase II trials were halted due to significant ADRs related to pulmonary exacerbations (PEs) (M. W. Konstan et al., 2014).

Nonpharmacological Management

Chest physiotherapy

This technique is used to drain mucus from five lobes of the lungs. As each position is designed in such a way that a major part of the lung is facing downward, it may be referred to as postural drainage and percussion (Cystic Fibrosis Foundation, 2017a). Devices like drainage tables, electrical and nonelectrical palm precursors, and vibrators are required to carry out this process.

Lung transplantation

It is a surgical procedure in which severely damaged lungs can be replaced with the healthy respiratory organs (Cystic Fibrosis Canada, 2014). Patients have to undergo several pretransplant tests including pulmonary function test, chest and sinus X-ray, arterial blood gas, ventilation-perfusion scan, abdominal ultrasound, blood work, MUGA scan, thallium persantine scan, ECG, bone mineral density scan, 6-min walk test, sputum analysis, and oximetry test.

Supplemental oxygen

Patients with CF may experience hypoxemia either during exercise or sleep (Balfour-Lynn et al., 2005; Urquhart et al., 2005). Supplemental oxygen (1–2 L/min via nasal cannula or 2–4 L/min via venturi mask) may increase daytime function at workplace or school, improve physical function, and decrease mortality rate (Zinman et al., 1989).

Gene therapy

In 1989, the discovery of CFTR gene has brought the expectations that gene therapy could be the new era in CF treatment. In the accomplishment of this goal, two approaches were considered, namely, viral vector and plasmid DNA encapsulated within cationic liposomes. The first method was not widely used due to low transfer efficiency and short retention time within the airways. However, the second approach is giving fruitful results in animal models by correcting CF epithelial chloride transport defect and 100 folds improvement in transfer of genes. UK Gene Therapy Consortium performed phase I clinical trial by using a single dose of PGM169/GL67A. Besides defective CFTR gene, various other genetic factors also impart their role in the pathogenesis of this disease. Therefore, future research is focusing on screening of genetic modifiers.

Cystic Fibrosis-Associated Diabetes

Insulin

Insulin is the drug of choice for CF-induced diabetes mellitus (**Fig. 2**). Insulin not only controls hyperglycemia but also plays an important role in stabilizing respiratory function and nutritional status. **Fig. 2** illustrates the principle for managing CF-associated diabetes mellitus by using insulin therapy. Normally, insulin is required in modest dose (0.5–0.8 units/kg/day) for maintaining the baseline state of health (Sunni et al., 2013). Patients with fasting hyperglycemia are recommended to be managed using basal bolus insulin therapy through insulin pump (continuous subcutaneous infusion) or multiple daily subcutaneous injections (Moran et al., 2010; Nousia-Arvanitakis et al., 2001; O'Riordan et al., 2009b) while in patients without fasting hyperglycemia, pre-meal rapid acting insulin is considered as a standard therapeutic regimen. However, in either case, the goal is to titrate insulin to a highest dose that can be safely tolerated by the patients (Moran et al., 2009).

Cystic Fibrosis-Associated Vitamin Deficiency and Bone Diseases

Multivitamins

Patients with CF often suffer from deficiency of vitamins and essential nutrients. Vitamin D deficiency occurs due to concomitant hepatic disease. Vitamin A deficiency is associated with poor respiratory function, because β-carotene has antioxidant property

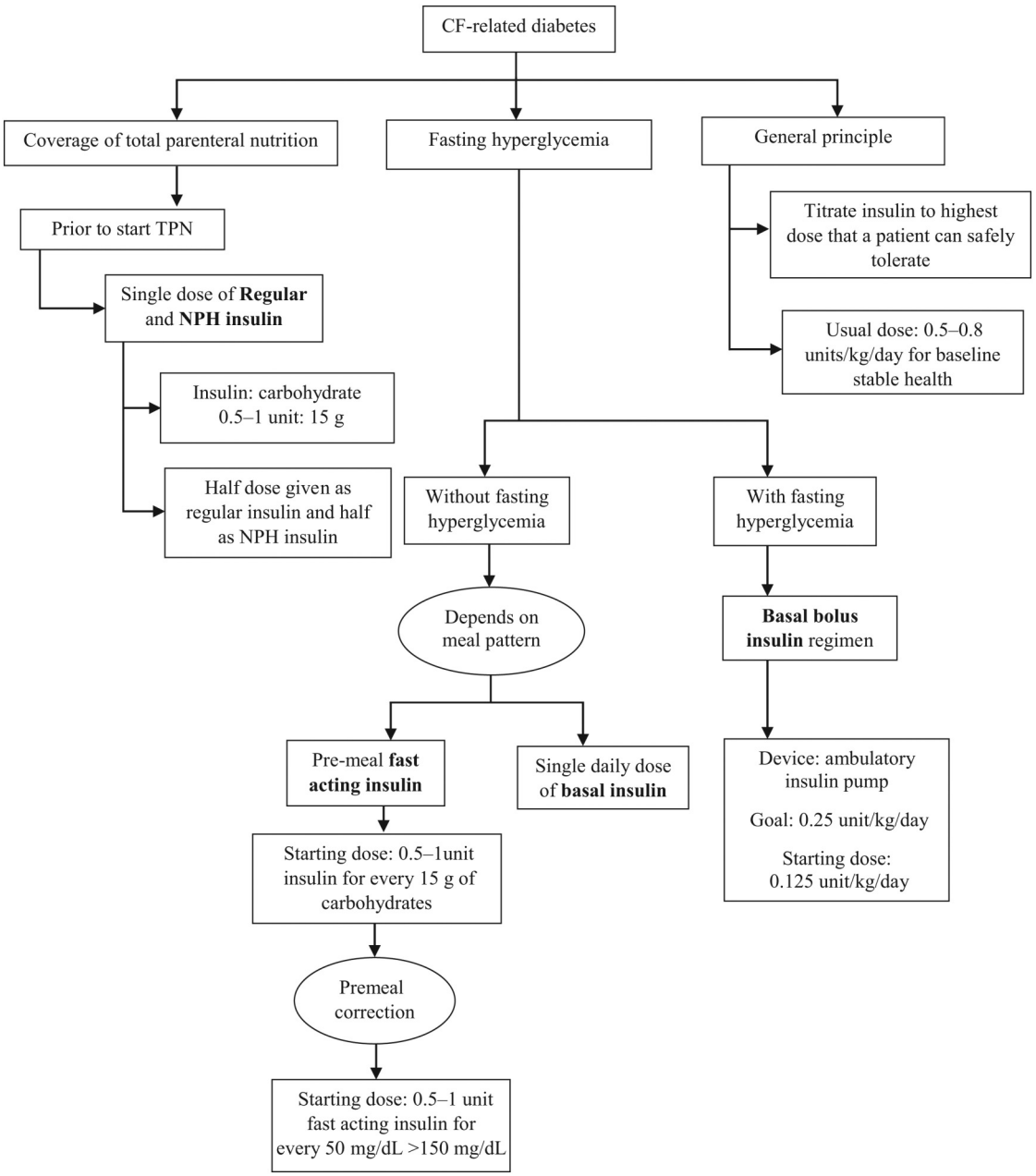

Figure 2 Algorithm for the management of CF-associated diabetes.

and its level becomes very low in patients with CF (Huet et al., 1997; Sinaasappel et al., 2002; Winklhofer-Roob et al., 1996). Similarly, due to increased oxidative stress, the daily requirement of body for Vitamin E also increases soon after birth and consequently gives rise to an impaired secretion of glutathione and low level of selenium (Freedman et al., 2004; Roulet et al., 1997; Thomas et al., 1995). Thus, patients with CF experience an impaired fat metabolism. Irrespective of the pancreatic function, the level of vitamin A and vitamin E must be closely monitored in all patients with CF. Vitamin K is involved in prothrombin synthesis and also acts as a cofactor in the carboxylation of osteocalcin during bone formation. Its deficiency leads to osteopenia especially in CF patients (Aris et al., 2005). The recommended doses of vitamins and calcium supplements for different age groups are outlined in **Fig. 3**.

Moreover, malnutrition, chronic infection, and pulmonary or intestinal bleeding may lead to poor level of serum ferritin, which reflects iron deficiency. Supplements containing iron are not regularly prescribed for patients with CF, because iron acts as an important substrate for the growth of *P. aeruginosa*. Zinc level also decreases and it can be improved by pancreatic enzyme replacement therapy (PERT) (Easley et al., 1998). The daily recommended doses of fat-soluble vitamins and vitamin content in specialty vitamin formulations for patients with CF are provided in **Table 4**.

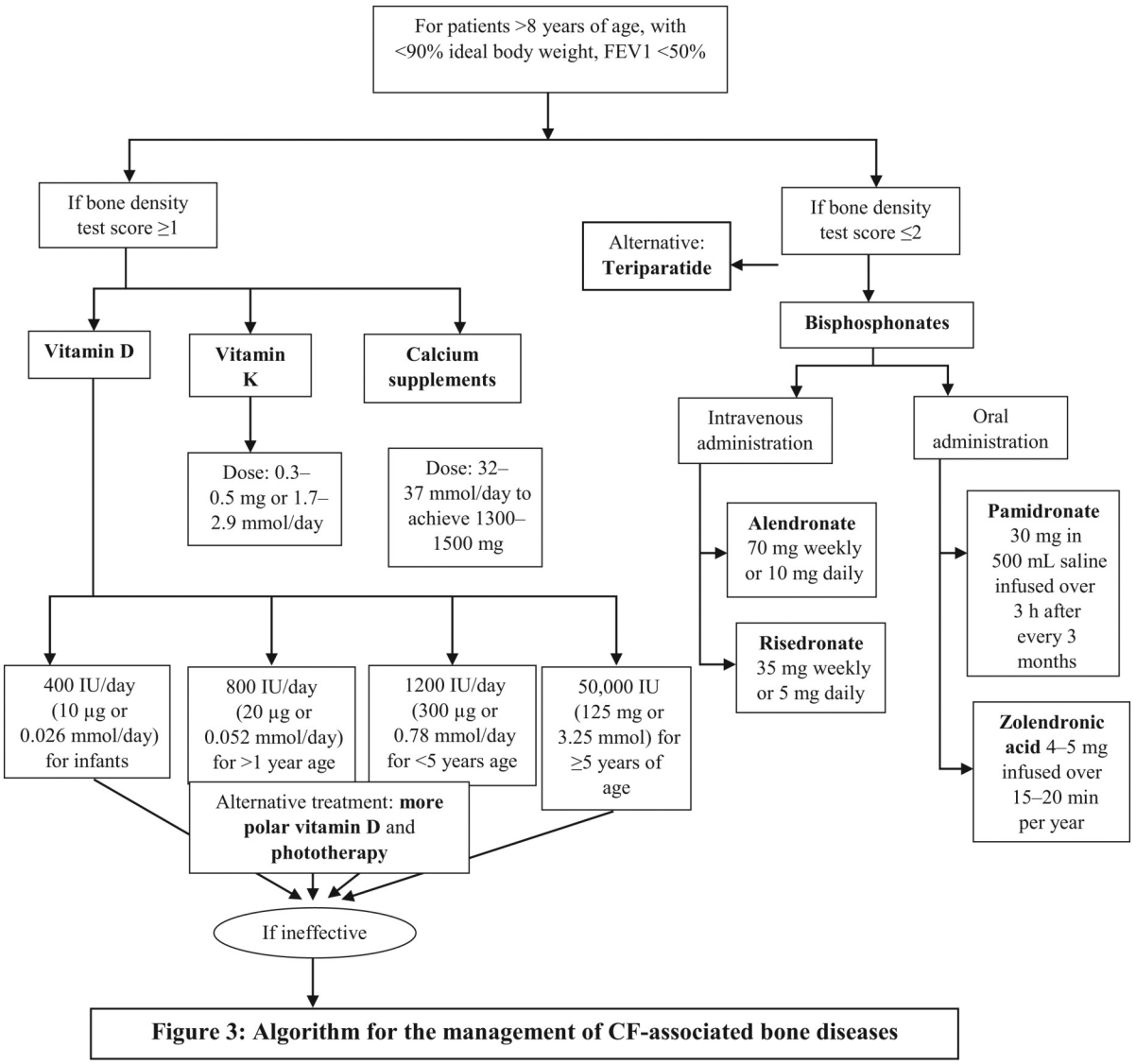

Figure 3 Algorithm for the management of CF-associated bone diseases.

Bisphosphonates

To overcome complications like osteoporosis, bisphosphates are recommended as first-line therapeutic agents for CF-induced osteoporosis (Fig. 3 describes the oral and intravenous administration of bisphosphonates) (Sermet-Gaudelus et al., 2011). This therapy not only leads to a decreased function and recruitment of osteoclasts but also shortens the lifespan of osteoclast and slows down the process of osteoblast apoptosis. However, bisphosphonates have a questionable safety and tolerability; therefore, these can be replaced by teriparatide (Marshall et al., 2014; Neer et al., 2001). If the bone density test score is more than 1, then the CF patients should be prescribed vitamins and calcium supplements (Sermet-Gaudelus et al., 2011).

Prevention of Cystic Fibrosis-Associated Complications

CF is a nonpreventive disease, but its symptoms and other complications can be managed using pharmacotherapy, nutrition, vaccination, exercise, and smoking cessation (B. L. Foundation, 2018). Routine immunization is recommended in children with CF. Influenza vaccine should be administered in children ≥6 months of age. However, it is contraindicated if the child is hypersensitive to egg with the evidence of previous incidence of anaphylactic shock. NHS guidelines suggest that children can receive nasal vaccines in case of mild hypersensitivity (National Health Service, 2018). Since pneumococcus does not have a prominent effect on CF patients, prevnar vaccine is not routinely recommended. Nevertheless, it is a compulsory vaccination course, especially in those pediatric patients (age >5 years) who undergo splenectomy. Furthermore, passive immunization with

Table 4 Recommended daily doses of dietary supplements

			Doses of different dietary supplements								
			Vitamin				*Minerals*				
Sr. no.	*Age*		*A*	*K*	*D*	*E*	*Iron*	*Zinc*	*Calcium*	*Magnesium*	*Sodium*
1.	Infants	0–6 months	2000 IU	300–1000 μg	400–1000 IU	40–80 IU	0.2 mg/day	2 mg/day	210 mg/day	30 mg/day	500–1000 mg/day
		7–12 months	2000 IU	300–1000 μg	400–1000 IU	40–80 IU	0.2 mg/day	3 mg/day	270 mg/day	75 mg/day	500–1000 mg/day
2.	Young children	1–3 years	2000–3000 IU	1000–10,000 μg	800–2000 IU	50–150 IU	9 mg/day	3 mg/day	500 mg/day	80 mg/day	1000–4000 mg/day
		4–8 years	2000–3000 IU	1000–10,000 μg	800–2000 IU	50–150 IU	10 mg/day	4 mg/day	500 mg/day	130 mg/day	1000–4000 mg/day
3.	Older children	9–11 years	5667 IU	1000–10,000 μg	800–4000 IU	150–300 IU	8 mg/day	6 mg/day	1000 mg/day	240 mg/day	1000–4000 mg/day
		12–13 years	5667 IU	1000–10,000 μg	800–4000 IU	150–300 IU	8 mg/day	6 mg/day	1300 mg/day	240 mg/day	1000–4000 mg/day
		14–18 years	5667 IU	1000–10,000 μg	800–4000 IU	150–300 IU	11 mg/day	8 mg/day	1300 mg/day	410 mg/day	1000–4000 mg/day
4.	Adults	19–30 years	10,000 IU	1000–10,000 μg	800–4000 IU	150–500 IU	8 mg/day	14 mg/day	1000 mg/day	400 mg/day	6000 mg/day
		31–50 years	10,000 IU	1000–10,000 μg	800–4000 IU	150–500 IU	8 mg/day	14 mg/day	1000 mg/day	420 mg/day	6000 mg/day
		51–70 years	10,000 IU	1000–10,000 μg	800–4000 IU	150–500 IU	8 mg/day	14 mg/day	1000 mg/day	420 mg/day	6000 mg/day
		>71 years	10,000 IU	1000–10,000 μg	800–4000 IU	150–500 IU	8 mg/day	14 mg/day	1000 mg/day	420 mg/day	6000 mg/day

(Cystic Fibrosis Foundation, 2017b; Thoracic Society of Australia and New Zealand, 2017)

Table 5 Major roles of a pharmacist providing care for cystic fibrosis

	Pharmacist's role in the management of cystic fibrosis
1	Counseling of parents on newborn screening
2	Routine review of medications
3	Therapeutic drug monitoring
4	Discussion of patient's medication history
5	Counselling on medication adherence
6	Monitoring the off-label use of medicines in CF
7	Implementation of antimicrobial stewardship
8	Communication with general practitioners and community pharmacists
9	Accessibility of patients towards novel drugs
10	Homecare pharmacy services
11	Medicine information services
12	Reduction in wastage of central intravenous additives
13	Prescription evaluation and dispensing of medicines
14	Medication supplies and cost-effective use of medicines
15	Participation in inpatient ward rounds
16	Medicine optimization and reconciliation

monoclonal antibodies (i.e., Palivizumab) against respiratory syncytial virus (RSV) is available in the market and can be administered intramuscularly five times in a month.

The Role of Pharmacist in the Management of Cystic Fibrosis

CF is a multi-organ system disease that requires multidisciplinary approach for its management. As discussed above, many therapeutic agents are used for the management of CF. Usually, a patient with CF has to take an average of 8–10 medicines on daily basis. It takes an average of 3h to administer this complex medication regimen (Sawicki et al., 2009). As a result, patients experience many problems including nonadherence to drug therapy, therapeutic failure, and poor therapeutic outcomes. Thus, pharmacists can help patients with CF due to their expertise in pharmacotherapy, pharmacokinetics (PK), pharmacodynamics (PD), and drug interactions. In this way, issues such as medication nonadherence, increased incidence of readmission, poor quality of life (QoL), and decreased QALY can be resolved (Prunty and Prunty, 2015). Some of the responsibilities of a CF specialist pharmacist are listed in **Table 5** (Abraham et al., 2018; Mooney et al., 2016).

Counseling of Parents on Newborn Screening

Patients and their families need proper counseling and education at the time of screening and discharge from the health care setting. Newborn screening (NBS) for CF is beneficial for reducing morbidity and mortality associated with CF. Most of the parents support it; however, the psychosocial harm due to NBS process, false positive results, and identification of infant are some of the major concerns. CF centers deal with these issues by giving swift and timely education to improve the impact of diagnosis on the families (Duff and Brownlee, 2008).

Routine Medication Reviews

Patients with CF must actively participate in comprehensive routine reviews of medications. The purpose of CF pharmacist in conducting these reviews is to check medications of each patient and make possible interventions. Philpott et al. reported that a CF pharmacist can make an average of 4.75 interventions per patient and most of these interventions were thought to be significant (Philpott et al., 2007). These interventions may include, but not limited to, changes to inhaled antibiotic formulations, recommending alternative therapeutic agents, and changing the time of administering medications. Review of records such as medication history, patient's most recent clinic visits, and discharge letters is a requisite before conducting the medication reviews. In this way, several issues like irrational prescribing, discrepancies, and nonadherence can be identified and CF pharmacist can discuss these problems during the review process. Problems like poor access to medicines can also be discussed during the review.

Therapeutic Drug Monitoring

Many therapeutic agents such as aminophylline and antifungal agents have to be administered for prolonged period of time among CF patients. A pharmacist can reduce the toxic effects and ensure the safe use of medicines by applying his knowledge of clinical pharmacokinetics (Abraham et al., 2018). The active participation of pharmacist in TDM is associated with: (1) the rapid

achievement of pharmacokinetic and pharmacodynamics targets within short interval of time, (2) increase in frequency of clinical improvement, and (3) a significant reduction in the number of administered doses of drugs, the mean total dose administered, and the alteration of serum creatinine from baseline (Murphy et al., 2007).

Discussion of Medication History with Cystic Fibrosis Patients

CF pharmacist must take medication history from each patient that may include previous medicines, intolerances, and allergic reactions. This discussion enables the pharmacist to include over-the-counter (OTC) drug, and recreational and herbal medicines in the prescription, and counsel the patients about possible ADRs and interactions with other conventional medicines.

Counseling on Medication Adherence

CF is an inexorable disease in which patient's health eventually declines even with complete adherence to therapy. This is because of the fact that its treatment is complex and mostly involves polypharmacy. In order to halt the progression of the disease, it is essential to optimize the patient's adherence by ensuring rational use of resources. In CF, FEV1 and body mass index (BMI) negatively affect the outcome of treatment. The role of a devoted CF pharmacist is to increase patient adherence to treatment. The importance of self-reported adherence has been recognized as a tool to measure medication adherence in routine practice (Mooney et al., 2016). It has also been found that the greater participation of a specialized pharmacist in CF treatment is beneficial in terms of adherence monitoring. On the basis of these findings, CF pharmacist can motivate patients, provide them with the required information, and design strategies to achieve treatment goals. It is also the responsibility of the pharmacist to counsel patients at the time of discharge. Patients must be provided with a list of medicines, purpose, and timings of administration. Pharmacist can communicate with patients about their supply of home medicines. There are circumstances where the patients require fewer drugs (e.g., when they have sufficient stock of medicines at home) or in need of extra supply of therapeutic agents (e.g., when they plan to go somewhere for vocations or work). In this way, the supply given from ward can precisely match with that of the requirements (Redfern and Webb, 2004). A devoted CF pharmacist can assess and monitor the patient's adherence to the dosage form of the drug. She/he may recommend alternative therapeutic agents, change the dosage form, and provide tablet crushers or clutters if needed. Pharmacist can assess the suitability of any therapeutic agent on the basis of patient compliance, and this may be supplied if potential benefits are foreseen. The role of the pharmacist becomes more profound when the patient with CF is a child instead of an adult. It is primarily because of the fact that in such cases, the parents are responsible for managing medications. Thus, the benefits of self-administration schemes are to spread knowledge, autonomy, and make the patient responsible toward therapy of CF.

Monitoring of Off-label Use of Medicines in Cystic Fibrosis

The complexity of CF disease requires the use of therapeutic agents outside their product license. For instance, a novel medication may not have undergone clinical trials, which are prerequisite for gaining the status of being used among pediatric patients, or it may be crucial to alter the dosage form of a drug so that it can be given through an unlicensed route. In this case, appropriate dosing is crucial. Thus, a pharmacist can play a significant role in making these medicines safe and effective by applying pharmacokinetic and pharmacodynamics principles in their formulation. A case study reported the use of posaconazole among CF pediatric patients suffering from allergic bronchopulmonary aspergillosis (ABPA). Although it had not been licensed to be used among patients with CF due to unavailability of data from previously published literature, pharmacist recommended pediatric dosing and evaluated the incidence of ADRs through TDM (Bentley et al., 2015). Furthermore, the limited supply of the unlicensed medicines restricts the physicians to prescribe these agents. In these cases, the CF pharmacist can evaluate the appropriate supply chain (e.g., specialist center or homecare services), which may enable the patients to get their prescribed medicines. The CF pharmacists, especially in those regions of the world where they allow to provide services as independent prescribers, can ensure seamless and timely ongoing supply of medicines to patients.

Implementation of Antimicrobial Stewardship Programs

Antimicrobial stewardship (AMS) program encompasses the selection of dosage and duration of antibiotic regimen for the treatment and prevention of infectious diseases that consequently gives the optimal therapeutic outcomes with limited adverse drug reaction (ADRs) (Gerding, 2001; Leonard et al., 2018). This program is a cascade of interventional strategies for designing the protocols to prescribe antibiotics, improving the rate of antibiotic susceptibilities, and optimizing the cost and utilization of resources across the continuum of care (NICE, 2015). The primary health care provider like pharmacist can play a significant role in this regard (Wickens et al., 2013). Respiratory exacerbations are among the major complications associated with CF; hence, antibiotics especially inhaled formulations are the mainstay agents in reducing these complications and enhancing the longevity of patients with CF (Working, 2009). However, there are several issues associated with the use of aminoglycosides and other antibiotics (Al-Aloul et al., 2005). In such cases, CF pharmacist can design individualized dosing regimens using their knowledge of PK. CF pharmacist is also responsible for observing the process of TDM along with the monitoring of renal, hepatic, blood, and electrolyte indices. CF patients are more prone to antibiotics associated hypersensitivity reactions. It is primarily because of the fact

that antibiotics can give suboptimal therapeutic outcomes in hypersensitive patients (Parmar and Nasser, 2005). Thus, CF pharmacists can identify and document these reactions and recommend alternatives or desensitizing regimens (Dworzynski et al., 2014). In this way, patients can attain optimal therapeutic outcomes with minimal loss of lung functions.

Communication with Community Pharmacists and General Practitioners after the Patient's Discharge from the Hospital

The management of CF in outpatient and inpatient settings requires a multidisciplinary team work because patients suffering from CF are prescribed with many therapeutic agents. Some of these medications are licensed products and are not commonly available. It is the prime responsibility of pharmacists working in CF centers to inform general practitioner and community pharmacist about change in treatment regimen of patients (Smith et al., 2010). Thus, the liaison of CF pharmacist with community pharmacist, clinical commissioning pharmacist, and general practitioner is beneficial in preventing delays to patients receiving their medicines and thus ensuring patients' safety and convenience (O'Riordan et al., 2009a).

Accessibility of Patients Toward Novel Drugs

The inequitable access of novel agents like gene-specific medicines has not only made the treatment regimen complex for CF patients but also economically burden the health care system (Helman, 2007). CF pharmacist is responsible for implementing patient access schemes, formulating guidelines, spreading awareness among patients, and health care professionals about beneficial aspects of optimal delivery of novel drugs, monitoring the adherence and outcomes of these agents, identifying eligible patients that can be treated under local funding agreement (Bucks et al., 2009). Thus, CF pharmacist is liable to gather information about specification of services, funding agreements, and patient's registry data. In this way, proper allocation of budget can be made possible without wastage of resources.

Homecare Pharmacy Services

It is the responsibility of the pharmacists and their coworkers to ensure proper access of therapeutic agents to the patients. The inaccessibility issues arise after the discharge of CF patients from health care settings especially when they are prescribed with orphan drugs. To resolve this issue, there are several homecare companies that provide home delivery services of therapeutic agents to the patients (Fajolle et al., 2004). The pharmacist is responsible to complete the process of registration, supply of prescriptions and liaise with homecare companies regarding delivery of medication and solve the problems of patients when required.

Medicine Information Services

The medication information services must be made available to all CF patients through email or telephone. Pharmacist must educate the patients about their newly prescribed agents, drug–drug interactions, and drug–food interactions (Kerem et al., 2005). This service must be supervised by those pharmacists who are specialized in medication information and work in collaboration with CF pharmacist. Although health care providers can be contacted for attaining medicine information, it is recommended that CF pharmacist must be contacted first (Conway et al., 2014).

Reduction in Wastage of Central Intravenous Additives

The availability of CF pharmacists in units and their active participation in ward rounds is mandatory in reducing the wastage of central intravenous additives (CIVA). Moreover, if the decisions about discharge of patients or change in therapeutic regimen are quickly communicated to the central pharmacy aseptic area, then the medication order can be canceled or changed. In this way, a considerable amount of money can be saved (Fajolle et al., 2004). There are several issues on which the longitudinal studies must be carried out and these mainly include (1) cost-effective analysis before and after the appointment of a devoted CF pharmacist, (2) comparison of outcomes when the pharmacist is available with those when the pharmacist is not available. It was predicted that CIVA wastage per week was reduced from £324 to £30 when the pharmacist was made available. Thus, the potential saving on CIVA is £16,848 annually (Redfern and Webb, 2004).

Medication Supplies and Cost-Effective Use of Medicines

Although the provision of optimal care to the patients can never be compromised while practicing cost-saving strategies, the wastage of health resources must be kept minimum (Institute of Medicine, 2003). Also, medicines free from value-added tax (VAT) can only be dispensed in the community pharmacies because hospitals are not able to pass on VAT to the patients. Thus, the CF pharmacists must encourage the prescribers to prescribe those medicines that can be dispensed in community pharmacies (Redfern and Webb, 2004). In this way, VAT on the expensive medicines can be reduced to a greater extent. It is the duty of pharmacist to reduce the issues of drug supply. The communication between manufacturer and purchaser can be useful in maintaining a constant supply of CF medicines (Narayana et al., 2014).

Participation in Inpatient Ward Rounds

A devoted CF pharmacist can play a vital role in various aspects during the ward rounds which are as follows:

1. He/she can help the physicians in making decisions about therapeutic regimen.
2. He/she can resolve various pharmaceutical problems that may arise due to the involvement of multidisciplinary team.
3. He/she can monitor the upgradation and maintenance of medication records.

Prescription Evaluation and Dispensing of Medicines in Cystic Fibrosis Centers

In CF centers, there is a limited availability of facilities like medicine dispensing. The limited prescriptions must be supplied by the dedicated CF pharmacist who is knowledgeable and experienced in providing services to the CF patients. In this way, number of queries regarding CF medication can be minimized to a greater extent (Moran et al., 2010). This method also ensures that counseling is provided particularly to the patients with respect to the ADRs of therapeutic agents, time of administration, and drug interactions. There is limited opportunity available for the pharmacist to dispense on the unit. However, a devoted CF pharmacist checks the prescription for legibility, completeness, and drug interactions before sending it for dispensing in the main pharmacy. Thus, the process of dispensing speeds up in the main pharmacy area. But such services are not widely available in all health care settings. The presence of a devoted CF pharmacist in the health care centers is acknowledged by many patients and some patients now make requests to see the CF pharmacist for medication advice during clinic visits (Tobacco, 2008).

Medicine Optimization and Reconciliation

It is a patient-centered approach to ensure the rational use of medicines. It is applicable to all patients whether they may or may not be able to take their medicines effectively (Cutler et al., 2011). This can be done retrospectively by using patient's data from the records of inpatient admission, annual reviews, and clinic attendance. The prime focus of this technique is to monitor the patients' adherence toward the prescribed therapeutic regimens and avert the medication errors and possible ADRs (Barton, 2009). A devoted CF pharmacist can counsel patients about the purpose of medication, administration technique, rational use of medicines, storage of drugs, expiry date of medicines, common ADRs, and the ways through which medicine related problems can be subsided. This will help the pharmacists in developing longstanding professional relationship and gives the opportunity to the families to resolve their medication-related doubts (Thomspon et al., 2015).

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Management of Gastrointestinal Disorders and the Pharmacist's Role: Coeliac Disease

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Learning Objectives

- Develop an understanding of the role of gluten in coeliac disease and the similarities and differences between this and other syndromes/symptoms associated with wheat/gluten ingestion.
- Develop an ability to recognize the main clinical presentations of coeliac disease.
- Confidently encourage members of the public to seek appropriate diagnosis of wheat/food reaction suspicions, as symptoms may have many etiologies.
- Development of an understanding of the Australian labeling laws regarding gluten and put this in context of labeling in other parts of the world.
- Develop an increased awareness of the sources of gluten in the pharmaceutical area, and when this may be an issue.

Take Home Messages

1. Coeliac disease affects greater than 1 in 100 people in Australia. Much of this goes unrecognized. Untreated coeliac disease may lead to osteoporosis, anemia, certain mental health conditions, infertility (female), and results in an increased risk of bowel cancer. On the other hand, many people unnecessarily follow gluten-free diets with potential long-term adverse health consequences given they often do this without consideration for dietary guidelines, resulting in a diet which may be inadequate in one or more key nutrients.
2. Should coeliac disease be suspected, the person should remain eating gluten and undergo a blood screening test for the condition. If the blood test is positive, a small bowel biopsy is required to confirm the diagnosis. This is the gold standard encouraged by gastroenterologists and other doctors specializing in coeliac disease in Australia.
3. Coeliac disease and dermatitis herpetiformis (a related skin condition) both require strict, lifelong avoidance of gluten, regardless of the presence OR absence of any symptoms.

4. There are a number of other wheat-related medical conditions. It is important to understand the nature of the particular condition under discussion, as this will determine how strictly gluten needs to be avoided. Of these, wheat/gluten intolerance would be the most frequently discussed with the Pharmacist. The mechanism to date is unclear, but may be due to a low tolerance to gluten; indigestible fructo-oligosaccharides (fructans); or to other components of wheat or indeed other grains or foods. Management of these issues is to determine tolerance thresholds for symptoms rather than strict food avoidance, and should only be done in consultation with a Dietitian, as it may not be a component of wheat which is causing the symptoms. It may be other components of the foods in which wheat is consumed, as wheat is not normally eaten in isolation.
5. There are different food standard requirements surrounding allowable concentrations of gluten in food labeled gluten-free, depending on the country where it is made. This will affect both food and pharmaceuticals which may be perceived as acceptable for someone with coeliac disease, as well as what can be sold as gluten-free in Australia.

Introduction to Condition

Whilst this chapter is primarily about coeliac disease (CD), this chapter will take a slightly different tack to some other chapters and will consider some of the common conditions which may present in a similar way to CD and provide context to an understanding of some of the issues around it.

There is in fact, no medication to be prescribed for this condition, management to date being diet alone. However, there are two major issues which the Pharmacist may encounter when assisting a person with CD or suspected wheat reactions. In the first instance the Pharmacist must understand the myriad conditions that may mimic CD and counsel clients to seek an appropriate diagnosis for their suspected wheat reactions.

Self-reported wheat intolerance has increased significantly over the past 10–15 years (Hischenhuber et al., 2006), with these people generally attributing decreased quality of life to gluten- or wheat-induced intestinal and extraintestinal symptoms (Golley et al., 2015). Coeliac disease, Non-Coeliac Gluten Sensitivity (NCGS), Dermatitis Herpetiformis (DH), Wheat Allergy (WA), or Wheat-Dependant Exercise-Induced Anaphylaxis (WDEIA) are all conditions associated with reactions to wheat and or gluten (Pietzak, 2012).

These reactions may be caused by a variety of wheat fractions. In CD, this is the result of gluten (Rubio-Tapia et al., 2013) from wheat, rye, barley, and to a lesser degree, oats (Hardy et al., 2015). Omega-5-gliadin (Palosuo et al., 2003) from wheat may cause WDEIA, while α-gliadin and α-amylase inhibitor (Maruyama et al., 1998; Palosuo et al., 2001) are major wheat allergens. Irritable bowel syndrome (IBS) may be provoked by gluten (Di Sabatino et al., 2015) from gluten-containing grains, or fructo-oligosaccharides (Biesiekierski et al., 2013) from wheat and other foods, or by other food compounds (Faulkner-Hogg et al., 1999).

Given the range of conditions associated with wheat, the pharmacist needs to understand that the diagnosis and management of each condition is unique to that condition. It is therefore crucial to understand the implications in terms of avoidance or exposure to gluten.

The second major role for the pharmacist is ensuring appropriate medications for those with CD, as medications for other conditions may contain gluten as an excipient. It is important to recognize where these small amounts of gluten really are a problem and where they are not.

This chapter will briefly explore other wheat/gluten-related conditions to provide a framework for understanding the management of those with CD and then provide an understanding of the role of the pharmacist within the wider health team of affected people.

Disease/Condition Information

When considering gut symptoms, a pharmacist will most likely find themselves discussing the symptoms suggestive of either CD or wheat intolerance. It is vital that a suggestion to trial gluten avoidance is NOT made, but rather the person is encouraged to pursue a correct diagnosis for their symptoms as current consumption of gluten is foundational to testing outcomes for CD and DH. More information on these two conditions is provided in this section.

Coeliac Disease Epidemiology

Well-known CD researcher, Alessio Fasano has described CD as "one of the most frequent genetically based diseases of humankind" (Fasano, 2003). It is understood that 99.6% of people with CD carry one or more of the human leukocyte antigens, HLA-DQ2 or HLA-DQ8 genotypes (Karell et al., 2003). Anderson estimates that approximately 55% of Australians have one or both of these genes (Anderson et al., 2013). Although roughly 30% of the world's population have these genes, only about 3% of those go on to develop CD (Green and Jabri, 2006). First degree relatives of someone with CD have a 10%–20% increased risk of developing CD (Ludvigsson et al., 2014; Rubio-Tapia et al., 2013).

The prevalence of CD has increased fourfold since the 1950s (Barbero et al., 2014). Today, it is believed that CD occurs in approximately 1% of populations in developed countries. It is estimated that 1 in 80 males and 1 in 60 females in Australia have CD, while Scandinavia and Ireland have the highest global prevalence at 3%. It is quite rare in Asia and Japan, occurs in

approximately 1 in 300 in Germany, and is considered to be common in North Africa and parts of the Middle East (Barbero et al., 2014; Fasano, 2003). It is thought that 80% of Australians who have CD remain undiagnosed (Anderson et al., 2013), leading to a lower quality of life (Gray and Papanicolas, 2010), and the implication of potential future medical issues beyond those mentioned above, due to the malabsorption of nutrients and resulting nutritional deficiencies, even in the presence of what appears to be an adequate diet.

Etiology

Wheat/Gluten-Related Conditions that may be Mistaken for Coeliac Disease

Before discussing the etiology of CD, it is important to have an understanding of conditions that may present in a similar manner to CD. The etiology and management of each of these conditions is uniquely different, and for some of the conditions, failure to appropriately manage the condition may result in a severe reaction or long-term negative health consequences.

Irritable bowel syndrome

Wheat and its components, including gluten, fructo-oligosaccharides, and potentially a number of other compounds, are implicated in provoking IBS symptoms for some people. Fructo-oligosaccharides are also known as fructans—one of the components of FODMAPs [Fermentable oligo-, di-, mono-saccharides and Polyols], a group of short chain sugars that may result in lower gastrointestinal symptoms in susceptible people (Biesiekierski et al., 2013). Specific food intolerances related to IBS and other functional gastrointestinal disorders are idiosyncratic, and there are other food components that may be implicated beyond those under discussion here. Ingestion of wheat and gluten-containing foods in IBS and NCGS does not damage the small intestine but may lead to a range of both intestinal and extraintestinal symptoms. Currently, there are no known diagnostic biomarkers and reduction in wheat/gluten intake, not total avoidance, is suggested for affected individuals.

Food is a complex cocktail of chemicals, and beyond those in wheat itself, natural and added chemicals such as salicylates, amines, glutamates, colors, flavors, and preservatives are also found in many processed wheaten products or foods eaten with wheat, each of which may cause similar symptoms in susceptible people (Faulkner-Hogg et al., 1999).

A formal, structured assessment, followed by a strict elimination diet and systematic challenge protocol should be undertaken under the supervision of an appropriately trained and experienced accredited practicing dietitian (APD) to determine the etiology of any food-related symptoms, and this only after appropriate medical diagnosis to rule out other conditions. An APD will also monitor intake to encourage nutritional adequacy throughout the process. Because of the complexity of food and diet, mistaken attribution is common, and often results in inappropriately restricted diets.

Wheat allergy (IgE-mediated) and wheat-dependent exercise-induced anaphylaxis

There are diagnostic indicators for both wheat allergy and WDEIA (Palosuo et al., 1999, 2001). No damage to the small bowel occurs in either condition. True IgE-mediated wheat allergy tends to be seen in babies and children, presenting with fast-spreading hives/rash, eczema flares, nausea, or vomiting closely following wheat ingestion (Keet et al., 2009). Anaphylaxis is rare, but possible, in this group. Clinical history combined with skin prick tests (SPTs) are used by suitably trained doctors to diagnose a wheat-allergic sensitization. Dietary wheat (not gluten) avoidance is often total when quite young and moderated a little as the child ages, based on subsequent testing and food challenges.

WDEIA is rare and is most commonly found in those working in the beauty industry, where sensitization can occur through damaged and abraded skin. The first presentation of WDEIA occurs mostly in young to middle-aged adults who develop symptoms when they exercise following a meal containing wheat. Symptoms include hives, flushing, nausea, and diarrhea, which may progress to more severe symptoms including angioedema, laryngeal edema, and hypotension, leading to anaphylaxis (Palosuo et al., 1999). Wheat/gluten avoidance is personalized for these people as symptoms severity which relates to exercise intensity and timing after eating wheat, varies from person to person. SPTs are not always positive to wheat, and omega-5-gliadin blood tests are positive in about 80% of those with WDEIA (Matsuo et al., 2008; Palosuo et al., 2003). Some allergists may perform, under supervision, wheat food provocation tests. An epipen is often prescribed. It should be noted that exercise-induced anaphylaxis may occasionally be caused by other food proteins.

Etiology of Coeliac Disease

CD is caused by a complex immunological T-cell response provoking damage to the villi in the small bowel in genetically susceptible people of all ages, by the gluten portion of grain proteins found in wheat (Ludvigsson et al., 2014; Rubio-Tapia et al., 2013), spelt, triticale, rye, barley, and, controversially, oats (Hardy et al., 2015). This small intestinal inflammatory disease was traditionally recognized by its gastrointestinal symptoms and nutritional malabsorption outcomes, such as failure to thrive in children. Today, however, its wide range of presentations see it classified as a multiorgan autoimmune disease, which engages the attention of doctors of many specialties. Undiagnosed CD carries significant potential for future medical complications. CD is also associated with numerous other autoimmune conditions, including autoimmune thyroid disease and type 1 diabetes.

For unknown reasons, in some people with susceptible genotypes, the immune system develops a reaction to gluten leading to inflammation, along with an increase in the number of intraepithelial lymphocytes and the destruction of the villous architecture of the small intestine. Enzymes and helper molecules, generally found on the villi, which aid the absorption of nutrients, are then lost. Malabsorption and nutritional deficiencies ensue and are responsible for many of the presentations of CD.

Table 1 Gluten proteins at the molecular level (Shewry and Tatham, 1990; Thompson, 1997)

	Gluten proteins		
	Prolamin	*% of PROLAMIN in the protein*	*Glutelin*
Wheat	Gliadin	40%–50%	Glutenin
Rye	Secalin	30%–50%	*Rye* glutelin
Barley	Hordein	35%–45%	Hordenin
Oats	Avenin	5%–15%	*Oat* glutelin

Gluten (Haraszi et al., 2011; Shewry and Tatham, 1990), which triggers the process, is not a single molecular structure, as it consists of two protein subfractions: a prolamin and a glutelin. The chemistry of each protein subfraction varies with the different grains. The wheat prolamin is called gliadin, and the wheat glutelin is called glutenin. The gliadin is further subdivided into alpha, beta, gamma, and omega gliadins. The alpha-gliadin is purported to be the most damaging to the small bowel; however, damage can occur with any gliadin or glutenin fraction (**Table 1**).

These protein subfractions are also found in rye and barley. The chemistry in each is slightly different, yet similar enough to provoke damage in the small intestine. On the other hand, oat gluten, called avenin, is significantly different from other forms of gluten, does not contain gliadin-like chemistry, and poorly activates disease (Comino et al., 2011).

The gluten (wheat, rye, barley, but not oats) prolamin portion is rich in the amino acids glutamine and proline. The spacing of these amino acids determines deamidation (Schuppan et al., 2009). For a reaction to occur (**Fig. 1**), tissue transglutaminase (an intracellular enzyme) needs to be extracellular, and gluten needs to be present. It is postulated (Schuppan et al., 2009) that during mechanical or chemical injury or during infection, tissue transglutaminase (tTG) is released from damaged cells and then when dietary gluten peptides reach the subepithelial connective tissue, a reaction could occur. tTG recognizes the spacing between the glutamines and the prolamins on the undigested gliadin and binds to it. The deamidation of the glutamine to glutamic acid creates a negatively charged protein, which enhances its binding via antigen-presenting cells to the HLA-DQ2/HLA-DQ8 molecules. These then display the resulting complexes to other immune helper T-lymphocytes. This triggers a twofold T-cell response. Some cause mucosal destruction leading to villi blunting, and others lead to the production of antibodies to the gliadin (anti-gliadin antibodies) and to tTG (anti-tTG antibodies). Both antibodies are used to screen for CD.

Many people with undiagnosed CD spend years seeking help for mild abdominal symptoms or complaints such as chronic tiredness and fatigue. It has been suggested (Brown, 2012) that classic gastrointestinal presentations such as nausea, vomiting, steatorrhea, diarrhea, bloating, and wind now make up less than 50% of those with CD. Roughly 20% are thought to be asymptomatic, and greater than 50% have weak GI symptoms or extraintestinal manifestations of CD.

Positive serological screening tests for CD require confirmation (Husby et al., 2018; Ludvigsson et al., 2014; Rubio-Tapia et al., 2013) by a duodenal biopsy and, if confirmed, significant, (often ongoing) education, monitoring, and support from a

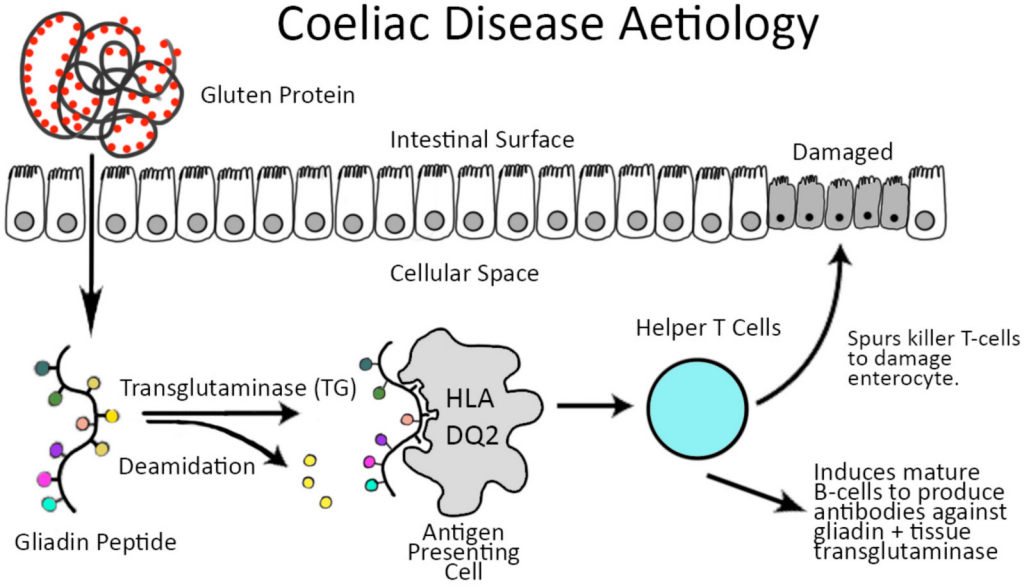

Figure 1 Aetiology of small mucosal injury from gluten in coeliac disease.

Table 2 The National Institute for Health and Care Excellence guidelines suggest testing for CD in these patient groups (National Institutes of Health Consensus, 2005, p. 54).

Offer serological testing for CD to these	*Consider serological testing in these groups*
First degree relatives of people with CD People with any of the following • persistent or unexplained abdominal or gastrointestinal symptoms • prolonged fatigue • faltering growth • unexpected weight loss • severe or persistent mouth ulcers • unexplained iron, vitamin B12 or folate deficiency • type 1 diabetes, at diagnosis • autoimmune thyroid disease, at diagnosis • IBS (in adults)	• metabolic bone disorder (reduced bone mineral density or osteomalacia) • unexplained neurological symptoms (particularly peripheral neuropathy or ataxia) • unexplained subfertility or recurrent miscarriage • persistently raised liver enzymes with unknown cause • dental enamel defects • Down's syndrome • Turner's syndrome

CD, Coeliac disease; *IBS*, irritable bowel syndrome.

specialist dietitian. Patient motivation is crucial, referral to Coeliac Australia is strongly encouraged and medical follow-up is also required (**Table 2**).

Currently, the sole treatment for CD is a lifelong gluten-free diet. Adherence to this is expected to improve not only symptoms, nutritional status, and small bowel villous damage but also to decrease risks from long-term medical complications of gluten ingestion, including infertility, osteoporosis, anemia, gastrointestinal cancers, and reduced life expectancy (Irvine et al., 2017). For these reasons, strict adherence to the gluten-free diet is essential for those with CD.

Dermatitis Herpetiformis (DH) (Cardones and Hall, 2012) is an uncommon skin disease characterized by eruptions of itchy blisters typically in the area of the elbows, knees, and buttocks. It is rare to have DH without having malabsorptive signs of CD (>10%) (Ludvigsson et al., 2014), so patients are advised to undergo testing for CD, if this has not been done. About 25% have normal villi, with increased intraepithelial lymphocytes (Ludvigsson et al., 2014). In many, the bowel symptoms experienced are not as severe, or are silent and there seems to be milder small bowel biopsy changes. The onset of DH is seen more often in people between the ages of 30 and 50 years (Ludvigsson et al., 2014). It is rare for children to have DH, and it occurs more frequently in males than in females, while CD occurs more frequently in females. DH is initially treated with dapsone, which the patient is weaned off over a 2-year period, as the gluten-free diet takes over the management (Ludvigsson et al., 2014). Pharmacists should seek further information on pharmaceutical management of DH as this is beyond the scope of this chapter.

Diagnosis

Symptom response to a gluten-free diet should not be used to diagnose CD, as this does not differentiate CD from IBS or NCGS, nor does it drive home to the patient the significance of CD and the importance of the gluten-free diet to their overall health.

An accurate diagnosis of CD should be established before commencing a life-long gluten-free diet. Coeliac-specific serology and mucosal villous damage need to be evidenced, and these will wane with time on a gluten-free diet.

Blood tests can only screen for the disease, not diagnose it. IgA antibodies to tTG are serological markers with very high sensitivity and specificity, used to screen for CD (Ludvigsson et al., 2014; Rubio-Tapia et al., 2013). People who are IgA-deficient have an increased risk for CD, so IgA testing is used to identify these people, and IgG markers are utilized instead. Many combined IgA/IgG tTG tests are performed.

Gluten must be currently consumed in the diet in order to diagnose CD. The duodenal biopsy remains the gold standard for diagnosis of adults, but there may be circumstances where the blood tests may be used to diagnose CD in children (Husby et al., 2018; Ludvigsson et al., 2014; Rubio-Tapia et al., 2013). The diagnostic process involves 3 steps, and it is essential that significant gluten is in the diet for parts 1 and 2.

If the person has a gluten-free or almost gluten-free intake, and is reluctant to return gluten to the diet, a blood test can be performed to determine if they carry the gene/s associated with CD. The main role for this serogenetic blood test is to rule out CD or make it highly unlikely, given the low chance that someone without these genes will develop CD (Husby et al., 2018). If the tests show that the patient carries one or both genes, the only way to diagnose the disease is to add gluten back to the diet for a period of time, then proceed with the testing as described below.

Gluten loading

It is imperative to ensure adequate gluten is in the diet prior to testing for CD. If the person is already on a gluten-free diet, Coeliac Australia recommend the consumption of four slices of wheat bread each day for at least 6 weeks before testing is performed (Coeliac Australia, 2017). Be aware that quantities and length of ingestion time vary around the world (Husby et al., 2018). Once adequate gluten has been consumed, diagnostic testing may proceed.

Some knowledge is required of gluten ingredients to estimate whether enough pretest gluten is being eaten, and a consultation with a dietitian familiar with the requirements will ensure this is understood by someone intending to undergo testing. Wheat flour products, such as bread, pasta, biscuits, cake, and pizza, are the preferable form of gluten. Spelt, rye, and barley products could also be eaten. Oats should not be used as the major source of gluten, because avenin is thought to activate the disease process in only about 5%–8% of people with CD (Comino et al., 2011; Hardy et al., 2015). The residual gluten alone in wheat starch, wheat thickeners, beer, or malt will not reach the required levels of gluten to stimulate villous changes in the majority of people. Wheat-derived glucose syrup and dextrose can be safely consumed by those with CD so will not contribute to the gluten load.

Diagnosis steps (Husby et al., 2018)

1. Coeliac-specific blood antibody tests
    a. Total Ig A
    b. Tissue transglutaminase IgA & IgG (tTG)
    c. Deamidated gliadin peptide IgA & IgG (DGP)
    d. +/− Endomysial antibodies (EMA)
    e. +/− Serogenetic tests (HLA-DQ2 and HLA-DQ8) (if not done earlier)
2. If antibodies are positive, a small bowel biopsy looking for villous damage is required
    a. Entails a day stay hospital procedure with a gastroenterologist
3. Follow-up biopsy 12–18 months after being on a gluten-free diet
    a. Improvement in the villi confirms the diagnosis

Serogenetic tests

Serogenetic tests determine whether or not the patient carries either or both of the HLA-DQ genes associated with CD. Gluten does not need to be in the diet to conduct this test, and buccal swabs can be offered to young children in order to collect the DNA. As previously mentioned, this test cannot diagnose CD (Husby et al., 2018) as it only screens out those who will *not* have CD, as the absence of HLA-DQ2 and HLA-DQ8 virtually excludes it. Testing for these genetic alleles, in those on self-imposed gluten-free diets, can better define which patients will be required to load gluten back to the diet to undergo usual coeliac-specific antibody tests and which do not.

Coeliac-specific blood antibody tests

- The IgA versions of the tests are preferred. Total IgA is ordered to ensure that the tests are properly interpreted. IgG versions are used in those IgA deficient.
- EMA is the best test but is expensive and not frequently ordered in Australia.
- tTG may be slightly raised for reasons other than CD, so small deviations from normal should not be interpreted as CD. If it is significantly higher than the reference range, this should generate a referral for a small bowel biopsy. This test is considered unreliable in children under the age of five, as their antibodies can fluctuate due to their developing immune system. It is suggested that tests in this age group are repeated 3 months apart (CoeliacAustralia, 2017).
- DGP is thought to be more reliable in the under 5 age group, but not as good as tTG in those over 5.

With concession to exceptional circumstances in some children (Husby et al., 2018), if antibodies are significantly raised, the patient should always be referred to a gastroenterologist for a small bowel biopsy (Ludvigsson et al., 2014; Rubio-Tapia et al., 2013) to diagnose CD.

Clinical Presentations

Clinical presentations of CD are varied, and these days, not often seen is the skinny pot-bellied child, which may have come to mind a number of years ago. Many of the symptoms may be typical of other conditions and diagnosis often now occurs as an adult. Thus, careful investigation is crucial for early diagnosis. **Table 3** outlines the main presenting symptoms of CD.

Management of Coeliac Disease

Place of Pharmacotherapy in Treatment Options

Currently, the only treatment for CD is a strict gluten-free diet. At this time, there are no medications or medical adjunct therapies for this condition. As such, there is no direct pharmacotherapy related to CD. Without hesitation, pharmacists should encourage all

Table 3 Possible disease presentations, or risks of untreated disease (Brown, 2012).

Malabsorption:
- Anemia
- Fatigue or weakness
- Reduced bone mineral density
- Osteoporosis/osteopenia
- Short stature
- Muscle cramps
- Arthritis/bone or joint pain
- Dental enamel defects
- Easy bruising
- Weight loss
- Failure to thrive in infants and children

Gastrointestinal:
- Increased risk of malignancy of the GI tract as well as non-Hodgkin lymphoma
- Nausea
- Wind
- Bloating
- Abdominal pain
- Constipation
- Vomiting

Reproductive: in women only
- Late menarche
- Early menopause
- Infertility
- Miscarriages

Neurological disorders:
- Depression
- Concentration and memory problems (brain fog)
- Decreased school performance
- Headache or migraine
- Mood swings or depression
- Cerebral ataxia
- Seizures
- Early onset dementia
- Peripheral neuropathy

Other
- Heart: Carditis
- Renal: IgA nephropathy
- Liver disorders
- Refractory coeliac disease

Skin:
- Dermatitis herpetiformis
- Hair loss
- Apthous mouth ulcers

clients with this diagnosis to consult a dietitian who specializes in this area if they have not already done so, as management is not only about what to avoid but also what to include in the place of gluten, to ensure nutritional adequacy.

To assist those with CD, local dietitians, skilled in the management of CD, can be found via the Dietitians' Association of Australia (DAA) website (https://daa.asn.au/find-an-apd/) on the "how to find an Accredited Practicing Dietitian" page or direct the person to the DAA website. In Australia, it is imperative that the nutrition health professional consulted carries the accredited practicing dietitian (APD) status, as these people hold appropriate qualifications to adequately assess and provide education and support for people with clinical conditions such as CD. They have university qualifications in nutrition and dietetics and have undertaken their training in a course accredited by the Dietitians' Association of Australia. Only an APD can provide a Medicare rebate with a care plan from their doctor. In other countries, a similarly suitably qualified nutrition professional should be consulted.

While there is no pharmacological management of CD per se, the pharmacist has a vital role to play when a person with CD has other comorbidities requiring medication. While vitamin and mineral supplementation is generally not recommended for the general public, except in certain disease states, at least in the short term, someone diagnosed with CD may be prescribed vitamin and/or mineral supplementation. It is essential for the pharmacist to ascertain that every medication, vitamin, elixir, or jelly bean/lolly sold to them for their use is gluten-free. If the pharmacist is suggesting alternate prescription brands to that being prescribed by the doctor, it is vital that only gluten-free generic brands be offered.

Pharmacological Management

In order to ensure all medications are strictly gluten-free for CD patients, it is vital that the pharmacist has an excellent understanding that the moniker "gluten-free" means different things in different countries according to food labeling regulations. "Gluten-free" refers to a legislated amount of gluten that may be present in a food or product labeled as such. It does not mean zero gluten. Australia has the strictest gluten-free standard in the world. Products declaring themselves to be gluten-free which do not originate in Australia are required to meet the Australian gluten-free standard if they are to be sold here using the "gluten-free" label. This will impact baby formulae, specialized foods and vitamins, minerals and medications sourced from overseas companies.

To call a product gluten-free in Australia, The Food Standards Australia New Zealand mandate that the product must not contain malt, oats, or ingredients derived from them, and it can contain no detectable gluten (FSANZ, 2017). This came into effect in 1994. Assays to detect gluten have become more sensitive so products once called gluten-free (previously up to 30 ppm gluten) may no longer carry the gluten-free label. Currently, the best ELIZA test can detect gluten to levels of 2–5 ppm (Mendez et al., 2005;

Table 4 Symbols used in Coeliac Australia's Ingredient List Phone App here (Coeliac Australia, 2017)

	"Ingredient list" symbols	*Can be eaten by people with coeliac disease*
✓	Gluten-free (GF)	Yes
☑	No detectable gluten even if wheat derived	Yes
✘	Contains detectable gluten	No

Sharma, 2012) and in Australia the current gluten-free limit is 3 ppm (FSANZ, 2017). Australia also has a "low gluten" food standard, allowing a food to contain oats, malt, and up to 200 ppm of gluten. It is rare to see this food label, and these foods are not recommended for people who have CD. They are considered suitable for consumption by those with a wheat intolerance.

The European Codex Alimentarius, and both the United States and Canadian food standards differ in their wording, yet all agree that products that contain up to 20 ppm of gluten can be labeled gluten-free. These nations accept the current research that approximately 50 mg of gluten daily needs to be eaten on a regular basis before damage starts to occur to the small bowel of the majority of people with CD (Catassi et al., 2007). It has been calculated that an average regular intake of foods labeled gluten-free at 20 ppm would contribute ~10 mg of gluten a day to the diet (Akobeng and Thomas, 2008; Collin et al., 2004). This is considered to be a good safety margin from the 50 mg/day "at risk" level of intake, particularly noting that symptoms can occur in the absence of bowel damage.

It is important to be aware of these differing standards and although internationally 20 ppm is accepted as appropriate for people with CD to consume, there is great resistance in Australia to endorse these products at this time as they fall outside the Australian standard, thus cannot be called gluten-free in the Australian context. The Australian public is therefore confused and often uninformed regarding the safety of these 20 ppm products and most do not purchase them.

The pharmacist may run into this issue with European-based baby formulae and baby food ranges, some bulking agents based on wheat starch, vitamins, other supplements, or medications sourced from overseas. Wheat starch was once a popular excipient in many tablets but has now largely been replaced by maize starch.

As an important point of difference, for most people with wheat/gluten intolerance, in the absence of CD, this level of attention to detail is not warranted. These people should be encouraged to liberalize their diet to their tolerance level, as achieving nutritional adequacy is far easier when gluten forms part of the diet. This is quite apart from the decrease in limitations on social situations and drain on finances from higher food costs when gluten must be stringently avoided. There is also emerging evidence of alterations to the gut microbiota when gluten is removed from the diet without consideration of the addition of alternative suitable foods, and the long-term implication of this is as yet unknown.

Reading a food label correctly is an important skill. The following wheat-derived ingredients are considered safe for people with CD because they are highly refined, removing the gluten component: glucose syrup, dextrose, fructose, maltose, caramel color, glucona-delta-lactone (575), MSG, distilled alcohol, and wheat germ oil (a common source and therefore ingredient in Vitamin E preparations).

The Coeliac Australia phone-App can assist the pharmacist to be aware of which wheat-derived ingredients are of concern and which are not. Ingredients are alphabetized, and symbols, as shown in **Table 4**, are used to indicate ingredients that can be safely consumed and those which must be avoided. It is clear and easy to understand and may be a useful resource for pharmacists, in order to check whether products and compounds are safe for use by someone with CD.

Medicine and supplement labeling for gluten differs slightly from food labeling. Food products, such as the packet lollies sold in a pharmacy, need to either:

- list the source grain beside any ingredient derived from wheat, rye, barley, or oats, OR,
- make a bolded allergen statement that the product contains wheat or gluten.

Pharmaceutical medicines and supplements need to declare the presence of wheat or gluten, but do not need to indicate which ingredient is the source.

Oat gluten controversy and food labeling

In Australia, oats are given equal footing with the other gluten-containing grains, when the reality is that the chemistry of the oat gluten barely resembles that of wheat, rye, or barley. Europe, Canada, and the United States allow "pure," "wheat free," or "uncontaminated" oats to be called gluten-free and consumed on a GFD (Gilissen et al., 2016). As such, "pure" oats can be an ingredient in a food labeled gluten-free overseas, but is not allowed in a product labeled gluten-free in Australia (FSANZ, 2017).

The prolamin portion of the oat gluten that triggers disease is called Avenin. It has been shown that a small proportion of people with CD exhibit a small intestinal T-cell response to oat peptides (Ellis and Ciclitira, 2008). Oats are tolerated by the majority because they contain very small amounts of avenin, compared with the proportion of gliadin in wheat, and the chemical structure of avenin is very different to wheat gluten, making it clumsy at activating the disease process. It is debated that about 5%–8% of people with CD react to oats (Comino et al., 2011; Hardy et al., 2015). As there is no way to predict which people with CD can successfully consume oats, they are currently discouraged on a gluten-free diet in Australia and excluded from the gluten-free food standards. People with NCGS should be able to consume oats in their diet on a regular basis.

Uncontaminated, wheat free or pure oats can only be called gluten-free outside Australia and New Zealand. These terms mean that the oats are specially produced so that they are grown from pure oat seed, on land that has not grown wheat, rye or barley for at least 2 years, and the rotational crop, (grown in the off season), is a gluten-free crop, and not the traditional wheat or barley. This ensures that at harvest and storage, gluten-containing grains do not mix with the oats. Australia does not grow these oats, but they can be imported and labeled "wheat free," "contaminant free," or "Pure," but not "gluten-free."

People who do not have many symptoms from CD are less likely to experience symptoms if they eat oats. However, symptomatic tolerance does not mean that the oats are not damaging the small intestine. The usual antibody bloods tests cannot monitor how the body is tolerating the oats. Only a small bowel biopsy can do this. If the client wishes to trial oats, their gastroenterologist must be informed and on board with this decision. It is generally recommended that good health and biopsy markers be restored before commencing a trial with oats (i.e., at least 6–12 plus months on the gluten-free diet and a follow-up biopsy to determine recovery). If all is well, pure oats can be trialed with follow-up biopsies at 3 and 12 months to determine short- and long-term tolerance (Pulido et al., 2009).

Need to supplement

People with newly diagnosed CD could be initially low in iron, folate, B12, zinc, calcium, vitamin D, fiber, protein, and total calories and may require supplementation of some kind. For many, life-long supplementation or dietary vigilance remains in terms of fiber, calcium, and vitamin D. Long-term requirements for other nutrients then depends on diet preferences and intake, just like in most other parts of the population.

Not all countries have mandatory fortification of wheaten products. In Australia, bread flour is fortified with thiamine and iodized salt is used. Wheat-based breakfast cereals are also commonly fortified with a range of nutrients, including B-group vitamins and iron. However, unlike wheat products, there is no mandatory fortification of gluten-free breads and cereals with iron and the B-vitamins, so attention to these is required in a long-term GFD and should be assessed and monitored by a dietitian. Iodine may also be compromised if people don't consume the iodine-fortified commercial gluten-free bread. This is easily remedied by using iodized table salt. Iodine supplements should only be prescribed by a doctor, as excess iodine is contra-indicated in some medical conditions.

What's Coming Up in Pharmacological Management

While there are currently no pharmaceutical options to treat CD, wheat allergy or wheat/gluten intolerance, research addressing these goals is ongoing. Below are short reports of innovative products and potential drugs under investigation.

Innovations to Combat Gluten Contamination

There is mental security in knowing it is possible to tackle the potential trace gluten contamination when served food made out of the control of the person eating it. Whether these innovations are used daily, twice a month, or only twice a year, they can potentially decrease the anxiety associated with gluten contamination when eating out and increase quality of life.

Tablet breaking down contaminant gluten

GluteGuard is an Australian innovation. It is a plant-based dietary enzyme called caricain that can break down proteins, including gluten. It is not a medical treatment for CD and does not allow a person to deliberately eat wheat, bread, or pasta meals. It is designed to be an adjunct to a gluten-free diet (Cornell et al., 2016).

It is intended to be taken just before a supposed gluten-free meal to prevent symptoms of inadvertent gluten ingestion, for example, where cross-contamination may occur, when ingredient labeling is uncertain, or when food preparation is out of the person's control, such as at a restaurant or friend's house (https://glutagen.com/gluteguard). Taking a GluteGuard tablet before eating the offered gluten-free meal may help protect from possible symptomatic consequences of inadvertent gluten contamination. It cannot be taken after the meal, or later that night if symptoms develop. As such, this product acts as a safety measure for gluten-sensitive individuals, helping to decrease the anxiety that often ensues whenever food preparation is out of their control.

Caution: This product can be suggested for those with CD but has the potential to make them complacent about determining if a food is gluten-free. Pharmacists should emphasize that a gluten-free diet is to be eaten and the tablet will give peace of mind about potential contamination. GluteGuard is suitable for those with a gluten intolerance, although they don't generally require strict vigilance with their gluten avoidance and most tolerate well the small amounts of gluten in cross-contamination situations.

Kits to test for gluten contamination

1. *Nima sensor* (NIMA, 2017)
   Nima is a small, portable device, designed by American scientists and CD researchers, to test small, on-the-spot samples of food for any detectable levels of gluten. A food containing up to 20 ppm of gluten is considered to be gluten-free, and therefore acceptable in America. Nima reports whether *any* gluten is present. It does not report the level. It can only be purchased online and has currently made little impact in Australia.

Caution: A limitation is that it only can report the gluten level in the snippet of food chosen to be tested, and this may not represent the entirety of the food on the plate.

2. *BIOHIT Healthcare Coeliac Quick Test* (http://www.biohithealthcare.com/products/diagnostics-tests/products/27/celiac-disease-quick-test.)
   This point of care (PoC) test, developed in Finland, has been available in Australia for a number of years. It proposes to diagnose CD from a fingertip blood sample, within 10 min. It is designed to detect antibodies (IgA/IgG/IgM) against human tissue transglutaminase in the whole blood sample. It has been suggested for "on-the-spot" use with dietitians, GPs, and pharmacists.
3. *Wesley Medical Research PoC Test:*
   Researchers at Wesley Medical Research Centre at Wesley Hospital in Brisbane are currently developing and testing a similar point of care finger prick test to diagnose CD.
   Caution: The use of the above two test kits has not generally been encouraged in Australia. The American Journal of Clinical Pathology (Bond and Richards-Kortum, 2015) reported that blood droplets from a pricked finger contain widely variable contents and only when five combined drops were tested were they able to get results accurate to the venous collected blood. False positives occur in up to 10% of PoC tests, while false negatives have been reported in 15%–20% of cases (https://www.coeliac.org.au/point-of-care-testing-poct/). While pharmacists who use these tests need to have extensive training, the preference is to "drive" patients toward consulting a GP and gastroenterologist for correct diagnosis. If CD is suspected, it is essential that they understand they must continue to eat wheat/gluten until all appropriate testing has been completed.

On the Horizon

The following products are not at the point where they have passed Phase I and/or II trials but are included as potential possible future directions.

Vaccine for those with coeliac disease

Nexvax2 is a vaccine developed in Australia to help those diagnosed with CD tolerate gluten (NEXVAX2, 2017).

The Phase I trials have shown it to be tolerated, safe to use, and has the anticipated bioactive response of being able to desensitize patients to the three specific peptides in gluten that have been identified as troublesome to people with CD.

The vaccine is being further developed by US biotechnology company ImmusanT, with phase 2 trials underway. This company also aims to develop improved serological tests, based on T-cells, to diagnose CD. As it is in the testing phase, this is not an available product.

Drug to reduce inflammation caused by consuming gluten

James Cook University doctors are working to create a drug to treat gluten intolerance and hopefully CD, by studying the way parasites reduce intestinal inflammatory responses. Animal experiments suggest intestinal worm parasites can suppress inflammation, leading to the novel approach of introducing hook worms into humans with CD, to study how they may be used to treat autoimmune or allergic disorders. Currently, trials show a reduced proinflammatory response to gluten in those infected. Small quantities of gluten were tolerated, but as yet, gastrointestinal symptoms could not be prevented with a steady, usual intake of gluten foods (Giacomin, 2015).

Monitoring and Measuring—How do we Know That Treatment is Working?

There are three measurable parameters to monitor the effectiveness of the gluten-free diet in those with CD.

1. Symptom reduction or remission
2. CD-specific antibodies returning to normal levels
3. Improvement or return to normalcy of the villi in the small intestine

Those with newly diagnosed CD will be able to report any improvement in symptoms after commencing a gluten-free diet. However, it is only through tests ordered by a doctor, namely, blood and biopsy results described above, that antibody and histological improvement in disease state can be assessed, which is the crucial part in ongoing management and decreased risk of future complications. It is well understood that while the antibodies may return to normal and symptoms recede, it does not always follow that the small bowel has recovered (Ludvigsson et al., 2014; Rubio-Tapia et al., 2010).

There is a perception by most that a gluten-free diet will rectify all parameters within weeks of initiation of a gluten-free diet. This is a misconception. Tissue transglutaminase antibodies usually take 9–12 months to return to normal serum levels. Small bowel villous recovery time is variable and often slow, taking 2–5 years (Newnham et al., 2016), with a median time of 3.8 years (Rubio-Tapia et al., 2010). Those first diagnosed with CD over the age of 40 (Selby et al., 1999) and those with a highly damaged gut at diagnosis (Rubio-Tapia et al., 2013), often find it difficult to return to a totally normal small bowel. Some struggle with symptoms for 6–12 months and in a proportion, symptoms improve but do not totally subside (Faulkner-Hogg et al., 1999; Newnham et al., 2016). While inadvertent gluten ingestion is principally the main suspect in this, other food intolerances (Faulkner-Hogg et al., 1999) may also be playing a role in some people, who for as yet unknown reasons, seem to have very sensitive guts.

In children, these parameters return to normal within 2 years in 95% of cases (Husby et al., 2018; Rubio-Tapia et al., 2010). Recovery is often faster and more complete than adults, supporting the observation that there is better compliance and fewer medical problems in those who start a gluten-free diet when they are young.

Increased morbidity outcomes are seen in those whose villi do not recover despite at least 12 months on a strict gluten-free diet (van Gils et al., 2015). This is known as refractory CD and is diagnosed after an in-depth dietary analysis from a dietitian and a series of tests with their gastroenterologist. This group has a greater risk of developing small bowel lymphomas (van Gils et al., 2015).

Nonpharmacological Management

As previously mentioned, nonpharmacological management, namely, a strict gluten-free diet is the sole management for this disease. Restoration of health can be a slow process for many. If the pharmacist has an understanding of the timeline of recovery, they can reassure slow-recovering patients and reiterate the need to avoid gluten. If someone with CD appears depressed or is financially constrained, a referral to a social worker or psychologist, or in the first instance, back to their GP for advice is warranted and helpful.

It is not uncommon, considering the damage to the small bowel, that people with newly diagnosed CD may have a transient lactose intolerance, until the villi recover. If gut symptoms remain uncomfortable at the start of the gluten restriction, removing lactose may help to settle symptoms. It's best for the pharmacist to suggest a visit to the dietitian and to stress that this is generally temporary, so as not to worry the patient excessively and to re-affirm that lactose-containing dairy products can often be returned to their diet after a period of avoidance. Avoidance of dairy food is not required. Lactose-free milk and hard cheeses, which are naturally gluten-free, remain good alternatives and lactose-digesting products such as Lacteeze can help enable tolerance of normal dairy foods. Yogurt is naturally low in lactose, and the lactose concentration reduces as the product ages, so this is generally quite well tolerated.

Prevention

Currently, there is no known way to prevent CD. In the last 20 years, several dietary approaches have been suggested when introducing food to babies and toddlers, in the hope that this will decrease the chances of the child developing CD. Although the incidence of CD appeared to decrease in the under 2 age group, absence of disease was not sustainable as childhood progressed, regardless of whether gluten was introduced or not introduced as an early food (Szajewska et al., 2016). Genetics still appears to be the strongest indicator of disease likelihood (Liu et al., 2014; Szajewska et al., 2016).

Parents may only be aware of the old dietary advice and many are reluctant to introduce gluten to their child's diet, with the hope that they may prevent the disease from developing. The recommendations in 2008 were to introduce gluten to the diet between 4 and 7 months of age, while the baby was being breastfed. New evidence prompted a revision of these guidelines by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2016 (Szajewska et al., 2016). The revised ESPGHAN guidelines are applicable to all infants, as outlined later especially those who carry at least one CD-risk genetic allele, not just those who have one or more parents with CD.

Neither breastfeeding alone nor breastfeeding during gluten introduction has been shown to decrease the risk of developing CD, but breast feeding should still be promoted for its otherwise well-established health benefits, according to the Australian Dietary Guidelines (AustralianDietaryGuidelines, 2018), and this is echoed in the ESPGHAN guidelines (Szajewska et al., 2016). Gluten can be introduced at any time between 4 and 12 months of age. Consumption of large quantities of gluten should be avoided during the first few weeks after gluten introduction and during infancy. The optimal quantity and type of gluten to introduce have not been determined.

Consumption of large amounts of gluten may potentially result in infants developing CD earlier than they otherwise might but is unlikely to change the inevitable outcome. The issue in developing CD in infancy rather than later in life is the potential for associated malabsorption resulting in failure to thrive. The only benefit of an early diagnosis is that it generally leads to better compliance and less long-term complications. Most people enquiring about timing of gluten introduction would have a family history of CD so someone in the family is consuming gluten-free foods. Feeding the infant both gluten-free and gluten-containing foods in order to both eat gluten and yet not eat large amounts of it appears to be a good option (Andren Aronsson et al., 2016).

The Role of the Pharmacist in the Health-Care Team

In CD, the main roles of the pharmacist can be mostly summed up as follows:

Evidence for role of pharmacist

- It is essential that the pharmacist supporting a person with CD is cognizant of the requirement for that person to be strictly gluten-free and be aware of the excipients in various drugs, supplements, nutritional formulae, and so on. They should ensure the client is receiving appropriate medications, suggesting alternatives if there is a problem. An understanding of Australia's strict laws

surrounding gluten-containing products is important. This comes to the fore particularly when a new medication is prescribed, when generic medications have the potential to be substituted for branded ones, and in nutritional supplement formulae (both food and micronutrients).

Medication management

- There is evidence that drug absorption may be impaired in those with undiagnosed or newly diagnosed CD, so it is important to identify those people who have CD and other comorbidities and monitor the efficacy of drugs.
- Every person is different, and dietary compliance and choice of nutritious food are variable. While it is preferable that a person gain their required nutrition from foods, sometimes supplementation is required, particularly in the early stages or if the person is very underweight and/or undernourished on diagnosis. Once the person has been assessed by a dietitian and has an understanding of additional supplementation required, if any, the pharmacist is important to ensure appropriate gluten-free products are selected.

Counseling/listening skills

- Where a client asks for gluten-free products and does not have CD, it is important to be able to counsel them around those products that contain little gluten and point them back to a dietitian if there is a concern about nutrition, and first and foremost to a GP if there are concerns the client may indeed have undiagnosed CD.
- Using effective listening skills is also important. It is obviously the doctor's role to diagnose, and the dietitian's role to manage the diet and prescribe nutritional supplements, both in terms of energy and micronutrients; but it is useful for the pharmacist to be aware of questions being asked and refer back to the dietitian, the doctor or another member of the health-care team if they are concerned.

Role in the interprofessional team

- Understanding the science and being able to assist a client who may present with either a self-diagnosis (especially IBS or NCGS) or misleading, inaccurate, or nonevidence-based information from an alternative practitioner is important, followed by referring back to an appropriate health-care team member. The pharmacist is potentially the first health-care professional to become aware of the person's symptoms, so has an important role here.
- Being aware of and understanding of quality of life issues. There are times when a person diagnosed with CD may suffer some kind of mental health issue as a result of the isolation they may feel following a long search for solutions, or dealing with coming to grips with their diagnosis and the inevitable lifestyle changes which ensue. Anxiety and depression are not out of the question for some. Food is at the center of our social fabric, and it can make socializing difficult when you have to be on guard around shared food. Gluten-free foods are also more expensive than regular foods, which can be a significant financial burden for those of lower income groups. Recognizing mood changes in a person with CD and using effective counseling skills can be helpful in pointing the client toward an appropriate member of the health-care team, such as a psychologist or social worker.

Triage

- This role should not be underestimated. Given people will present to the pharmacy looking for medications, as well as pre and probiotics to manage symptoms caused by possible IBS or NCGS, the pharmacist is in a unique role to be able to ask a few questions and encourage those who have not been adequately diagnosed to see their GP to ensure appropriate diagnosis and long-term management of their condition. The outcomes of this action may decrease the risk of a person undertaking tests or therapies, which are not validated, often expensive, and which may result in them either restricting their diet unnecessarily or, more importantly, failing to have CD identified.

Thus, the role of the pharmacist may be nontraditional and quite different from most other conditions, but it is nonetheless valuable and not to be trivialized.

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Relevant Websites

Dietitian's Association of Australia. Find an APD

- https://daa.asn.au/find-an-apd/

Coeliac Australia – National not-for-profit organisation supporting Australians with Coeliac Disease

- https://www.coeliac.org.au/
- https://www.coeliac.org.au/diagnosis/ information regarding diagnosis
- https://www.coeliac.org.au/uploads/65701/ufiles/Fact_sheets/DiagnosingCoeliacDisease.pdf fact sheet regarding diagnosis
- https://www.coeliac.org.au/point-of-care-testing-poct/

Other websites

- http://www.foodstandards.gov.au/ Standard 1.2.7 and schedule 4 of the Code outlines the requirements/criteria for the making of gluten-free claims.
- The National Institute for Health and Care Excellence. (NICE) 2015 [29/3/2017]. Available from: https://www.nice.org.uk/guidance/ng20/evidence/full-guidance-pdf-438530077
- The Australian Dietary Guidelines: https://www.eatforhealth.gov.au/guidelines/australian-dietary-guidelines-1-5

Company websites

- Nima sensor: https://nimasensor.com/gluten/
- Nexvax2: https://www.wehi.edu.au/news/coeliac-disease-vaccine-shows-promising-results-phase-i-trial
- Biohit: http://www.biohithealthcare.com/products/diagnostics-tests/products/27/celiac-disease-quick-test

Constipation

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Learning Objectives

- Understand the factors most likely to contribute to constipation
- Know that the consequences of constipation may affect many different body systems and cause a wide variety of symptoms
- Have knowledge of medicines and medical conditions that may contribute to or cause constipation
- Be able to take a comprehensive medical history
- Understand the patient barriers that may occur when discussing constipation
- Be aware of alarm symptoms
- Deliver nonpharmacological and pharmacological counseling and treatments
- Be aware of the onset of action and precautions/contraindications of laxatives
- Be aware of new treatments for constipation

Take Home Messages

- People may have many misconceptions about constipation and the medicines used to treat it. It is important that health-care professionals have a clear understanding to correct these misconceptions
- Constipation may cause a wide variety of intestinal and extra-intestinal symptoms
- It may not be possible to deprescribe medicines suspected of contributing to constipation
- Many older people may consider bowel health a private matter, which they find difficult to discuss. Conversely, many health-care professionals may feel uncomfortable in asking questions and discussing the issue, which requires a proactive approach and appropriate communication skills
- Constipation in children occurs for different reasons than in older people and treatments may differ
- Appropriate treatment for certain groups of patients includes the prophylactic use of laxatives

Introduction

Constipation is a common functional gastrointestinal disorder (FGID) and refers to a change in bowel habit that involves the passage of hard stools less frequently than is normal for the patient (APF, 2015). Although abdominal pain and/or bloating may be present, they are not predominant symptoms and should not meet criteria applicable to irritable bowel syndrome (IBS) (Lacy et al., 2016)—see chapter on IBS. The term "functional" has been used to describe a disorder that affects function or performance, causing signs or symptoms of an organic disease, but with no obvious evidence of structural or physiologic abnormalities. Other FGIDs include functional dyspepsia, gastroparesis (delayed stomach emptying), IBS, and functional diarrhea. Diagnosis is based on

symptoms, with minimal tests and investigations unless the patient has clinical features that warrant further investigation (eTG complete, 2016).

Functional disorders can be classified according to the Rome criteria, whose development began in 1988 when a team of experts worked to develop consensus criteria for the diagnosis of IBS (Drossman, 2016). The Rome Foundation classification of FGIDs is based primarily on symptoms rather than physiological criteria. This is because of limited evidence that physiological disturbance (e.g., motility) fully explained patient symptoms and that symptoms are what bring patients to health-care providers. While IBS was not the only FGID, at that time there existed no overarching operational definition or classification for them. The first set of criteria ("Rome I") for 21 functional GI disorders were compiled into a book in 1994. Studies began being published using these criteria, which progressed their acceptance and further use and development through Rome II (1999–2000), III (2006), and IV (2016). Rome III differed from Rome I and Rome II with the use of more evidence-based rather than consensus-based data. This was because a greater number of research studies published using the Rome criteria allowed for more precise patient selection and presented data more representative of these disorders (Drossman, 2016).

To advance the field of FGIDs, Rome IV had to address limitations and make changes which have included an improved definition of FGIDs that is positive (rather than by the exclusion of other disease), reflective of current scientific knowledge and nonstigmatizing. Rome IV now defines FGIDs as disorders of gut–brain interaction (Lacy et al., 2016).

There is an increased prevalence of constipation in older (greater than 60 years) adults, believed to be due to reduced physical activity and polypharmacy rather than age-related physiological changes (Emmanuel et al., 2017). The people with sedentary life style are three times more likely to report constipation (Rao and Go, 2010). Whole gut transit time is prolonged in immobile people (AMH Aged Care Companion, 2016), and it may not be possible to deprescribe medicines suspected of contributing to constipation. However, it has also been stated that there are two main causes of constipation in the elderly—age-related slow colonic transit time and pelvic floor dysfunction causing a functional defecation disorder (Roque and Bouras, 2015).

Many older people may consider bowel health a private matter, which they find difficult to discuss. Consequently, many patients may resort to self-medication and therefore do not benefit from the experience of health-care professionals (Emmanuel et al., 2017). Conversely, many health-care professionals may feel uncomfortable in asking questions and discussing the issue, which requires a proactive approach and appropriate communication skills.

In children, most constipation is functional or idiopathic and related to behavioral withholding after an unpleasant stool event (Waterham, 2017). Constipation may also occur secondary to other medical conditions.

Misconceptions About Bowel Habits

There are many misconceptions about bowel habits and what is viewed as normal. Normal stool frequency can vary between 3 motions per day and 3 motions per week (Gandell et al., 2013). However, a hard stool passed with difficulty (straining) once or twice daily indicates constipation, while a soft stool passed comfortably every 2–3 days does not (APF, 2015). Some may believe that having a daily bowel movement is necessary for health, rationalizing that toxins arising from prolonged residence of undigested food may be absorbed, resulting in illness and a variety of nonspecific symptoms. There are also many misconceptions about which laxatives are safe and effective. Some falsely believe that stimulant-type laxatives damage the colon with chronic use (Wald, 2006). The availability of over-the-counter laxatives and fiber supplements means that without intervention, idiosyncratic beliefs may perpetuate irrational self-treatment. Patients need to understand that bowel habits vary considerably between individuals and for individuals over time (Australian Medicines Handbook, 2018).

Although not normally life threatening, the impact of constipation can be as great in older patients as other common chronic conditions such as diabetes and osteoarthritis (Emmanuel et al., 2017). In susceptible older people who are frail, excessive straining can trigger a syncopal episode or coronary or cerebral ischemia (Gandell et al., 2013). Laxatives (also known as aperients) are used to prevent straining, particularly for those at increased risk such as during the postoperative period, in those who have ischemic (coronary) heart disease, and in those with hemorrhoids. In addition to gastrointestinal symptoms, constipation in children may cause reduced appetite and irritability (eTG complete, 2016).

Effective management of childhood functional constipation depends on securing a therapeutic alliance with the parents, particularly through the first years when children cannot accurately report symptoms. Clinicians may depend on the reports and interpretations of the parents, who know their child best, in addition to their own training and experience, to differentiate between health and illness (Gordon et al., 2016).

Incidence and Burden of Disease

The prevalence of constipation has been estimated to be 16%–20% in the general population (Emmanuel et al., 2017; Roque and Bouras, 2015). Its prevalence rises with age, with some estimates as high as 50% in those over 80 years old. Up to 40% of older people living in the community and 50%–60% of those in aged care facilities may be affected (Gandell et al., 2013). It should be noted that prevalence varies with the definition used. Severe constipation is more common in elderly women, with rates two to three times higher than their male counterparts. Chronic constipation negatively impacts health related quality of life, with psychological and social consequences (Roque and Bouras, 2015). Improperly diagnosed "overflow" incontinence resulting from impaction with

leakage of liquid stool can be a trigger for nursing home admission (Emmanuel et al., 2017). Constipation is a common reason for primary care visits and referrals to gastroenterologists (Selby and Corte, 2010).

Chronic constipation can lead to bowel obstruction, urinary incontinence, urinary tract infection, hemorrhoids, rectal bleeding, and anal fissures (APF, 2015) and may cause or contribute to delirium in older people (AMH Aged Care Companion, 2016). Constipation has been reported to occur in greater than 50% of patients taking opioid analgesics for noncancer pain (APF, 2015) and to become almost universal in palliative care patients (eTG complete, 2016). In a study of adverse events associated with the combined effects of multiple medicines in elderly inpatients, constipation was one of the most commonly occurring events (in addition to events such as arrhythmia, bleeding, orthostatic hypotension, sedation, and seizures (Bottiger et al., 2018).

Children—Constipation is a common problem in children, with up to 1 in 10 seeking medical attention. Incidence has been reported to be up to 30% in some settings (Waterham, 2017). Constipation in children can cause abdominal pain, perianal pain on passage of stools, reduced appetite, and irritability. It may present with soiling due to overflow incontinence. Urinary tract infections are more common in children with constipation (eTG complete, 2016).

Etiology of Constipation

Normal defecation has been stated to require several factors—a diet adequate in fiber and fluid, normal peristalsis, adequate power in the abdominal and pelvic musculature, normal rectal and perianal sensation, and patient mobility (eTG complete, 2016).

The elderly exhibit age-related cellular dysfunction such as decreased number of gastrointestinal contractions and delayed transit time; neuronal loss; dysfunctional myenteric ganglia and altered control of the pelvic floor. Pelvic floor dysfunction may frequently occur in elderly women, particularly those with a history of anorectal or pelvic surgery and other pelvic floor trauma such as childbirth. Such dysfunction may result in inadequate relaxation of the pelvic floor muscles and inadequate propulsive forces during attempted defecation (Roque and Bouras, 2015). However, while age-related changes have been acknowledged, others do not consider them to be major contributors to chronic constipation (Emmanuel et al., 2017; Gandell et al., 2013).

Causes of constipation more easily identified include certain medicines, metabolic abnormalities, disease states, and some general factors. These factors include lower socioeconomic class, non-white race, regular medication use, female sex, older age, a history of sexual abuse, and symptoms of anxiety and depression. They have all been associated with increased prevalence of constipation (Gandell et al., 2013; Selby and Corte, 2010).

Lifestyle factors that have been reported to predispose people to constipation include inadequate fluid intake, insufficient dietary fiber, insufficient physical activity, suppressing the urge to defecate, and social conditions (such as lack of privacy, reliance on others for toileting assistance, a change in surroundings) (AMH Aged Care Companion, 2016; APF, 2015). However, while exercise and consumption of dietary fiber and fluids represent healthy choices, deficiencies in any or all these factors do not seem to be major causes of chronic constipation (Wald, 2006). In those with fiber deficiency, fiber and water intake (to maximize the benefit of fiber) increase stool bulk and frequency and a dietary history will reveal whether there is sufficient fiber in the diet from cereals, grains, fruit, and vegetables. Increasing dietary fiber to approximately 30 g/day may therefore be effective in such patients. Increasing fiber intake beyond the required amounts may result in bloating and flatulence without relieving (or even aggravating) constipation (Selby and Corte, 2010).

In opioid-induced constipation, opioids bind to mu opioid receptors leading to a decrease in propulsive peristalsis, a reduction in pancreatic and biliary secretions, and an increase in intestinal fluid absorption. This effect is dose related. Unlike other opioid side effects, tolerance to constipation rarely develops (APF, 2015).

Medicines commonly associated with constipation appear in **Table 1**.

Medical conditions commonly associated with constipation appear in **Table 2**.

Children

Functional fecal retention and stool withholding behavior are the most common causes of constipation in children (eTG complete, 2016). Other causes are listed in **Table 2**. Constipation occurs after an unpleasant or painful stool event. Stool builds up within the colon and rectum, leading to the absorption of water and, therefore, accumulation of hard fecal matter. This stretches the lower bowel and rectum. Over time, the sensation of needing to defecate diminishes with persistent rectal stretching from chronic stool loading. The rectum becomes less sensitive, which can lead to involuntary soiling and will persist until chronic stretching is alleviated and prevented from recurring. Soiling is unpleasant and embarrassing (Waterham, 2017).

Diagnosis

The following information is based on clinical history but not physical examination, which may form part of the medical practitioner's assessment.

Table 1 Medicines commonly associated with constipation (AMH Aged Care Companion, 2016; APF, 2015; Clinical Practice Guideline, 2018; Gandell et al., 2013; Roque and Bouras, 2015; Selby and Corte, 2010; Waterham, 2017).

- Analgesics—NSAIDs, opiates including tramadol and tapentadol
- Antacids containing calcium or aluminum
- Anticholinergic agents (which include antihistamines, antispasmodics, and antidepressants—aclidinium, amantadine, amitriptyline, atropine, belladonna, benzhexol, benztropine, biperiden, brompheniramine, chlorpheniramine, clomipramine, cyclizine, cyproheptadine, darifenacin, dexchlorpheniramine, dimenhydrinate, diphenhydramine, disopyramide, dothiepin, doxepin, glycopyrronium, hyoscine butylbromide or hydrobromide, hyoscyamine, imipramine, ipratropium (nebulized), mianserin, nortriptyline orphenadrine, oxybutynin, phenelzine, pheniramine, pizotifen, prochlorperazine, promethazine, propantheline, solifenacin, tiotropium, tolterodine, tranylcypromine, trimeprazine, triprolidine, umeclinidium
- Anticonvulsants—carbamazepine, oxcarbazepine, zonisamide
- Antihypertensives—calcium channel blockers (mainly verapamil), clonidine, diuretics
- Antiparkinson agents—dopamine agonists (apomorphine, pramipexole, ropinirole, rotigotine, bromocriptine, cabergoline), COMT inhibitors (entacapone)
- Antipsychotics—aripiprazole, asenapine, brexpiprazole, chlorpromazine, clozapine, droperidol, flupentixol, haloperidol, lurasidone, olanzapine, paliperidone, periciazine, quetiapine, risperidone, trifluoperazine, ziprasidone, zuclopenthixol
- Calcium channel blockers—verapamil most commonly
- Bile acid binder—colestyramine
- Calcium supplements
- Dopamine agonist—quinagolide
- Iron supplements
- Sucralfate
- Vinca alkaloids
- 5HT3 antagonists—granisetron, ondansetron, palonosetron, tropisetron

Table 2 Medical conditions commonly associated with constipation (AMH Aged Care Companion, 2016; APF, 2015; eTG complete, 2016; Gandell et al., 2013; Roque and Bouras, 2015).

- Chronic renal disease
- Connective tissue—amyloidosis, scleroderma
- Dehydration
- Electrolyte disturbances—hypercalcemia, hypokalemia, hypermagnesemia
- Endocrine—diabetes, hypothyroidism, hyperparathyroidism
- Dyssynergic defecation— difficulty in expelling stool due to failure of recto-anal coordination
- Gastrointestinal—celiac disease, colorectal carcinoma, diverticulosis, hemorrhoids, IBS, perianal conditions, rectal prolapse, slow transit, stricture
- General disability
- Neurologic—autonomic neuropathy, dementia, multiple sclerosis, Parkinson's disease, spinal cord lesions, stroke
- Pelvic floor dysfunction (e.g., as a consequence of childbirth)
- Pregnancy
- Psychiatric—anorexia nervosa, anxiety, depression, somatization

Children

- Anatomic malformations of anus
- Allergy to cow's milk protein
- Celiac disease
- Reduced stool volume and dry stools caused by poor diet
- Slow-transit constipation
- Pelvic floor muscle dyssynergia
- Sexual abuse
- Hirschsprung disease, metabolic disease (hypercalcemia, hypothyroidism), and spinal cord abnormalities (rare)

The Rome III criteria have been used to define chronic functional constipation in adults, when the presence of two or more of the following occur (Gandell et al., 2013; Selby and Corte, 2010);

- Straining during at least 25% of bowel movements
- Lumpy or hard stools in at least 25% of bowel movements
- Sensation of incomplete evacuations for at least 25% of bowel movements
- Sensation of anorectal obstruction/blockage for at least 25% of bowel movements
- Manual maneuvers to facilitate at least 25% of bowel movements (such as digital evacuation or support of the pelvic floor
- Fewer than 3 spontaneous bowel motions per week
- Loose stools are rarely present without the use of laxatives
- There are insufficient criteria for IBS (added in Rome IV)

The last point was added by Rome IV to specify that abdominal pain and/or bloating may be present but are not predominant symptoms. That is, the patient does not meet criteria for IBS. This supports the concept that functional constipation (FC) and IBS with constipation-predominant symptoms (IBS-C) are disorders that exist on a continuous spectrum (Lacy et al., 2016).

These criteria must have been present for the last 3 months, with symptom onset at least 6 months before diagnosis. However, many people who complain of constipation do not meet all these criteria. Older patients may not always present with the expected decreased bowel frequency and altered consistency, but with almost daily bowel movements that require excessive straining, rectal digitation to facilitate stool expulsion, and accompanied by a sensation of incomplete evacuation and abdominal discomfort (APF, 2015; Roque and Bouras, 2015). Severe constipation may lead to upper gastrointestinal (GI) symptoms due to alterations in GI motility such as abdominal cramping, bloating, flatulence, nausea, and dyspepsia (Roque and Bouras, 2015).

A method to identify clinical factors that impact bowel function in the elderly consist of looking for nine "D"s; drugs (side effects), defecatory dysfunction, degenerative disease, decreased dietary intake, dementia, decreased mobility/activity, dehydration, depression, and dependence (on others for assistance) (Roque and Bouras, 2015).

In older people, constipation may present as confusion, overflow diarrhea, abdominal pain, urinary retention, nausea, or loss of appetite (APF, 2015). In patients where urinary incontinence is present, it may be exacerbated by constipation. Conversely, treatment in those with urinary incontinence may contribute to constipation through use of fluid restriction and anticholinergic drugs (AMH Aged Care Companion, 2016).

In taking a medical history, the following points could be considered (Rao and Go, 2010);

- What does the patient mean by constipation? Why do they think they have constipation?
- Has there been a change in the patient's bowel movements?
- Has the type of stool changed? This relates to stool frequency and consistency (with reference to the Bristol stool chart (Continence Foundation of Australia, 2018. Types 3–4 represent ideal stools).
- Ask if they ever need to strain on the toilet
- Have there been circumstances requiring postponing or ignoring a call to defecate? This may reflect upon difficult social conditions or poor access to toileting facilities
- Ask about diet to assess fiber and water intake
- List all medical conditions and all medications (prescription and nonprescription)
- Assess mobility
- Has there been previous use of laxatives and if so, what was their effectiveness?
- If using a laxative, for how long has this occurred and are you satisfied with the results?

It has been suggested that an accurate bowel chart be kept recording time, amount, and consistency of stool. This will facilitate assessment of laxative requirements and if so, response to treatment (AMH Aged Care Companion, 2016).

Children and Infants

Most children pass stools every 2–3 days, whereas breastfed babies may only pass stool once a week. Common times for constipation to occur in children and infants include transition to solids, toilet training, and school entry. Other causes may consist of painful bowel actions due to anal fissures or perianal skin conditions, change of diet, and psychosocial stressors (Waterham, 2017).

The Rome IV criteria are used for the diagnosis of functional constipation in children and must include two or more of the following criteria for at least 1 month (Clinical Practice Guideline, 2018);

- Two bowel movements or less per week
- A history of withholding or incomplete evacuation
- A history of large-diameter stools
- Presence of a large fecal mass in the rectum

In toilet-trained children, there is one additional criteria; at least one episode per week of incontinence which, after evaluation, cannot be fully explained by another medical condition.

In taking a medical history in children, the following points could be considered (Clinical Practice Guideline, 2018; Waterham, 2017)

- What has been the stool consistency (per Bristol stool chart)?
- Has there been straining?
- Has there been blood on wiping and/or in the nappy?
- Have bowel actions been painful?
- Has there been an event (painful, frightening, or challenging such as school entry) prior to onset of constipation?
- Has there been toilet refusal or withholding behaviors (e.g., crossing legs)?
- Has fecal or urinary incontinence occurred?
- For children with fecal incontinence, what has been the frequency of soiling episodes and what was their relationship to bowel motions

- Is there a family history of celiac disease?
- Have laxatives been used previously and if so, what has been their effectiveness?
- With the introduction of solids, has there been adequate fiber and water intake?
- Has general growth and development been within normal parameters?

Need for Referral

The presence of alarm symptoms may indicate an underlying organic cause such as colorectal neoplasia or inflammatory bowel disease (Selby and Corte, 2010). Referral has been recommended when constipation is accompanied by any of the following symptoms (APF, 2015; Australian Medicines Handbook, 2018; Selby and Corte, 2010);

- Blood and/or mucus in the stools
- Persistent or severe abdominal pain
- Anorexia, nausea, vomiting, or fever
- Unintentional or unexplained weight loss
- Obstipation (obstructive constipation)—stool cannot be passed
- Tenesmus—a continuous feeling of the need to defecate
- A sudden change in bowel habits lasting two weeks or longer
- A family history of inflammatory bowel disease or colorectal cancer
- Constipation persisting after appropriate treatment with laxative(s)

Children

In children, the following alarm symptoms have been identified (Clinical Practice Guideline, 2018; Waterham, 2017);

- Ribbon/pencil-thin stools (may indicate an anorectal malformation)
- Delay in general growth and development
- Other physical signs; lethargy, fever, vomiting, weight loss
- Blood in stool

Treatment—Nonpharmacologic

Fluid and exercise—While adequate water intake and exercise have been recommended, there is little evidence for their effectiveness (Rao and Go, 2010; Wald, 2006). The small intestine handles 7–10 L of fluid each day, so it should not be surprising that extra fluid intake makes little difference, except to increase urinary output. Fluid restrictions should be noted in those with medical conditions such as heart or renal failure.

Fiber—it has been shown that increased consumption of fiber increases stool weight and frequency in healthy individuals and decreases colonic transit time (Wald, 2006). However, the prescription of many medicines (**Table 1**) and the presence of multimorbidity (**Table 2**) in patients may result in little or no benefit from fiber supplementation. Notwithstanding this, constipated patients without a motility disorder have been reported to improve or become symptom free with fiber supplementation (Rao and Go, 2010). A dietary history will reveal whether there is sufficient fiber in the diet. Fiber is the indigestible parts of plant foods such as vegetables, fruits, grains, beans, and legumes (peas, beans, chickpeas, lentils, soybeans, peanuts). Both soluble (which includes some grains (e.g., oats, rye, barley, millet, buckwheat), some fruit and vegetables (e.g., artichoke, onion, garlic), seed husk (e.g., psyllium husk), and cooked (from dried) or canned legumes, and insoluble fiber (which include most whole grains (e.g., whole wheat, wheat bran, brown rice, rye, quinoa, wholegrain cereals [barley, buckwheat, oat, rye, rice, spelt], wholemeal or mixed-grain products), skins of fruits and vegetables, nuts and seeds, raw lentils, kidney beans, and chickpeas have been recommended, with benefits generally seen within 3–5 days (APF, 2015; Selby and Corte, 2010). However, evidence for any benefit has been found to be unclear (Ford, 2012). The recommended daily fiber intake for adults is 25–30 g. For children, the number of grams should be their age in years plus 5—for example, 10 g/day in a 5 year old (APF, 2015). Fiber content should be increased gradually to avoid adverse effects such as bloating or flatulence.

Regularity— colonic motor activity increases after waking and after a meal (the gastrocolonic reflex). This suggests that constipated patients may establish a regular pattern of defecation by ritualizing a bowel habit that takes advantage of this normal physiologic stimulus (Rao and Go, 2010).

Position—When seated on the toilet, correct positioning (i.e., with knees above the level of the hips to reduce the rectal angle—a footstool may be needed) is recommended (eTG complete, 2016).

Urge—People should be encouraged to respond to an urge to defecate rather than delay (eTG complete, 2016).

Infants and children (Clinical Practice Guideline, 2018)—use of a footstool has been recommended to ensure knees are higher than hips. The child should lean forward and put their elbows on their knees. A toilet ring can be placed over the toilet seat if needed. Toilet sits should be organized of up to 5 min three times a day, preferably after meals. Encouragement should be given so that the exercise is treated as a positive experience. A toileting diary may reinforce positive behavior and record frequency of bowel actions. Toilet training attempts should be delayed until the child is painlessly passing soft stool.

Treatment—pharmacologic (AMH Aged Care Companion, 2016; APF, 2015; Australian Medicines Handbook, 2018; Clinical Practice Guideline, 2018; Ford, 2012; Gandell et al., 2013; Selby and Corte, 2010; Serrano-Falcon and Rey, 2017; Wald, 2006)

The term "laxative" is an imprecise term, since it encompasses drugs with different mechanisms of action, thus implying heterogeneity in their efficacy and safety and rendering comparison difficult. Further, the exact mechanism of action of most laxatives is unknown because there are complex factors involved in colon function. Determination of the influence of factors such as cyclic-AMP, electrolyte transportation, hormones, and enzymes may change currently accepted mechanisms. However, some general classes of mechanism of action can be described (below).

Evidence is insufficient to assess the relative effectiveness or tolerability of laxatives. Drug choice may therefore be based on onset of action, patient preference, adverse effects, effectiveness of previous treatments, and cost (Australian Medicines Handbook, 2018).

Laxatives (aperients) have been described as foods or drugs that, when ingested, act directly on the gut (or gut contents) to increase stool frequency or to ease stool passage. They differ from motility agents such as metoclopramide, domperidone, and prucalopride, which exert a promotility effect after systemic absorption (Ford, 2012). Long-term laxative use is not necessary unless constipation or fecal impaction is likely to recur. This may occur in opioid-induced constipation; where there are progressive neurological conditions; in immobility due to old age or illness and in some children to prevent relapse (Australian Medicines Handbook, 2018).

Patients approaching the end of life may tolerate food and fluid poorly, have little or no mobility, inadequate power of abdominal and pelvic musculature, or reduced rectal and perianal sensation, such that constipation becomes almost universal (eTG complete, 2016). Despite this, a recent Cochrane review was unable to determine the effectiveness and differential efficacy of laxatives used to manage constipation in people receiving palliative care, although a previous review identified the effectiveness of the peripherally acting opioid antagonist methylnaltrexone (Candy et al., 2015), which is administered subcutaneously once every 24–48 h.

Laxative use is contraindicated in intestinal obstruction (Australian Medicines Handbook, 2018). The use of fiber supplements may worsen constipation in those patients with constipation-predominant IBS, slow transit constipation, or primary defecation disorder (Wald, 2006).

Opioid-induced constipation is largely the result of reduced peristalsis and hardened feces, so the most useful laxatives are those that increase peristalsis and soften the stool (APF, 2015). The effect of opioids on peristalsis can be reduced by the concomitant use of naloxone (an opioid antagonist commonly used together with oxycodone [Targin] in moderate to severe pain), which undergoes extensive first-pass metabolism resulting in a systemic bioavailability of less than 3% and no significant effect on the central nervous system at approved doses (Ward et al., 2017).

Because most laxatives are not absorbed and none cross the blood–brain barrier, there appears to be no pharmacologic basis for addiction. Those individuals who do abuse laxatives are often individuals with psychiatric disorders. As with any substance, laxatives may be abused because of psychologic dysfunction (Wald, 2006).

In children, osmotic and lubricant laxatives are usually required on a long-term basis (months to years). Parents should be reassured that this is safe and will not produce a "lazy bowel." Laxative should be titrated to obtain one soft, easy to pass bowel action per day. A common cause of recurrence is stopping laxatives too early (Waterham, 2017).

Serotonin (or 5-hydroxytryptamine [5-HT]), commonly viewed as a central neurotransmitter, is most abundant in the gastrointestinal tract where it is synthesized and stored in enterochromaffin cells. Serotonin is involved in intestinal secretion, motility, and sensation and is therefore a natural target for treatment of chronic constipation. Of its various receptors, serotonin 5-HT3 and 5-HT4 receptors have attracted the greatest attention in the intestine; the former for their role in visceral sensation, the latter for their role in motor activity. Consequently, 5-HT4 receptor agonists have been developed as prokinetic agents (Quigley and Neshatian, 2016).

A stepwise approach has been suggested in the management of constipation in older people (Gandell et al., 2013);

(1) Identify the predominant symptoms, (2) identify possible secondary causes (medications, disease states), (3) exclude fecal impaction, (4) optimize behavioral factors (seating position, timing), (5) trial dietary modification (fiber) for 2–4 weeks, (6) trial a previously preferred laxative for 2–4 weeks, (7) trial macrogol or lactulose if not in, (6) for 2–4 weeks, (8) trial a combination of agents from different classes for 2–4 weeks, and (9) refer to a gastroenterologist or geriatrician.

There are four major groups of laxatives (AMH Aged Care Companion, 2016; APF, 2015; Australian Medicines Handbook, 2018; Clinical Practice Guideline, 2018; Ford, 2012; Gandell et al., 2013; Selby and Corte, 2010; Serrano-Falcon and Rey, 2017; Wald, 2006).

Bulk forming laxatives—includes isphagula, psyllium, and sterculia

- Onset of action is 2–3 days. Full effect may take 3–4 days
- Act to sequester extra water in the stool, increasing stool weight and colonic distention to stimulate intestinal activity and increase the speed of transit. Adequate fluid intake should be ensured.
- Fermentation by colonic bacteria may cause bloating and flatulence. A gradual increase in quantity will minimize these effects
- May worsen constipation in immobile or fluid restricted patients. They have no role in nonambulant patients or those taking opioids or other constipating drugs
- Contraindicated in obstruction, impaction, colonic atony, and dysphagia

Osmotic laxatives—includes glycerol, lactulose, macrogol, saline laxatives (containing magnesium, sodium citrate, sodium phosphate), and sorbitol

- Onset of action for lactulose, macrogol, and sorbitol is 1–3 days. Saline laxatives ½—3 h. Rectal (glycerol—used for stool in the lower rectum) 5–30 min
- Ions such as magnesium, sulfate, phosphate, and citrate are poorly absorbed and retain fluid in the colon through an osmotic effect. Other molecules such as lactulose, macrogol, and sorbitol are completely unabsorbed and to maintain an iso-osmolar state, draw water into the intestinal lumen. The increase in intraluminal pressure stimulates peristalsis. Water ingested with them is retained in the gut
- Fluid augments their osmotic effect
- Some brands of macrogol contain approximately 8 mmol (186 mg) of sodium per sachet. This should be considered in patients who may have heart or kidney failure or hypertension or who are taking diuretics—which aim to eliminate sodium
- Fluid and electrolyte disturbances are less of a risk with macrogol laxatives than with other osmotic laxatives
- Common adverse effects include nausea, abdominal distention, flatulence, cramps, or pain
- Tolerance may be limited by the taste of lactulose and sorbitol
- Laxatives containing sodium phosphate may cause serious fluid and electrolyte disturbance in the elderly, which are more likely in dehydrated patients or those taking diuretics, angiotensin
- -converting enzyme inhibitors, angiotensin-2-receptor antagonists, or nonsteroidal anti-inflammatory drugs. They should not be used in heart failure or renal impairment
- Lactulose or macrogol laxatives have been recommended for use in infants 1–12 months old. Macrogol (and/or liquid paraffin) has been recommended for use in children
- Macrogol has the best and most recent evidence base of all laxatives for efficacy. It is generally recommended as first choice

Stimulant laxatives—includes bisacodyl, frangula, senna, and sodium picosulfate

- Onset is 6–12 h
- May act to increase peristalsis by a direct effect on the smooth intestinal musculature by stimulation of intramural nerve plexi. They have also been shown to promote fluid and ion accumulation in the colon. Bisacodyl may inhibit water absorption through an action on endogenous esterases; sodium picosulfate through an action on colonic flora; senna following mucosal contact
- They are contraindicated in inflammatory bowel disease
- They do not damage the neuromuscular apparatus of the colon
- May cause abdominal discomfort and cramping
- They are recommended in combination with a stool softener as the best initial choice in palliative care patients and in opioid-induced constipation

Stool softening laxatives—include docusate, liquid paraffin, and poloxamer (or poloxalkol)

- Onset is 24–72 h
- Docusate and poloxamer are detergents (surfactants) and act to facilitate penetration of water into feces. Liquid paraffin is a lubricant to facilitate passage of feces
- Evidence for their efficacy when used alone is lacking
- Poloxamer can be used in children less than 3 years old and mixed with fruit juice or in bottle feeds. Docusate can be used in children older than 3 years. Other guidelines recommend poloxamer use only in infants less than one month old
- Liquid paraffin may cause anal leakage, reduce absorption of fat-soluble vitamins with regular use, and may be aspirated in those with predisposing factors (e.g., gastro-oesophageal reflux, Parkinson's, and other neurological diseases). It should not be administered immediately before lying down
- It is recommended in combination with a stimulant as the best initial choice in palliative care patients and in opioid-induced constipation

Prokinetic Agents

Cisapride was one of the first serotonin receptor agonists shown to have some efficacy in constipation. Lack of selectivity for the 5-HT4 receptor and resultant interactions with the human ether-a-go-go-Related Gene (hERG) channel (resulting in cardiac arrhythmias) led to worldwide withdrawal of the drug. After this came tegaserod, a 5-HT2B receptor agonist, which was also withdrawn due to the occurrence of cardiovascular ischemic events (Quigley and Neshatian, 2016).

Prucalopride is an agent that has highly selective agonist activity and high affinity for 5-HT4 receptors. This results in reduced colonic transit time due to longitudinal smooth muscle contraction and propulsion of luminal contents. A decrease in the resistance potentially produced by circular smooth muscle contractions also occurs. Prucalopride neither interacts with the hERG potassium channel (such as cisapride) nor with the 5-HT2B receptors (such as tegaserod), resulting in the selective stimulation of gastrointestinal motility without arrhythmogenic side effects (Bassotti et al., 2016).

Prucalopride is indicated for chronic idiopathic constipation when other regular laxatives are inadequate. It is taken once a day. The tablets have a high oral bioavailability and can be taken with or without food. There is little metabolism of prucalopride. Most of

the dose is excreted unchanged in the urine. A bowel movement occurs within a median of 50–54 h (Bassotti et al., 2016). Benefit should be evident within 4 weeks and if not, the medicine should be ceased. It has been recommended that further studies are needed to establish efficacy in the elderly, in patients with secondary causes of constipation, with long term use and in combination with other laxatives (Australian Medicines Handbook, 2018). This is because prucalopride has been mainly tested on patients recruited for clinical trials and data on "real-life" patients, or those with different subtypes of constipation, are scarce (Bassotti et al., 2016). The cost of prucalopride may represent a considerable barrier —approximately 75 (Australian) dollars per month (2 mg tablets × 28).

Velusetrag, Naronapride, and Mosapride are other highly selective 5-HT4 agonists, which are undergoing development, with the latter also being a partial 5-HT3 antagonist.

Prosecretory agents (secretagogues)—Modulation of epithelial ion channels promote intestinal secretion and therefore facilitates stool passage and enhances GI transit. Lubiprostone, the first secretogogue introduced for the treatment of chronic constipation, is a fatty acid derived from prostaglandin-1. It activates a specific chloride channel located on the enterocyte, thereby increasing water secretion in the intestinal lumen. It may also act through prostaglandin E4 receptors (Quigley and Neshatian, 2016). It may cause nausea in up to 30% of patients, limiting its effectiveness (Roque and Bouras, 2015).

Linaclotide is a 14-amino acid peptide that binds to and activates the guanylate cyclase-C (GC-C) receptor, which generates cyclic guanosine monophosphate (cGMP). Intracellular cGMP activates the cystic fibrosis transmembrane conductance regulator (CFTR), which increases the secretion of chloride and bicarbonate into the lumen, thereby increasing colonic secretion and intestinal motility (Gandell et al., 2013).

Plecanatide, a uroguanylin analog, is a GC-C receptor agonist. Uroguanylin is a naturally occurring intestinal hormone that has its downstream effects through the activation of the GC-C receptor (Quigley and Neshatian, 2016).

Pregnancy —Fiber supplements, sorbitol, lactulose, and docusate have been recommended, with occasional macrogol if necessary. Stimulant laxatives should be avoided (Australian Medicines Handbook, 2018; Selby and Corte, 2010).

Role of the Pharmacist

- Many older people may consider bowel health a private matter which they find difficult to discuss. Consequently, many patients may resort to self-medication and therefore do not benefit from the experience of health-care professionals. Conversely, many health-care professionals may feel uncomfortable in asking questions and discussing the issue, which requires a proactive approach and appropriate communication skills. Asking open-ended questions (that is, those beginning with "how," "when," "where," "why" or "what") may open communication and allow better assessment of the problem. For example, "for how long have you experienced this problem?"; "what kind of change have you experienced in your bowel motions?" and "what have you tried in the past to fix it?"
- It may not be possible to deprescribe medicines suspected of contributing to constipation. It is therefore important that patients' misconceptions about constipation and the medicines used to treat it are addressed. For example, there appears to be no pharmacologic basis for addiction. A medication review may be necessary to investigate the possibility of medication adjustment or cessation.
- The availability of over-the-counter laxatives means that without intervention, idiosyncratic beliefs may perpetuate irrational self-treatment. This includes use of complementary and alternative (CAMs) medicines. Idiosyncratic beliefs may be able to be changed, depending upon the behavioral stage-of-change that the patient may be currently experiencing—are they in a precontemplation, contemplation, preparation, action, or maintenance stage?) A patient in a precontemplation stage will be resistant to correction of erroneous beliefs.
- The significant consequences of inadequately treated constipation should be explained to patients. These include the effects of excessive straining, occurrence of overflow fecal incontinence, bowel obstruction, urinary incontinence, urinary tract infection, hemorrhoids, rectal bleeding, anal fissures, abdominal pain, nausea, anorexia, upper gastrointestinal symptoms, and delirium in older people. They should be considered when assessing patients' medical history/presenting symptoms. These issues can be communicated by explaining that we are very much concerned about people becoming constipated because, apart from constipation being uncomfortable and slow to reverse, it can affect other parts of the body like the urinary system.
- In patients where urinary incontinence is present, exacerbation by constipation should be considered.
- In children, reduced appetite and irritability may be associated with constipation
- The frequency of occurrence of constipation in patients taking opioid analgesics for non-cancer pain, those approaching the end of life and in palliative care patients means that appropriate treatment includes prophylactic laxative use for all such patients. Addition of naloxone to oxycodone in combined preparations for analgesia may often not be enough to prevent constipation and additional laxatives may often be required.
- Familiarity with alarm symptoms is important, as certain symptoms may indicate an underlying organic cause such as colorectal neoplasia or inflammatory bowel disease, requiring referral to a doctor for investigation.
- Counseling regarding nonpharmacological advice and treatment such as appropriate fiber intake, attention to regularity, defecation position, and avoidance of delaying urge should be considered in all patients.
- In children, osmotic and lubricant laxatives are usually required on a long-term basis. This means that appropriate counseling of parents/carers is important with respect to the safety of laxatives.

It should be explained to patients that laxatives do not cause tolerance or dependence or damage the gut. For example, it could be explained that macrogol, one of the most effective laxatives available, is a chemical that keeps fluid inside the gut. This pushes out or distends the gut wall, which causes it to push back, thus moving along gut contents. The chemical itself never enters the body. Simplified explanations such as this appear likely to deal with the common issue of inadequate health literacy.

There should be an awareness that older people in the community or in low-level care facilities may have difficulty with nonpharmacologic options because they are afraid to exercise (walk) alone, fruit and vegetables may be difficult to access or too expensive and they may be concerned that increased fluid intake may worsen urinary incontinence. Awareness of these issues will allow them to be discussed.

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Management of Gastrointestinal Disorders and the Pharmacist's Role: Gastroesophageal Reflux Disease

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Gastroesophageal Reflux Disease

According to a Montreal consensus panel, the globally accepted definition of gastroesophageal reflux disease (GERD) is "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" (Vakil et al., 2006). Although there is no standard criterion for the symptoms exhibited, heartburn and regurgitation are the most prevalent indicators of GERD, and a weekly occurrence of these symptoms is typically sufficient to make a clinical diagnosis (Fock and Poh, 2010). This definition of GERD may be further classified as nonerosive reflux disease (NERD) and erosive reflux disease (ERD) depending on whether esophageal erosion is absent or present, respectively (Kroch and Madanick, 2017).

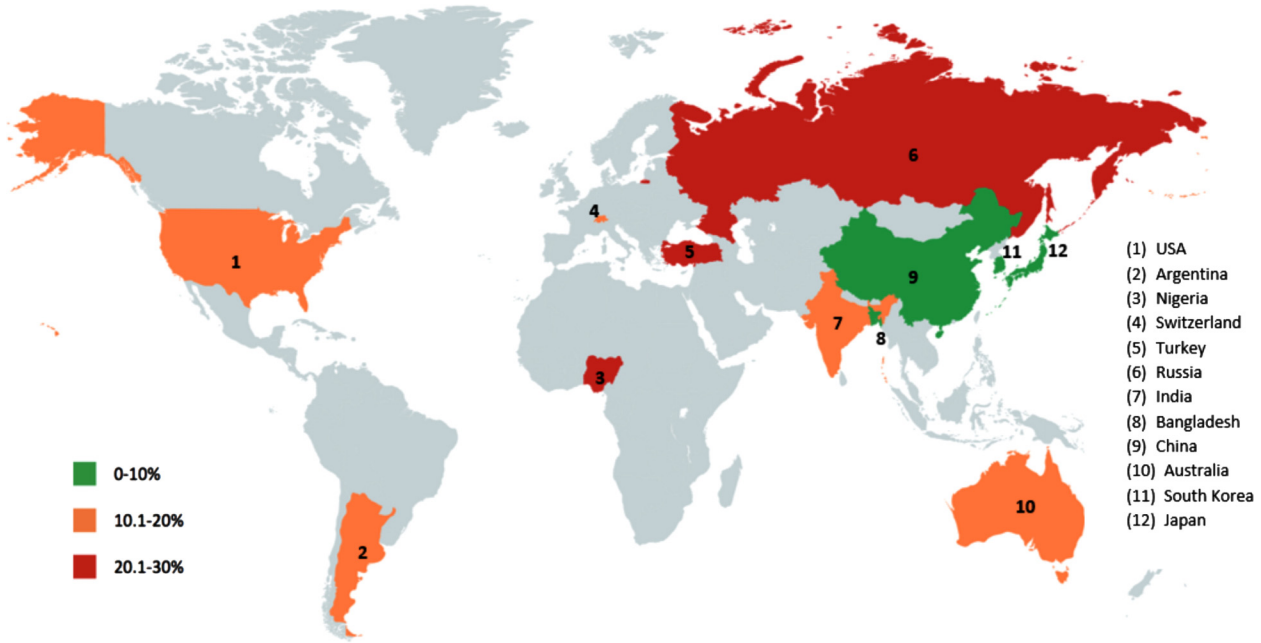

Figure 1 World map showing the global prevalence of GERD. *(1) Jung et al. (2007); (2) Chiocca et al. (2005); (3) Nwokediuko (2009); (4) Schwenkglenks et al. (2004); (5) Mungan (2012); (6) Bor et al. (2015); (7) Kumar et al. (2011); (8) Shaha et al. (2012); (9) Wang et al. (2009); (10) Eslick and Tallet (2009); (11) Watanabe et al. (2003); (12) Kim et al. (2012).*

Besides causing a significant decrease in the quality of life of patients, GERD may also facilitate the development of more serious and potentially life-threatening conditions (Nwokediuko, 2012).

Epidemiology

GERD is a highly prevalent condition worldwide, although language and cultural differences in symptom interpretation make it difficult to determine an accurate global estimate of its prevalence (Ronkainen et al., 2005). Nevertheless, prevalence estimates of GERD vary significantly between regions and are more prevalent in western societies than other societies (8.8%–25.9% in Europe and 17.6%–28.8% in US) (Darbà et al., 2011; El-Serag et al., 2013; Orlando, 2000; Ronkainen and Agréus, 2013). A similar prevalence of the disease has also been found in Middle Eastern and West Asian societies (8.7%–27.6%) (El-Serag et al., 2013; Ronkainen and Agréus, 2013). However, East Asian societies have consistently shown a low prevalence of GERD (2.5%–7.27%), although evidence has shown that this is rapidly rising (Cheung et al., 2009; Kim et al., 2012; Wong et al., 2003, 2004). The distributions of prevalence estimates around the world are displayed in **Fig. 1**.

Etiology

Excessive retrograde movement of acid-containing gastric secretions or bile and acid-containing secretions from the duodenum and stomach into the esophagus is the etiologic effector of GERD. A functional (transient lower esophageal sphincter relaxation (TLESR)) or mechanical (hypotensive LES) problem of the lower esophageal sphincter (LES) is the most common cause of GERD. Transient relaxation of the LES could also be due to food (coffee, alcohol, chocolate, and fatty meals), medications (beta-agonists, nitrates, calcium channel blockers, and anticholinergics), hormones (e.g., progesterone), and nicotine.

Pathophysiology

Early understanding described hiatus hernia as the main pathophysiological factor for GERD. This theory was replaced when a hypotensive LES was consistently observed in GERD patients and there was a theory that a hypotensive LES pressure may contribute toward GERD via strain-induced reflux (Herregods et al., 2015). Strain-induced reflux is caused by an abrupt increase in intragastric pressure and mainly occurs when LES pressure is less than 10 mmHg. Alternatively, free reflux is identified by a fall in intraesophageal pH without a change in intragastric or LES pressure and mainly occurs when LES pressure is less than 4 mmHg (Orlando, 2000).

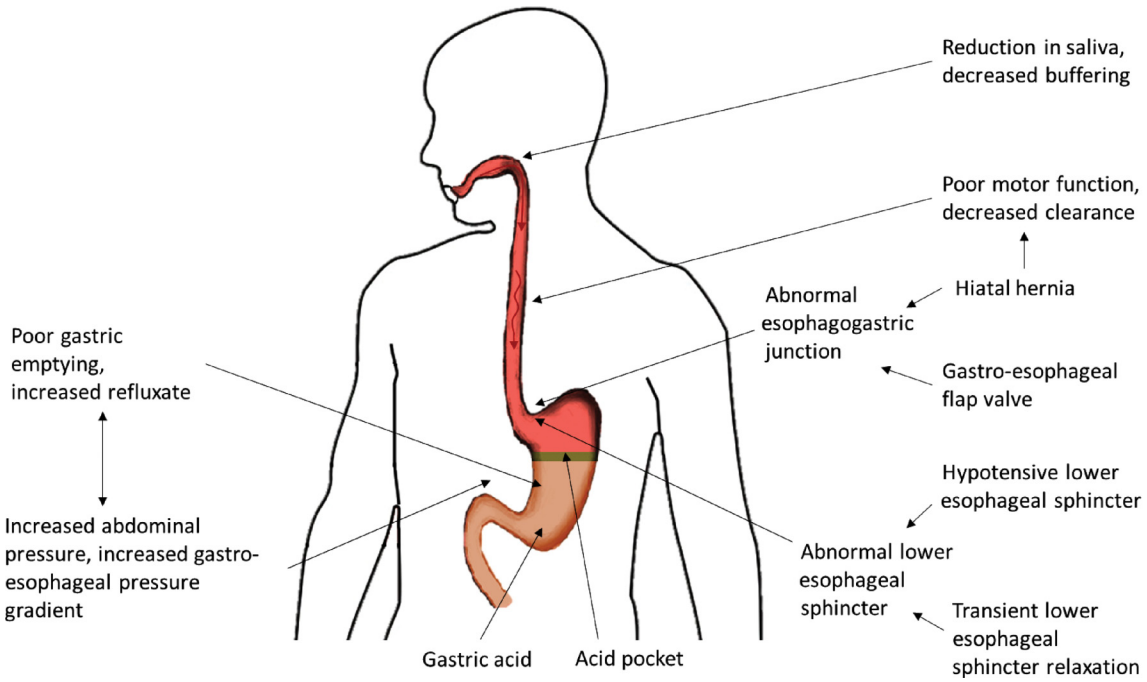

Figure 2 Pathophysiology of GERD.

However, further developments in the techniques available to measure LES pressure lead us to our current understanding, which describes the pathophysiology of GERD as multifactorial (**Fig. 2**) (Lee and McColl, 2013). TLESR is the main cause of gastroesophageal reflux leading to 70% of the cases. Although the rate of TLESRs in healthy individuals is similar to those with GERD, the latter are more likely to suffer from acid reflux during the process (Herregods et al., 2015). Therefore, TLESR is not responsible for causing reflux but instead a pathway to allow reflux to occur. A number of mechanisms have been suggested which may cause acid reflux during TLESR. These include (1) an increase in compliance of the LES, (2) a higher-pressure gradient across the esophagogastric junction (EGJ), and (3) differences in the meal distribution or the localization of the acid pocket on top of the meal (Hershcovici et al., 2011).

Natural Barriers Against Gastroesophageal Reflux Disease

In healthy individuals, reflux of gastric contents is prevented by a number of natural barriers including the LES, the angle of His, the diaphragm, and the length of the intraabdominal esophagus (**Table 1**) (Menezes and Herbella, 2017). The most important of these barriers are the LES and the crural diaphragm that, along with the anatomical flap valve, make up the EGJ, which acts as a defense system against reflux.

Lower Esophageal Sphincter

The LES is a composite of tonically contracted muscles with multiple functions spanning 2.4–4.5 cm in length located at the distal end of the esophagus (Menezes and Herbella, 2017). One function of the LES is to prevent the flow of acid secreted by the most

Table 1 Description and functions of the barriers against GERD

Barrier	*Description*	*Functions*
Lower esophageal sphincter	A composite of tonically contracted muscles with multiple functions spanning 2.4–4.5 cm in length located at the distal end of the esophagus	Behaves as a "one-way system" by allowing ingested food and liquids into the stomach from the esophagus while inhibiting the reflux of gastric contents and gastric juice
Crural diaphragm	An external sphincter on the esophagus. It wraps around the proximal 2–4 cm of the LES and augments pressure during inspiration	Contracts to augment the LES pressure and prevent reflux
Angle of His	The acute angle between the cardia and the esophagus	Forms a valve that prevents the reflux of gastric contents and gastric juice into the esophagus

proximal gastric mucosa into the esophagus and ensures the flow is directed toward the stomach, thus preventing damage to its squamous mucosa. It also behaves as a "one-way system" by allowing ingested food and liquids into the stomach from the esophagus while inhibiting the reflux of gastric contents and gastric juice (Lee and McColl, 2013).

One of the most complicated and least-understood functions of the LES also happens to be the most common cause of GERD. This is defined as simultaneous spontaneous relaxation of the LES and crural diaphragm lasting 10–60 s and independent of swallowing (Hershcovici et al., 2011). During this period, the LES and crural diaphragm are completely relaxed, and the longitudinal smooth muscle of the esophagus contracts. The EGJ ascends 2–8 cm into the chest causing a temporary hiatal hernia, which disfigures the flap valve, opening the LES, and allowing air located in the proximal stomach to escape via the esophagus (Lee and McColl, 2013).

Crural Diaphragm

The crural diaphragm also plays an important role in preventing GER by acting as an external sphincter on the esophagus (Hershcovici et al., 2011). In fact, it has been suggested that simultaneous crural diaphragm inhibition and LES relaxation are essential for GER to occur. The pressure gradient between the stomach and esophagus is increased during inspiration due to the production of a negative intraesophageal pressure. The pressure gradient is further increased by the contraction of the abdominal wall. These two processes favor GER; therefore, the crural diaphragm contracts to augment the LES pressure and prevent GER (Mittal, 2011).

Angle of His

The angle of His is the acute angle between the cardia and the esophagus. The acute angle forms a valve, which prevents the reflux of gastric contents and gastric juice into the esophagus and an obtuse angle would facilitate recurrent regurgitation (Menezes and Herbella, 2017).

Risk Factors

Obesity

A higher body mass index (BMI) is linked to an increase in the prevalence of GERD due to disruption of the EGJ resulting in a hiatal hernia caused by a change in pressure morphology across the EGJ, an increase in intragastric pressure, and an increase in the gastroesophageal pressure gradient (Pandolfino et al., 2006). Obese patients are also twice as likely to possess a defective LES compared to healthy individuals (Ayazi et al., 2009).

However, abdominal obesity is more important than general obesity as symptoms of GERD are positively associated with abdominal obesity independent of BMI. Therefore, improvement of GERD symptoms can be achieved by weight loss and improvement of diet (Park et al., 2016).

Age

Infants and Children

Reflux of gastric contents is a common occurrence in the pediatric population with 75% of infants experiencing GER. Fortunately, 65%–95% of the patients experience spontaneous resolution of their symptoms by 2 years of age. However, 7%–20% of the pediatric population suffers from GERD with high-risk groups including those with prematurity, esophageal atresia, congenital diaphragmatic hernia, neurologic impairment, obesity, and specific genetic disorders (Barnhart, 2016).

The high prevalence of GERD in infants may be attributed to underdeveloped barriers against reflux. For instance, the LES in infants only measures a few millimeters compared to 2.4–4.5 cm in adults (Menezes and Herbella, 2017). Additionally, the angle of His in infants is less acute than in adults and may even direct the flow of gastric contents into the esophagus. Furthermore, the behavior of infants also increases the risk of GER. Crying and awkward movements due to poor trunk control can increase intragastric pressure, therefore, causing GER (Di Lorenzo and Vandenplas, 2012).

Diagnosis of GERD may be difficult due to infants being unable to communicate their symptoms accurately or at all. However, many common symptoms are clear and easy to recognize such as regurgitation and vomiting. Other visible symptoms may include coughing, wheezing, choking, apnea, and apparent life-threatening events (Slater and Rothenberg, 2017).

Elderly

It is believed that there is a positive correlation between the incidence of GERD and age, possibly due to anatomical and physiological degradation of GER barriers at the EGJ (Becher and Dent, 2010). Symptoms of GERD have also shown to be atypical in elderly patients compared to young or adult patients. These atypical symptoms include vomiting, dysphagia, anorexia, anemia, weight loss, belching, and respiratory problems (Pilotto et al., 2006).

Pregnancy

GERD is very common during pregnancy with 40%–85% of pregnant women suffering from the condition. A combination of hormonal imbalances and anatomical alterations causes GERD favoring changes such as lowering of LES pressure, increased abdominal pressure, and slow gastric emptying. The predominant factor of GERD during pregnancy is the reduction of LES tone caused by progesterone and estrogen. Moreover, the resting LES pressure is lower than normal during all three trimesters of pregnancy, reaching a nadir at 36 weeks of pregnancy (Fill Malfertheiner et al., 2012).

Smoking

Smoking significantly exacerbates GERD symptoms and a strong dose-dependent association between smoking and GERD exists (Nilsson, 2004). Activation of nicotinic receptors on the enteric neurons of the EGJ smooth muscle results in the release of substances, such as nitric oxide, norepinephrine, and GABA, which relax the gastric clasp and sling fibers, and LES smooth muscle. Additionally, individuals who smoke exhibit a decrease in LES pressure, as well as a decrease in the secretion of salivary bicarbonate. An increase in coughing and deep inspiration in smokers is also responsible for increasing intraabdominal pressure, thus, favoring reflux (Kahrilas and Gupta, 1990).

Hiatal Hernia

Hiatal hernia is caused by the weakening or rupture of the phrenoesophageal ligament and it has been observed that almost all patients with severe GERD and many with mild GERD have evidence of hiatal hernia (Lee and McColl, 2013). Four types of hiatal hernia have been identified (**Fig. 3**):

1. Sliding hiatal hernia (type I)
2. Paraesophageal hiatal hernia (type II)
3. Mixed hiatal hernia (type III

Giant paraesophageal hiatal hernia (IV). The mechanism leading to reflux is different in patients with hiatal hernia who also experience more frequent and prolonged TLESRs. It is believed that one of the ways a hiatal hernia facilitates GERD is by hindering LES function. A sudden increase in intraabdominal pressure, such as during inspiration or coughing, increases the possibility of reflux, which is related to both low LES pressure and hiatal hernia. Reflux can also be caused by an acid pocket becoming trapped in the hiatal hernia sac during esophageal acid clearance, which then refluxes into the esophagus during LES relaxation (Savas et al., 2008).

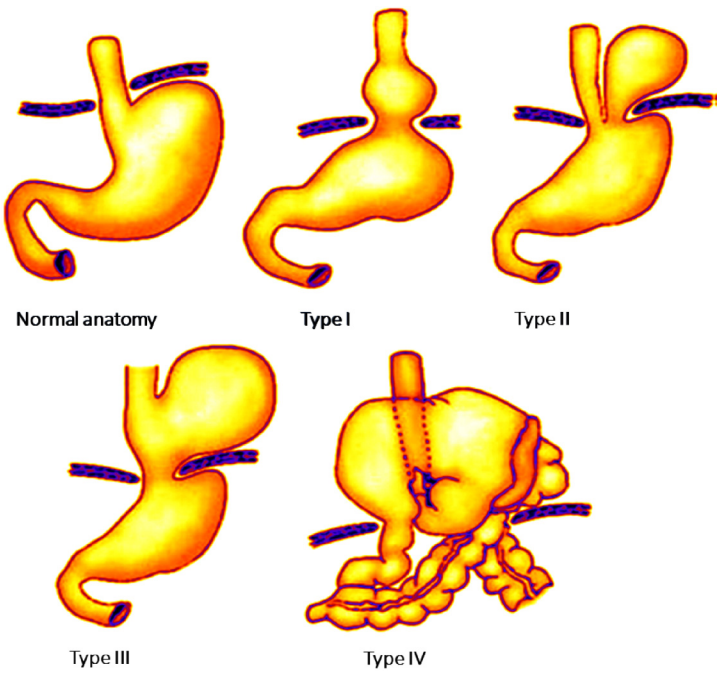

Figure 3 The four types of hiatal hernias.

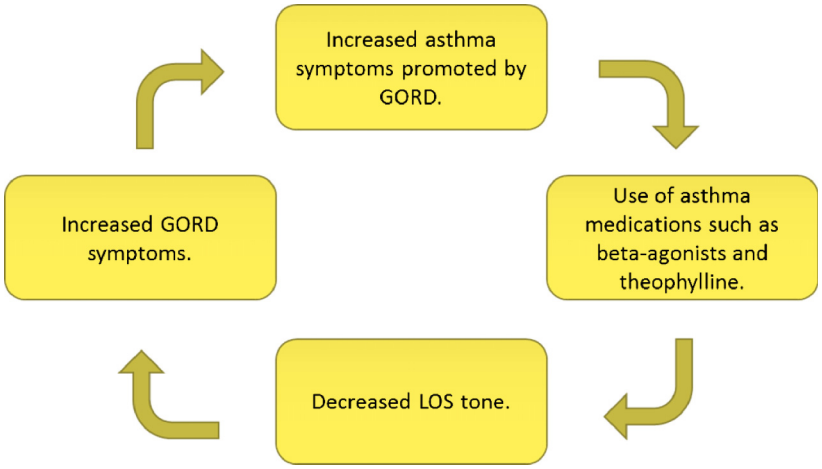

Figure 4 Illustration showing the relationship between asthma medications and GERD.

Asthma

The prevalence of GERD in individuals with asthma is a common occurrence with up to 82% of the adult population with asthma also suffering from GERD (Aras et al., 2012). Potential causes of this relationship include an increase in the rate of TLESRs caused by bronchial obstruction and herniation of the LES into the chest due to lung hyperinflation in asthmatic patients (McCallister et al., 2011).

However, GERD has also shown to cause and exacerbate asthma symptoms via two theorized mechanisms: (1) exposure to acid refluxate causing damage to the pulmonary tree (reflux theory) and (2) stimulation of vagal nerve endings in the esophagus causing bronchial constriction (reflex theory). Additionally, a vicious cycle between the two conditions has also been discovered (Fig. 4). Asthma medicines, such as beta-agonists and theophylline, have been shown to promote GERD by decreasing LES tone. This results in an increase in asthma symptoms promoted by GERD which, in turn, lead to an increase in the use of asthma medications (McCallister et al., 2011).

Prognosis

Most patients with GERD respond well to medications, although a relapse after cessation of medical therapy is common and indicates the need for long-term maintenance therapy. Identifying the subgroup of patients who may develop the most serious complications of GERD and treating them appropriately is important. Surgery at an early stage is most likely indicated in these patients. After a laparoscopic Nissen fundoplication, symptoms resolve in approximately 92% of patients. The LOTUS trial—a 5-year, exploratory randomized, open, parallel-group trial—demonstrated that with antireflux therapy for GERD, either using drug-induced acid suppression with esomeprazole or laparoscopic antireflux surgery, most patients achieve remission and remain in remission at 5 years.

Most cases of GER in infants and very young children are benign and respond to conservative nonpharmacologic treatment (developmental disabilities represent an important diagnostic exception); 80% resolve by age 18 months (55% resolve by age 10 months). Some patients require a "step-up" to acid-reducing medications, and only a very small minority requires surgery. Because symptomatic GER after 18 months of age likely represents a chronic condition, long-term risks are increased. For patients whose GER persists into later childhood, long-term therapy with antisecretory agents is often required.

In refractory cases or when complications related to reflux disease are identified (e.g., stricture, aspiration, airway disease, Barrett's esophagus), surgical treatment (fundoplication) is typically necessary, and the prognosis with surgery is considered excellent. The surgical morbidity and mortality are higher in patients who have complex medical problems in addition to GER.

Signs and Symptoms

The signs and symptoms of GERD may vary from individual to individual and can be categorized into typical and atypical symptoms (Table 2). However, typical symptoms, such as heartburn and acid regurgitation, are most common and are sufficient to make a diagnosis of GERD with high specificity (Klauser et al., 1990).

Table 2 Typical and atypical symptoms of GERD

Typical symptoms	*Atypical symptoms*	*Symptoms of possible complicated GERD*
Heartburn	Chest pain	Vomiting
Acid regurgitation	Chronic cough	Weight loss
	Globus	Early satiety
	Asthma	Dysphagia
	Recurrent laryngitis	Odynophagia
	Subglottic stenosis	Iron deficiency anemia
	Recurrent sore throat	Gastrointestinal bleeding
	Dental enamel loss	

Typical Esophageal Symptoms

Heartburn is the most common typical symptom of GERD and is felt as a retrosternal sensation of burning or discomfort that usually occurs after eating, when lying supine or bending over. Regurgitation refers to reflux of gastric and/or esophageal contents into the pharynx. This may also lead to respiratory complications if gastric contents enter the tracheobronchial tree. Additionally, dysphagia occurs in approximately one-third of the patients. These patients experience a sensation of food being stuck, particularly in the retrosternal area. Dysphagia can be an advanced symptom and may be due to a primary underlying esophageal motility disorder.

Atypical Esophageal Symptoms

Atypical symptoms of GERD can be severe and may lead to further complications. Coughing and/or wheezing are respiratory symptoms resulting from the inspiration of gastric contents into the tracheobronchial tree or from the vagal reflex arc producing bronchoconstriction. Hoarseness results from irritation of the vocal cords by gastric refluxate and is often experienced by patients in the morning. Furthermore, reflux is the most common cause of noncardiac chest pain, accounting for approximately 50% of cases. Additional atypical symptoms from abnormal reflux include damage to the lungs (e.g., pneumonia, asthma, idiopathic pulmonary fibrosis), vocal cords (e.g., laryngitis, cancer), ear (e.g., otitis media), and teeth (e.g., enamel decay) (Heidelbaugh et al., 2003).

Diagnosis of Gastroesophageal Reflux Disease

The diagnosis of GERD is typically carried out using a combination of clinical symptoms, response to acid suppression, and a set of diagnostic tests. The most commonly used tests are empirical trials, upper endoscopy, ambulatory pH monitoring, barium esophagram, and esophageal manometry (**Table 3**) (Kahrilas, 2003).

Empirical Trial

In many cases, patients exhibit typical symptoms of uncomplicated GERD. For these patients, an initial empiric medical therapy can be used before other invasive tests are employed. An empirical trial is a presumptive diagnosis of GERD, which can be conducted in the setting of existing typical symptoms of heartburn and regurgitation for the empirical management of the symptoms. Based on these symptoms, a therapeutic trial of high-dose proton pump inhibitors (PPIs) is administered for 2–4 weeks. This test has shown sensitivity and specificity to GERD as compared to the other diagnostic methods (Fox and Forgacs, 2006).

Table 3 Diagnostic tests for GERD, explanation of indications, evidence, and recommendation

Diagnostic test	*Indication*	*Highest level of evidence*	*Recommendation*
Proton pump inhibitor Trial	Atypical symptoms, no alarm symptoms	Metastudies	Negative results shows absence of GERD
Endoscopy	Warning signs, chest pain, screening of patients at a high risk	Randomized controlled studies	Early for elderly, those who doesn't respond to PPI trial
Esophageal biopsy	Must not include non-GERD patients	Case control	Not indicated for GERD diagnosis
Esophageal manometry	Preoperative, surgery evaluation	Observational	Rule out hypomotility, preoperatively, not recommended for GERD
Ambulatory reflux monitoring	Preoperatively, for nonerosive GERD	Observational	Monitoring enhanced to 90% when impedance is added

Upper Endoscopy

Endoscopy is the best diagnostic method for patients experiencing typical symptoms such as heartburn and acid regurgitation and is preferred when the patient does not respond to the empiric therapy or in the presence of alarm symptoms of complicated GERD. This method is also preferred for analyzing alarm symptoms such as dysphagia, bleeding, weight loss, anemia, and recurrent vomiting (Shaheen et al., 2012). Additional factors that can lead to the need of upper endoscopy are nocturnal reflux symptoms, hiatal hernia, elevated BMI, and detection of esophageal adenocarcinoma and Barrett's esophagus (Lichtenstein et al., 2007).

However, it is not suitable to undergo endoscopic studies in every patient with uncomplicated reflux symptoms. Therefore, patients experiencing long-term, mild, typical reflux, and no alarm symptoms may be given an empiric trial. Patients exhibiting symptoms that progress during therapeutic trials may indicate the presence of severe or complicated esophagitis (DeVault and Castell, 2005).

Ambulatory pH or Reflux Monitoring

Esophageal pH monitoring is a method used to measure the extent of acidic reflux into the esophagus from the stomach. This is one of the best methods used to measure abnormal esophageal acid exposure and to determine whether the acidic reflux is occurring during the day or night. It is necessary to remember that 70%–80% of patients continue to secrete some acid despite the administration of PPIs twice daily and some proportion of the acid is susceptible to reflux back into the esophagus.

This test is also used to determine the occurrence of abnormal acid exposure, reflux frequency, and some symptoms that are linked to reflux episodes. In a consensus statement, it has been suggested that the addition of impedance for reflux monitoring increased the sensitivity to around 90% as it has the capability to distinguish between acid and nonacid GER (Sifrim et al., 2004).

Esophageal Manometry

Esophageal manometry is a technique that does not play any role in the diagnosis of GERD but plays an important key role in determining the preoperative condition of the esophagus. This procedure is recommended before undergoing antireflux surgery with the aims of ruling out severe hypomotility and some conditions that may be contraindicatory to fundoplication. This method is also used to measure the strength and function of the esophagus and plays a significant role in determining the functionality of the esophagus when any food or liquid passes through it (Katz et al., 2013; Murray et al., 2003).

Barium Esophagram

Barium esophagram was once recommended as a screening test for GERD, but is no longer a part of the diagnostic evaluation. The sensitivity and specificity of barium radiography for abnormal degrees of acid reflux have been found to be insufficient and therefore this test is no longer recommended for the diagnosis of GERD. On the other hand, it is frequently used in the evaluation of complications related to GERD (e.g., peptic stricture) as well as in the evaluation of dysphagia in the post antireflux surgery patient.

Management of Gastroesophageal Reflux Disease

The aim of the treatment is to relieve and prevent symptoms, heal esophagitis, and prevent further complications (Heidelbaugh et al., 2003). As the GERD severity varies from patient-to-patient, treatment also varies depending upon the pathophysiological factors. The treatment of GERD can be classified into two categories: nonpharmacological interventions and pharmacological interventions.

Nonpharmacological Interventions

Nonpharmacological interventions primarily include lifestyle modifications, which assist in the reduction of esophageal acid exposure, promoting gastric emptying, and to prevent symptomatic relapses (Kaltenbach et al., 2006). These lifestyle modifications include modifications in diet, behavior, sleeping body position, and weight reduction (**Fig. 5**) (Kang and Kang, 2015).

Dietary modifications can also include avoidance of high fat food, which exacerbate the gastric emptying from the stomach, decreasing mucosal injury by avoiding spicy foods, and avoidance of coffee or chocolate for the reduction of reflux. Based on the individual physiology, maintenance of gastric pH and by avoiding citrus foods and carbonated beverages (Dutta and Moayyedi, 2013; Fox et al., 2007; Johnson et al., 2010).

Furthermore, modifications of behavior include avoidance of alcohol intake and smoking cessation. There are a number of reasons why alcohol and smoking cessation has a significant role in the management of GERD. Alcohol increases acid secretion

Figure 5 Illustration showing the different life style options for managing GERD.

through stimulation of gastrin, decreasing LES pressure, increasing LES relaxation, impaired emptying of the stomach, and impaired gastric motility. Whereas, smoking prolongs the esophageal acid clearance, reduces the pressure of the LES, and decreases the secretion of salivary bicarbonate (Dua et al., 1998; Smit et al., 2001).

Additional life style modifications include weight reduction to decrease intragastric pressure, and elevation of the head of the bed by approximately 4–8 in. in patients experiencing nocturnal GERD, which helps to reduce acid reflux symptoms, it also helps to increase the esophageal pH (Khan et al., 2012).

Pharmacological Interventions

Pharmacological interventions applicable for the management and treatment interventions of GERD include nonraft-based formulations (Table 4) and alginate-based raft formulations. Common pharmacological therapy of GERD includes administration of antacids, proton pump inhibitors, sucralfate, histamine-2 receptor antagonists (H_2RAs), and alginate-based raft formulations (Savarino et al., 2012).

Two therapeutic approaches for the management of GERD exist. First strategy is the "Step Up" approach, which includes life style modifications and use of antacids, followed by H_2RA (Ranitidine 150 mg × 2) and, if symptoms still persist, then switch to proton pump inhibitors (PPIs). Alternatively, the treatment may begin with the most effective regimen and stepped down gradually, which is known as the "Step Down" approach. In this approach, treatment is initiated with a PPI such as Omeprazole 20 mg to help control the patient's symptoms (Katsanos et al., 2003).

Table 4 Nonraft-based pharmaceutical formulations used in the treatment of GERD

Drugs	*Dose*	*Mechanism of action*	*Adverse effects*	*Recommendation*	*Level of evidence*
		Antacids			
Aluminum hydroxide/magnesium hydroxide combinations	30 mL 1 h after meals and at bedtime	Neutralizes stomach acid	Constipation, diarrhea, nausea, headache	Conditional recommendation	Low level of evidence
Calcium carbonate (single or in combination with magnesium hydroxide and simethicone)	10–20 mL of suspension, or 2–4 regular strength tablets takes four times a day 20–60 min after meals and at bedtime	Neutralizes stomach acid	Diarrhea, constipation, nausea, belching. Risk of drug interaction, use concurrently with some drugs	Conditional recommendation	Low level of evidence
		Histamine 2 antagonists			
Cimetidine	600 mg twice daily	Blocks H_2-receptor to reduce acid production	Diarrhea, constipation, headache, fatigue, confusion, cardiac effects, rash	Conditional recommendation	Low level of evidence
Famotidine	10–20 mg twice daily	Blocks H_2-receptor to reduce acid production	Diarrhea, constipation, headache, fatigue, confusion, cardiac effects, rash	Conditional recommendation	Low level of evidence
Nizatidine	150 mg twice daily	Blocks H_2-receptor to reduce acid production	Diarrhea, constipation, headache, fatigue, confusion, cardiac effects, rash	Conditional recommendation	Low level of evidence
Ranitidine	75–150 mg twice daily	Blocks H_2-receptor to reduce acid production	Diarrhea, constipation, headache, fatigue, confusion, cardiac effects, rash	Conditional recommendation	Low level of evidence
		Proton pump inhibitors			
Esomeprazole	20–40 mg once daily 30 min before food; usual: 40 mg once daily before food	Inhibition of active proton pumps to reduce acid production	Abdominal pain, diarrhea, headache. Potential for cytochrome P450-mediated drug interactions	Strong recommendation	Moderate level of evidence
Lansoprazole	30 mg once daily 30 min before food	Inhibition of active proton pumps to reduce acid production	Diarrhea, abdominal pain, headache. Cytochrome P450-mediated	Strong recommendation	Moderate level of evidence
Omeprazole	20 mg once daily 30 min before food	Inhibition of active proton pumps to reduce acid production	Abdominal pain, nausea, headache. Mediated by CYP450	Strong recommendation	Moderate level of evidence
Pantoprazole	40 mg once daily 30 min before food	Inhibition of active proton pumps to reduce acid production	Diarrhea, headache, dizziness, pruritus. Mediated by CYP450	Strong recommendation	Moderate level of evidence
Rabeprazole	20 mg once daily 30 min before food	Inhibition of active proton pumps to reduce acid production	Diarrhea, headache. Mediated by CYP450	Strong recommendation	Moderate level of evidence

Nonraft-Based Pharmaceutical Formulations

Antacids

Antacids are basic in nature and are composed of different combinations of acid-neutralizing agents such as aluminum and magnesium hydroxide, calcium carbonate, sodium citrate, and sodium bicarbonate. These bases combine with acid in the stomach and result in the neutralization of gastric acid, providing relief from the acidity.

Over-the-counter acid suppressants and antacids are usually administered for the initial therapy for GERD and are primarily used on demand for episodic heartburn which is most commonly postprandial heartburn (Jones, 2000). Antacids have been used for the management of GERD for a long period of time and are very popular among consumers of over-the-counter (OTC) medications.

Sucralfate

Sucralfate is a prescription medicine, which is used to treat peptic ulcers and acts by stimulating the secretion of growth factors implicated in ulcer healing. It also works as a binding agent and binds to the ulcer base in conditions when the pH of the stomach is reduced (Isolauri and Laippala, 1995.

Histamine-2 receptor antagonists

H_2RA therapy results in reliable healing of peptic ulcers along with the healing of mild to moderate erosive esophagitis. H_2RAs suppress the secretion of gastric acid from the parietal cells of the stomach by competitively inhibiting the histamine at H_2-receptors. H_2RAs also reduce the volume of gastric acid in the stomach by an unidentified mechanism as a result of reduction in pepsin output (Wolfe and Sachs, 2000).

Proton pump inhibitors

Proton pump inhibitors are the cornerstone of treatment for GERD owing to their consistent inhibitory effect on acid secretion. The introduction of PPIs revolutionized the treatment related to acid reflux and they are currently considered the best therapeutic option for GERD and the most successful antisecretory agent in terms of symptom relief and mucosal healing (Chiba et al., 1997; Howden, 1994). PPIs are also considered to be the most efficient suppressants of gastric acid and they act by inhibiting the common pathway of gastric acid secretion also known as H^+/K^+ ATPase pump (Dean et al., 2004; Moayyedi et al., 2007).

Alginate-Based Raft Pharmaceutical Formulations

Alginate-based raft formulations work on the principle of floating drug delivery systems. The bulk density of these systems is lower than that of the gastric fluid and hence they remain floating on the surface of the stomach where they swell and form a raft, which remains floating on the surface of the stomach contents. This system contains a gel-forming agent (e.g., sodium alginate), alkaline bicarbonates, or carbonates for generating the carbon dioxide, which helps in making the system less dense and help the formulation float on the surface of gastric fluid, along with the presence of an acid neutralizer (Fabregas et al., 1994; Shah et al., 2009).

In cases in which therapeutic agents such as H_2RAs, PPIs, and antacids act by acid neutralization while interfering in the normal physiology of the stomach, raft-forming antireflux formulations can prove to be an ideal therapeutic class, which exhibit a unique nonsystemic mechanism. The therapeutic effect is achieved by protecting the esophageal mucosa by forming a viscous, gelatinous neutral barrier on the top of the stomach contents (Mandel et al., 2000).

This raft prevents the acidic gastric content from getting refluxed into the esophagus, giving symptomatic relief to GERD patients (Mandel et al., 2000; Sun et al., 2015; Wang et al., 2013).

Surgical Treatment

Justifications for surgery include failed medical management, patient preference for surgery despite successful management, complications of GERD, medical complications attributable to a larger hiatal hernia, or atypical symptoms with reflux documented on 24-h pH monitoring (Heidelbaugh et al., 2003).

The basic principle of surgery includes the reduction of hiatal hernia, repair of diaphragmatic hiatus, strengthening of the EGJ-posterior diaphragm attachment, and strengthening of the antireflux barrier through placement of a gastric wrap around the EGJ (fundoplication) (So et al., 1998).

Mild symptoms of GERD such as heartburn and regurgitation can be eliminated by surgery more effectively (beneficial in 75%–90% of patients), whereas moderate and severe symptoms of GERD, such as coughing, asthma and laryngitis, can be eliminated to a lesser degree by the use of surgery (beneficial in 50%–75% of patients) (So et al., 1998).

Role of Pharmacist in the Management of Gastroesophageal Reflux Disease

Pharmacists are one of the most accessible and trusted health-care professionals and are the first point of contact for many patients. Therefore, it is necessary for them to be aware of typical and atypical GERD symptoms and to be able to determine the relevant course of action to ensure that patients receive effective and individualized treatment (Fig. 6). Additionally, pharmacists must have

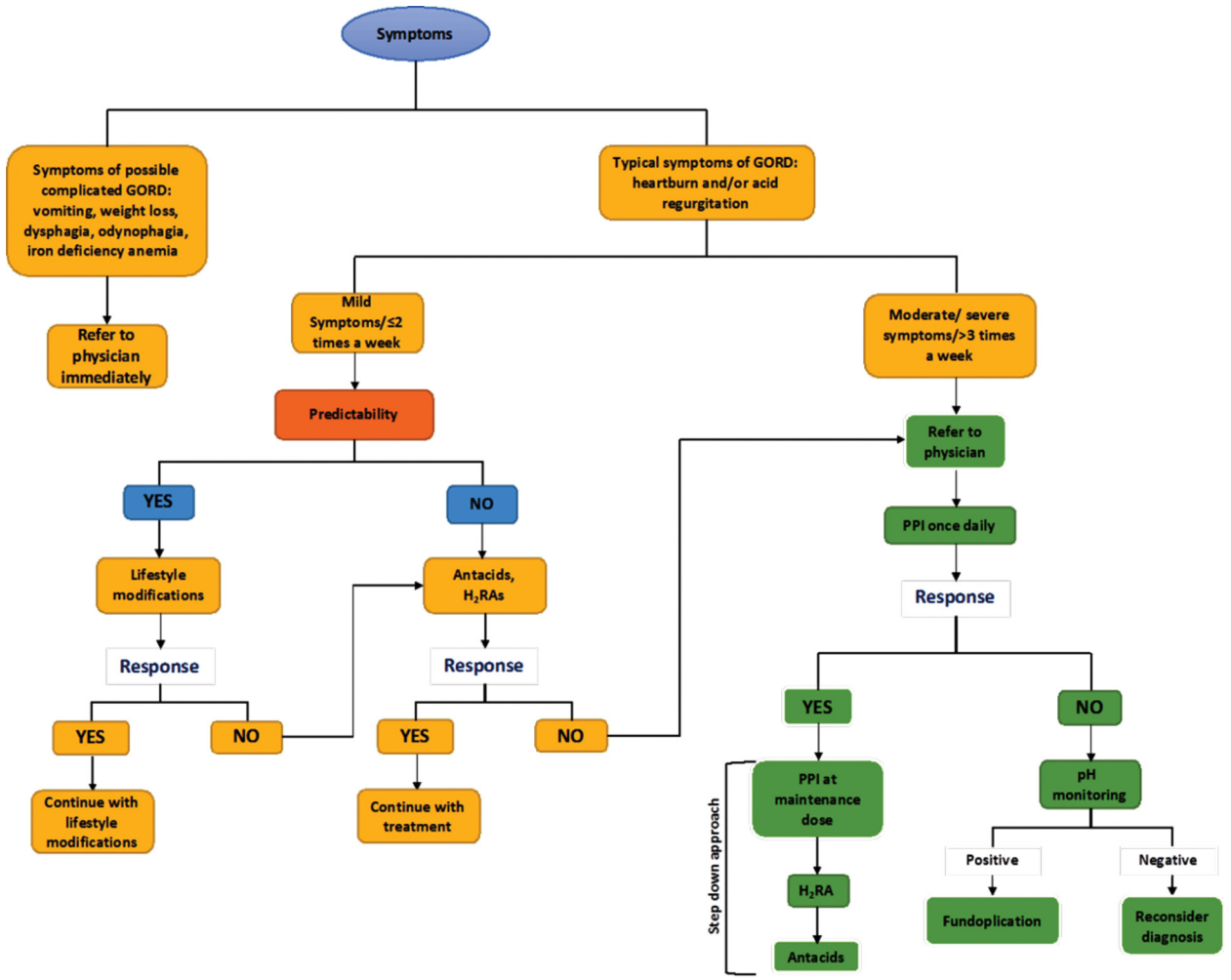

Figure 6 Flow diagram detailing the diagnosis and treatment methods for GERD.

knowledge of possible risk factors, clinical presentations, adverse drug interactions, adverse effects, dosage intervals, dosage titration, complications, and most important of all, therapeutics of GERD (Zeid and Confer, 2016).

Pharmacist's Initiative to Treat Different Gastroesophageal Reflux Disease Conditions

In cases where the patient visits the pharmacy and complains of symptoms consistent with GERD, diagnosis begins with a short interview to determine the characteristics of their symptoms including the nature, frequency, and severity of symptoms (Veldhuyzen van Zanten et al., 2000).

For patients presenting with mild GERD symptoms (symptoms ≤2 times a week), treatment typically begins with lifestyle modifications. This includes advice on smoking cessation, avoiding alcoholic drinks, losing weight, avoiding acidic drinks, elevating the head of the bed, and avoiding foods that may trigger symptoms such as food high in spices or fat (Nilsson, 2004; Pandolfino et al., 2006). However, although effective, lifestyle modifications alone are not sufficient to completely control symptoms in most cases. Therefore, pharmacological treatment of patients exhibiting mild symptoms of GERD begins with an initial OTC therapy of H_2RA or a PPI inhibitor to be taken 30–60 min before the first meal of the day (Colin-Jones, 1995; des Varannes et al., 2010).

If the patient is experiencing typical symptoms of GERD frequently (>3 times a week) and these symptoms affect their quality of life, it becomes evident that the patient is suffering from moderate to severe symptoms of GERD (Moayyedi and Talley, 2006). In this case, the pharmacist should refer the patient to a physician immediately.

The treatment strategy for moderate to severe symptoms of GERD includes gastric acid suppression, which will ultimately suppresses the acidic reflux contents. There are two categories of drugs, which can significantly lower the pH of stomach contents; H_2RAs and PPIs. Patients with moderate to severe GERD are likely to require long-term treatment with PPIs or even surgery in certain circumstances (Sheikh et al., 2014).

Pharmacists are advised to ask questions regarding alarm symptoms in a short interview with the patient. Patients presenting any alarm symptoms should be referred to their physician or to a hospital emergency room immediately.

Pharmacists can treat patients with a family history of GERD displaying mild symptoms. However, if symptoms become uncontrollable or severe, it is the responsibility of the pharmacist to refer the patient to a physician (Flook et al., 2008).

Approximately half of all pregnant women experience GERD during their second or third trimester. If a woman visits a pharmacy and complains of GERD symptoms, pharmacists should educate the patient on appropriate lifestyle modifications (Akbari and Wolf, 2017; Patti, 2016).

Education and Counseling Approaches on Medicine Usages

It is the duty of the pharmacist to provide information to patients regarding available treatment options. Patients should also be made aware of lifestyle changes they could implement to manage GERD symptoms (NICE Guideline Draft, 2014). Other information pharmacists should give includes use of OTC medication, duration of therapy, proper route of administration, dosages, and dosage intervals between consecutive medication (NICE Clinical Guidelines, 2004; Wagner, 2000).

Pharmacists should educate patients on potential adverse reactions of prescribed medications. For example, general adverse effects of PPIs are headaches, diarrhea, and dyspepsia (Katz et al., 2013). Furthermore, long-term use of PPIs may lead to conditions such as B12 deficiency, iron deficiency, hypomagnesemia, increased susceptibility to pneumonia, enteric infections, and hypergastrinemia (Sheen and Triadafilopoulos, 2011). Adverse effects of H_2RAs may include hepatotoxicity and nephrotoxicity (Fisher and Le Couteur, 2001; McGuigan, 1981).

Pharmacists should also examine the medical history of the patient to determine any potential drug interactions. Commonly, ketoconazole, simvastatin, vitamins, and digoxin show drug interactions when administered with PPIs (Blume et al., 2006). Antacids also show drug interactions with a few classes of drugs such as quinolones, NSAIDs, and cephalosporin (Sadowski, 1994). Some other common possible adverse drug interactions of drugs used for the treatment of GERD are presented in **Table 5**.

Pharmacist's Role in Treatment Follow-up

Patients visiting a pharmacist after undergoing treatment for moderate to severe GERD symptoms should have a follow-up with the patients regarding the recovery from GERD. If GERD symptoms persist, the pharmacist should refer the patient to the physician again. If the symptoms are subsiding and the patient is healing, the same treatment regimen of PPIs once daily should be continued unless the treatment is suspended by the physician (Marchetti and Chan, 2009). Pharmacists should also check whether patients are taking medicines properly hence they can evaluate the extent pharmacist-led counseling is helping in controlling the symptoms of

Table 5 Summary of common drug–drug interactions associated with antacid, PPIs, and H_2RAs

	Antacids	*PPIs*	*H_2RAs*
Antivirals	Aluminum and magnesium containing antacids cause a small decrease in exposure to antiviral drugs	PPIs are life threatening or contraindicated with rilpivirine and administered with closed monitoring in some combinations	Dose adjustment and close monitoring are needed
Antidiabetics	No interaction or no interaction of clinical significance	No interaction of clinical significance	Dose adjustment and closed monitoring are needed
Antiasthmatics	No interaction or no interaction of clinical significance	No interaction of clinical significance	Dose adjustment and closed monitoring are required in very few cases otherwise no clinical interaction is found
Anticholinergics	No interaction or no interaction of clinical significance	Dosage adjustment, closed monitoring, and guidance are needed in few cases	Dose adjustment and closed monitoring are required
Antiarrhythmic	Contraindicated or administered with closed monitoring and dose adjustment	No interaction of clinical significance	Dose adjustment and closed monitoring are required
Antibiotics	Dose adjustment and close monitoring are required	Dose adjustment or closed monitoring is needed in few case, administer with guidance	Dose adjustment and closed monitoring are required
NSAIDs	Monitoring and guidance about suitable adverse effects need to be given when antacids are administered with salicylic acid derivatives of NSAIDs, no clinically significant interaction is evident with other NSAIDs	The antiplatelet activity and pharmacokinetic properties are not affected at all	No interaction of clinical significance
Alcohol	No clinical evidence	No interaction of clinical significance	No interaction of clinical significance
Food	Dosage adjustment and closed monitoring are required	No interaction of clinical significance, dose adjustment, and close monitoring is required in few cases	No potential or clinical significance

GERD. Getting the prescription reviewed helps pharmacists maintain a record regarding the improvement of the disease condition (NICE Guideline Draft, 2014).

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Further Reading

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Management of Gastrointestinal Disorders and the Pharmacist's Role: Inflammatory Bowel Disease

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Learning Objectives

At the end of this chapter, the reader would be able to:

- Develop a basic understanding of the etiopathogenesis and epidemiology of different forms of inflammatory bowel disease (IBD).
- Describe the main clinical features and complications associated with ulcerative colitis and Crohn's disease.
- Discuss various pharmacological approaches and their selection criteria.
- Explain the roles and activities of pharmacists in the pharmacotherapy of IBD.

Introduction

Inflammatory bowel disease (IBD) is an idiopathic immune-mediated chronic inflammatory condition of the gastrointestinal (GI) tract that involves episodes of relapse and periods of remission. The two main forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD) that are characterized by continuous mucosal and intermittent transmural inflammation, respectively. UC affects the colorectal part of the GI tract; whereas CD primarily affects the terminal ileum and cecum (ileocecal CD), however esophagus, small intestine, large intestine and rectum may also be affected.

Epidemiology

The epidemiology of IBD varies substantially over time and across various geographical regions. Although the incidence and prevalence of IBD has stabilized in high-incidence areas including North America and Europe, it continues to rise in previously low-incidence areas such as Eastern Europe and Asia (Ng, 2014; Sharara et al., 2018). A recent systematic review has reported the highest prevalence rates of IBD in Europe (UC: 505 per 100,000 people in Norway; CD: 322 per 100,000 people in Germany) and North America (UC: 286 per 100,000 people in the United States; CD: 319 per 100,000 people in Canada). On the contrary, an increased prevalence of IBD has been reported in recently developed countries across Africa, Asia, and South America (Ng et al., 2018). The incidence of IBD peaks at the second and third decade of life (during 20s and 30s) with a subsequent peak at the age of 60–80 years, but it may occur in individuals of any age (Duricova et al., 2014; Jeuring et al., 2016). Compared to males, the risk of CD is lower in females till the age of 10–14 years, however the risk of the disease increases thereafter. The incidence of UC is similar in both males and females until the age of 45 years, but increases in men afterwards (Shah et al., 2018).

Etiology and Pathophysiology

The exact cause of IBD remains unclear but abnormal immune system, intestinal microbiota, and various genetic and environmental factors are believed to play an important role in its pathogenesis (Ray and Longworth, 2019; Rohr et al., 2018). Intestinal microbiota in the presence of damaged GI mucosal barrier and impaired immune response may result in chronic inflammation. An increased secretion of interferon-γ by the T_1-helper cells and cytokines by the T_{17}-helper cells has been detected in CD. Whereas, an increased secretion of cytokines by the T_2-helper cells has been reported in UC (Yadav et al., 2016). Furthermore, the abundance of proinflammatory microbiota (dysbiosis) has been proved to play an important role in the pathogenesis of IBD and related complications (Rohr et al., 2018; Yadav et al., 2016).

Genetic predisposition is well established in the first-, second-, and even third-degree relatives of patients with IBD. Genetic predisposition is primarily associated with polymorphism of the caspase recruitment domain family member 15 (CARD15) gene in CD and human leukocyte antigen class-II gene in UC (Cho and Brant, 2011; Yadav et al., 2016). Polymorphism of numerous other genes has also been associated with the increased risk of IBD.

Lifestyle factors including diet, cigarette smoking, and stress can significantly affect the pathogenesis of IBD. An increased consumption of fast food, fats, proteins, milk, and refined sugars has also been associated with IBD (Rohr et al., 2018). In addition, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, isotretinoin, and several antibiotics may increase the risk of IBD (Ananthakrishnan et al., 2012; Rohr et al., 2018). Cigarette smoking has been reported to increase the risk of CD by twofold but is suspected to reduce the risk of UC (Yadav et al., 2016).

Clinical Presentation

The clinical manifestations of IBD are related to the nature and severity of the disease. Typically, UC is presented with bloody diarrhea, tenesmus, and fecal incontinence (Magro et al., 2017). Nocturnal defecation and fatigue have also been frequently reported. Rectal inflammation results due to passage of frequent, but small volumes of loose stools that is associated with abdominal

pain (Matsuoka et al., 2018). In severe cases, anorexia, weight loss, fever, tachycardia, nausea, vomiting, dehydration, hypokalemia, and hypoalbuminemia can also occur.

Patients with CD may present with abdominal pain, fatigue, low-grade fever, intermittent nonbloody diarrhea, and weight loss (Gomollón et al., 2016). Malabsorption and weight loss are common in patients with CD involving the small intestine. Patients with perianal disease may experience severe perirectal pain, foul-smelling discharge from the fistula, and disfiguring scars of active disease or prior surgery. Growth retardation and delayed or failed sexual maturation may also be manifested in children with CD (Yangyang and Rodriguez, 2017).

Diagnosis

IBD is best diagnosed by a collective assessment of the clinical signs and symptoms, and findings of hematological, histologic, colonoscopic, and radiologic investigations (Gomollón et al., 2016; Magro et al., 2017; Rohr et al., 2018).

Sigmoidoscopy and colonoscopy allow direct visualization of the rectum and colon. They also permit tissue biopsy for histopathological assessment (Gomollón et al., 2016; Magro et al., 2017). Sigmoidoscopy is primarily used for the diagnosis of UC or proctitis due to its limited length of scope (i.e., 60 cm), while colonoscopy can examine the whole large intestine. However, these procedures increase the risk of bleeding and perforations.

Radiological imaging including computed tomography scan and magnetic resonance imaging are noninvasive alternatives of sigmoidoscopy and colonoscopy (Rohr et al., 2018). They permit visualization of the large and small intestine and offer initial diagnosis (particularly when the small intestine is involved) and evaluation of related complications (Rohr et al., 2018). Radiolabeled leukocyte scans may also be used to identify the site and severity of disease.

Hematological and biochemical assays involving complete blood count, liver function tests (LFTs), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are all useful to assess the extent and severity of disease as well as its extraintestinal manifestations (Gomollón et al., 2016; Magro et al., 2017). Altered LFTs are common in patients with hepatic complications. ESR and CRP levels are markers of inflammation and are useful in monitoring the disease activity and response to therapy (Gomollón et al., 2016; Magro et al., 2017).

Serologic tests such as the perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) tests ascertain the type of IBD. A positive pANCA test with negative ASCA test is highly specific for patients with UC, whereas a positive ASCA with a negative pANCA is suggestive of CD (Gomollón et al., 2016; Magro et al., 2017; Mitsuyama et al., 2016). However, serologic tests are associated with false-positive results and should not be used exclusively for the diagnosis of IBD.

Stool tests cannot be used for the diagnosis of IBD, but they can be used to rule out alternative conditions (Gomollón et al., 2016; Magro et al., 2017). Microscopic examination of stool can help identify occult blood or other infective cells such as amoeba, whereas stool culture and toxin assay can be used to identify *Clostridium difficile* infection (Mowat et al., 2011).

Complications

IBD is associated with a number of intestinal and extraintestinal complications. The intestinal complications include strictures, fistulae, abscesses, perforations, toxic megacolon, and superinfections (Matsuoka et al., 2018). Fistulae and abscesses, strictures, and perianal complications are commonly found in patients with CD, whereas toxic megacolon, perforations, and superinfections are frequent in patients with UC. IBD also increases the risk of GI malignancies.

The extraintestinal complications are more frequent in patients with CD. They commonly affect the liver, joints, eyes, skin, and blood (Yangyang and Rodriguez, 2017). The hepatobiliary complications include fatty liver, pericholangitis, autoimmune hepatitis, cirrhosis, cholelithiasis, and cholangiocarcinoma. Severe asymmetric arthritis affecting one or few large joints and osteoporosis can be seen. Ocular complications comprise iritis, uveitis, and conjunctivitis (Vavricka et al., 2015). The mucocutaneous complications include erythema nodosum, pyoderma gangrenosum, and aphthous ulcer. Anemia is a common complication possibly because of chronic blood loss, malnutrition, or drug-induced bone marrow suppression (Vavricka et al., 2015).

Treatment

The primary aim of therapy is to induce and maintain remission of symptoms, promote mucosal healing, and prevent the occurrence of complications. For this purpose, various nonpharmacological and pharmacological strategies are employed.

Nonpharmacological Therapy

Incessant use of elemental, semi-elemental, and defined diets have been demonstrated to reduce inflammation and promote mucosal healing (Alastair et al., 2011). Therefore, they are recommended for the treatment of mild CD along with proper monitoring of disease progression (Lichtenstein et al., 2018). Enteral dietary supplements have also been recommended as adjuvant

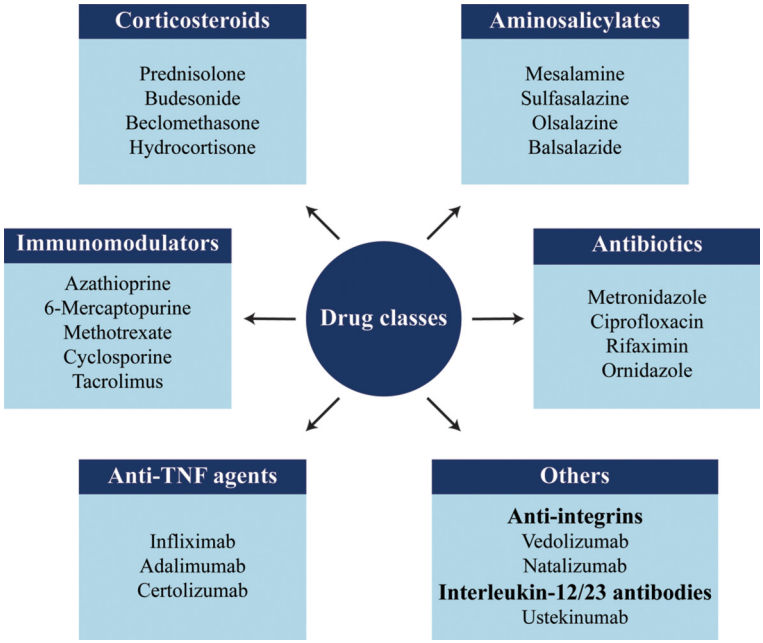

Figure 1 Drugs used for the treatment of inflammatory bowel disease.

therapy. They are mainly used in patients with severe CD involving the small intestine because of significant malnutrition and weight loss (Alastair et al., 2011). Consumption of low-residue diet can prevent intestinal obstruction in patients with small bowel strictures. However, dairy products (a low-residue diet) may cause diarrhea in lactose-intolerant patients (Bitton et al., 2012). Parenteral nutrition therapy is costly and associated with an increased risk of infections. Therefore, it is typically reserved for patients with severe malnutrition or intolerance to enteral therapy (Alastair et al., 2011). Probiotics have been demonstrated to be of some benefit and are recommended as an adjuvant therapy in selected patients considering their efficacy and cost (Wasilewski et al., 2015).

Surgery is one of the recommended options in patients with an advanced IBD. Common surgical procedures involve resection of the affected segment of intestine, closure of fistula or perforation, and drainage of abscess. Colectomy (resection of a segment of large intestine) may be necessary in patients with UC who do not respond to the recommended pharmacotherapy, have signs of premalignant changes, or present with complications such as toxic megacolon (Biondi et al., 2012; Kornbluth et al., 2010). Colostomy is performed in patients with severe perianal or rectal disease. Surgery may also be performed for treating strictures (stricturoplasty) (Lichtenstein et al., 2018).

Pharmacological Therapy

The pharmacological therapy involves the use of various drugs such as aminosalicylates, corticosteroids, immunomodulators, anti-TNF agents (TNF-α antibodies), anti-integrins (integrin antibodies), interleukin-12/23 antibodies, and antibiotics (**Fig. 1**). Their recommended doses are given in **Table 1**.

Although a variety of guidelines are available for the management of IBD (see further reading for details), the ones published by the American College of Gastroenterology and the European Crohn's and Colitis Organization are widely used (Gomollón et al., 2016; Harbord et al., 2017; Kornbluth et al., 2010; Lichtenstein et al., 2018).

Aminosalicylates

Aminosalicylates are the recommended first-line agents for the treatment of IBD because of their local (intestinal) anti-inflammatory activity and better safety profile. They include sulfasalazine, mesalamine, balsalazide, and olsalazine. Several formulations of aminosalicylates such as suppositories, enema, foam, and oral tablets/capsules are available. The choice of a specific dosage-form depends on the severity and location of the disease (Harbord et al., 2017).

Corticosteroids

Corticosteroids are rapid acting, potent anti-inflammatory agents. They are recommended for induction of remission. In IBD, both topical and systemic corticosteroids are used. Topical corticosteroids are administered as enema or foam and systemic corticosteroids are administered via oral (prednisolone) or intravenous route (hydrocortisone). Topical preparations and ileal release budesonide are preferred in patients with mild to moderate disease, whereas systemic preparations are commonly used in severe disease.

Table 1 Recommended doses for the pharmacotherapy of inflammatory bowel disease

	Dosage		
Drugs	*Ulcerative colitis*	*Crohn's disease*	*Special considerations*
Sulfasalazine	**Remission**: Oral 1–2 g/day in three divided doses (maximum 4 g/day) **Maintenance**: Oral 2 g/day	**Remission**: Oral 3–6 g/day in divided doses (off-label)	**CI**: Hypersensitivity, intestinal or urinary obstruction and porphyria **DA**: In GI intolerance, discontinue for few days and reintroduce therapy with 50% daily dose then gradually increase.
Mesalamine	**Remission**: Oral 2.4–4.8 g/day; the dosage and cumulative daily dose depends on available formulations **Maintenance**: Oral 1.5–2.4 g/day; the dosage and cumulative daily dose depends upon the available formulations	**Remission**: Oral 1 g every 6–8 h	**CI**: Hypersensitivity **DA**: None required **Precautions**: Do not administer delayed release mesalamine with antacids
Balsalazide	**Remission**: Oral 2.25 g three times daily **Maintenance**: Oral 1.5–2 g twice daily	–	**CI**: Hypersensitivity **Precautions**: Effectiveness and safety of use >12 weeks is not established
Budesonide	**Remission**: Oral 9 mg once daily; rectal foam 2 mg twice daily; rectal enema 100–125 mL (2 mg/100 mL) once daily	**Remission**: Oral 9 mg once daily **Maintenance**: Oral 6 mg once daily	**CI**: Hypersensitivity to budesonide, milk proteins, and primary treatment of asthma **DA**: Reduce dose in moderate or severe hepatic impairment; use lowest effective dose in geriatrics
Prednisolone	**Remission**: Oral 5–60 mg once daily	**Remission**: Oral 5–60 mg once daily	**CI**: Systemic infections **DA**: None required; use lowest effective dose in geriatrics **Precautions**: Do not stop abruptly, taper dose gradually
Hydrocortisone	**Remission**: IV 100–500 mg every 2, 4, or 6 h; Oral 20–240 mg/day	**Remission**: IV 100–500 mg every 2, 4, or 6 h; Oral 20–240 mg/day	**CI**: Hypersensitivity, systemic infections **DA**: Reduce dose in hepatic impairment **Precautions**: Do not stop abruptly, taper dose gradually
Azathioprine	**Remission**: Initiate 20–40 mg/kg infusion over 36 h then oral 2 mg/kg/day **Maintenance**: Oral 1.5–2.5 mg/kg/day (off-label)	**Remission/Maintenance**: Oral 1.5–4 mg/kg/day	**CI**: Hypersensitivity, Pregnancy **DA**: Reduce dose or discontinue therapy in bone marrow suppression; reduce dose in lower doses by 25% in moderate renal impairment and 50% in ESRD
6-Mercaptopurine	**Remission/Maintenance**: Oral 50 mg daily; adjust dose according to response (off-label)	**Remission/Maintenance**: Oral 1–1.5 mg/kg daily (off-label)	**CI**: Hypersensitivity, resistance to 6-mercaptopurine **DA**: Use the lowest effective dose in renal or hepatic impairment and geriatrics; adjust dose to maintain WBC >4500 and platelets >100,000
Methotrexate	–	**Remission/Maintenance**: IM 15–25 mg once weekly	**CI**: Pregnancy, breast-feeding, chronic liver disease, hypersensitivity, kidney failure, compromised immunity and bone marrow suppression **DA**: Reduce dose by half in moderate renal impairment; reduce dose by 25% if bilirubin is 3.1–5 mg/dL or avoid use if bilirubin is >5 mg/dL
Infliximab	**Remission**: IV 5 mg/kg over 2 h at weeks 0, 2, and 6 **Maintenance**: IV 5 mg/kg over 2 h every 8 weeks	**Remission**: IV 5 mg/kg over 2 h at weeks 0, 2, and 6 **Maintenance**: IV 5 mg/kg over 2 hours every eight weeks	**CI**: Hypersensitivity **DA**: Use doses ≤5 mg/kg in moderate or severe heart failure **Precautions**: Infusion reaction, infuse slowly, and consider preventive therapy with corticosteroids, acetaminophen and antihistamines; discontinue if sepsis or infection develops during therapy
Vedolizumab	**Remission/Maintenance**: Infuse 300 mg over 30 min at weeks 0, 2, and 6 followed by 300 mg every 8 weeks	**Remission/Maintenance**: Infuse 300 mg over 30 min at weeks 0, 2, and 6 followed by 300 mg every 8 weeks	**CI**: Active and severe infection, hypersensitivity **Precautions**: Discontinue if jaundice or hepatic injury develops

(*Continued*)

Table 1 Recommended doses for the pharmacotherapy of inflammatory bowel disease (*cont.*)

	Dosage		
Drugs	*Ulcerative colitis*	*Crohn's disease*	*Special considerations*
Ustekinumab	–	**Remission/ Maintenance**: Initiate ~55 kg weight: Infuse 260 mg over 1 h, 55–85 kg weight: Infuse 390 mg over 1 h, >85 kg weight: Infuse 520 mg over 1 h followed by subcutaneous 90 mg every 8 weeks	**CI**: Active infection, hypersensitivity **Precautions**: Discontinue ustekinumab if infection develops during therapy
Metronidazole	Oral or IV 500 mg thrice daily	Oral or IV 500 mg thrice daily	**CI**: Hypersensitivity, alcohol consumption, first trimester of pregnancy. **DA**: Reduce dose by half in severe hepatic impairment
Ciprofloxacin	Oral 500–750 mg twice daily or IV 400 mg twice or thrice daily	Oral 500–750 mg twice daily or IV 400 mg twice or thrice daily	**CI**: Hypersensitivity **DA**: Administer 200–400 mg every 18–24 h in moderate or severe renal impairment Renal impairment (CrCl 5–29 mL/min): 200–400 mg intravenous every 18–24 h

CI, Contraindications; CrCl, creatinine clearance; DA, dose adjustments; ESRD, end-stage renal disease; GI, gastrointestinal; IM, intramuscular; IV, intravenous; WBC, white blood cells.
Sources: ASHP (2018), Lexicomp (2018), and Micromedex Drugdex (2018)

Guidelines do not recommend the long-term use of corticosteroids as a maintenance therapy because of limited proven efficacy and increased risk of serious adverse effects (Harbord et al., 2017; Lichtenstein et al., 2018).

Immunomodulators

Immunomodulators suppress the immune system by disrupting the cellular signaling processes, which result in apoptosis of immune cells. They include azathioprine, 6-mercaptopurine (6-MP), methotrexate, cyclosporine, and tacrolimus. Immunomodulators exhibit corticosteroid sparing effect and are used for maintenance of remission (particularly in corticosteroid-dependent patients). They are not recommended for induction of remission because of delayed onset of clinical effect (Gomollón et al., 2016; Lichtenstein et al., 2018).

Immunomodulators such as azathioprine or 6-MP are also used in combination with infliximab because they attenuate the development of antibodies against infliximab and maintain its efficacy for an extended period of time (Harbord et al., 2017; Lichtenstein et al., 2018). Methotrexate is an effective alternative to azathioprine and 6-MP (thiopurines) for the maintenance of remission and is used in a similar manner as thiopurines. Parenteral formulations of methotrexate are more effective than oral preparations but the latter are preferred by practitioners because of better treatment adherence (Herfarth et al., 2015). Cyclosporine and tacrolimus are reserved for patients with severe refractory disease (Harbord et al., 2017; Lichtenstein et al., 2018).

Anti-TNF Agents

Monoclonal anti-TNF agents include infliximab, adalimumab, and certolizumab. They effectively reduce inflammation and promote mucosal healing, and are recommended for induction as well as maintenance of remission (Harbord et al., 2017; Lichtenstein et al., 2018). The choice of a specific agent is based on its cost, availability, and route of administration. Combination therapy of infliximab with immunomodulator has greater efficacy than either agents alone (Gomollón et al., 2016; Harbord et al., 2017). A number of more affordable biosimilar products of infliximab and adalimumab have also been approved (Danese et al., 2016; Lichtenstein et al., 2018).

Anti-Integrins

Anti-integrins include natalizumab and vedolizumab. They reduce inflammation by preventing the adhesion of leukocytes surface integrins to endothelial cell adhesion molecules. Anti-integrins are indicated for the maintenance of remission either alone or in combination with immunomodulators (Harbord et al., 2017; Lichtenstein et al., 2018).

Interleukin-12/23 Antibodies

Ustekinumab is recommended for patients who do not respond to immunomodulators and anti-TNF agents (Lichtenstein et al., 2018). Ustekinumab is considered safe with no apparent risk of opportunistic infections and malignancies (Papp et al., 2015).

Novel Agents

An estimated one-third patients with CD do not respond to anti-TNF agents, whereas one-third of patients lose response to biologics over time (Lichtenstein et al., 2018). To fulfill the therapeutic needs of such patients, various novel agents are under investigation. They include etrolizumab, ozanimod, risankizumab, brazikumab, filgotinib, upadacitinib, tofacitinib, and mongersen (Chan and Ng, 2017; Lichtenstein et al., 2018; Sands, 2017).

Others

Antibiotics such as metronidazole and ciprofloxacin are primarily used for the prevention and treatment of septic complications (Lichtenstein et al., 2018). They have no direct effect on remission of symptoms; however, they may help suppress the immune response by eliminating bacterial antigenic triggers (Nitzan et al., 2016). Moreover, an enteric formulation of rifaximin may be of some benefit in mild disease (Prantera et al., 2012).

Treatment Approaches: Ulcerative Colitis

Induction of Remission

Remission therapy for UC aims to alleviate symptoms. The selection of pharmacotherapy for the induction of remission depends on the site and severity of disease (Fig. 2). Treatment algorithm for the induction of remission in patients with UC is presented in Fig. 3.

Mild–Moderate Distal Colitis

Oral aminosalicylates (sulfasalazine, mesalamine, olsalazine, or balsalazide), topical aminosalicylate (mesalamine), or topical corticosteroids are recommended in patients with mild to moderate distal colitis (Kornbluth et al., 2010). Topical mesalamine is considered to be more effective than oral aminosalicylates (Hanauer, 2016). Whereas, combination therapy with oral and topical aminosalicylates has been reported to be more effective than monotherapy with either agents alone (Ford et al., 2012). Oral prednisolone or infliximab may be considered in patients who present with systemic manifestations or who do not respond to aminosalicylates or topical corticosteroids (Kornbluth et al., 2010).

Mild–Moderate Extensive Colitis

Oral aminosalicylates (sulfasalazine or mesalamine) either alone or in combination with topical aminosalicylates are the recommended first-line therapy in mild to moderate extensive colitis. Alternatively, oral corticosteroids (prednisolone) may be considered in patients who do not respond to the combination of aminosalicylates (oral and topical) or whose condition demand speedy remission. Following failure of oral corticosteroids, immunomodulators (azathioprine or 6-MP), or anti-TNF agents (infliximab)

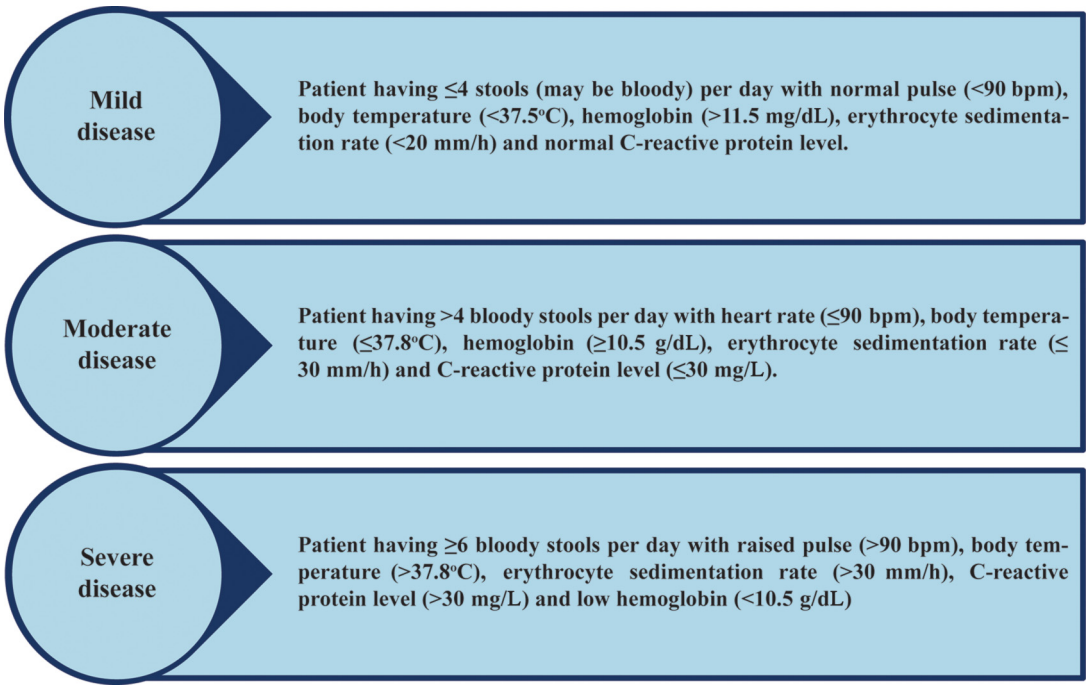

Figure 2 Classification of ulcerative colitis on the basis of severity.

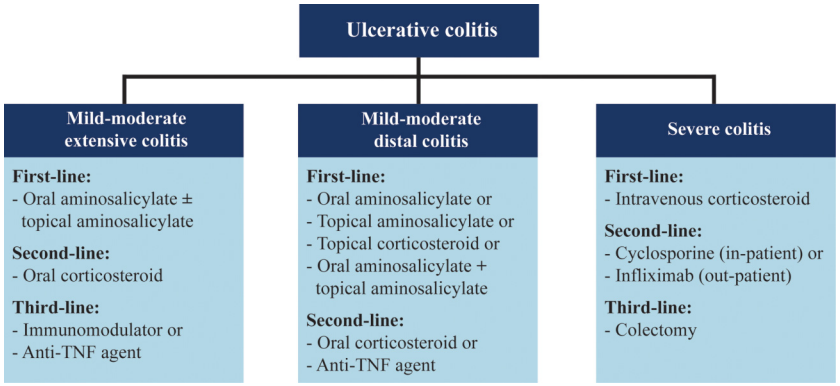

Figure 3 Treatment algorithm for the remission of ulcerative colitis.

should be used (Harbord et al., 2017; Kornbluth et al., 2010). Adjuvant therapy with probiotics, fecal transplant, modified release phosphatidylcholine and *Andrographis paniculata* (herbal remedy) has been shown to improve the clinical response (Karner et al., 2014; Rossen et al., 2015; Sandborn et al., 2013b; Shen et al., 2013).

Severe Colitis

Patients with severe colitis should be hospitalized. Supportive therapy needs to be administered that includes intravenous fluids (as fluid replenishment), low molecular weight heparin (for thromboprophylaxis), electrolytes (for electrolyte imbalance), and blood transfusion (for anemia) (Dignass et al., 2015; Harbord et al., 2016; Nguyen et al., 2014). A collaborative management by medical and surgical experts is highly recommended for timely selection of appropriate therapy and improved health outcomes (Bartels et al., 2013; Harbord et al., 2017). Intravenous corticosteroids (hydrocortisone) are recommended as first-line treatment for severe UC (Bossa et al., 2007). Response to corticosteroid therapy is best assessed after three days. Cyclosporine (in hospitalized patients) or infliximab (in outpatients) may be considered as salvage therapy (Harbord et al., 2017; Järnerot et al., 2005). Whereas, colectomy is recommended provided patient's condition does not improve following 4–7 days of salvage therapy (Harbord et al., 2017). Antibiotics such as metronidazole or ciprofloxacin are indicated in septic complications. Total parenteral nutrition may be considered in malnourished patients (Harbord et al., 2017; Kornbluth et al., 2010).

Maintenance of Remission

Patients with UC require long-term pharmacotherapy for the maintenance of remission in order to delay or prevent the relapse of symptoms.

Mild–Moderate Distal Colitis

Topical mesalamine (enema or suppository) is the recommended first-line therapy for the maintenance of remission. Combination therapy with oral (sulfasalazine) and topical (mesalamine) aminosalicylates is more effective and may be used in patients who can tolerate them. Alternatively, immunosuppressants (azathioprine or 6-MP) or infliximab may be considered in patients who do not respond to aminosalicylates (Harbord et al., 2017; Kornbluth et al., 2010).

Mild-Moderate Extensive Colitis

Oral aminosalicylates including sulfasalazine, mesalamine, or balsalazide are effective for the maintenance of remission. The long-term use of corticosteroids should be avoided. Azathioprine or 6-MP is recommended for maintenance of remission in corticosteroid-dependent patients and for those who fail to respond to aminosalicylates (Kornbluth et al., 2010). Infliximab should be used in patients who have achieved remission with its use (Kornbluth et al., 2010).

Therapy for Refractory Disease

Patients with persistent active disease, despite the use of combination therapy consisting of oral corticosteroids combined with oral and rectal aminosalicylates, are considered refractory (Harbord et al., 2017). Such patients should be carefully evaluated for nonadherence or resistance to previous drug therapy, inadequate delivery of drug to the inflamed tissue, undiagnosed or misdiagnosed conditions, and the presence of complications (Gecse and Lakatos, 2014; Harbord et al., 2017). Hospital admission is indicated in patients with systemic manifestations for intravenous therapy, whereas patients without systemic manifestations can be treated as out-patients (Harbord et al., 2017; Mehta et al., 2013). Intravenous corticosteroids are the recommended first-line therapy (Harbord et al., 2017). Alternatively, azathioprine/6-MP or infliximab/adalimumab may be used (Archer et al., 2016; Gecse and Lakatos, 2014; Harbord et al., 2017). Limited evidence also supports the use of oral/rectal cyclosporine or tacrolimus (Harbord

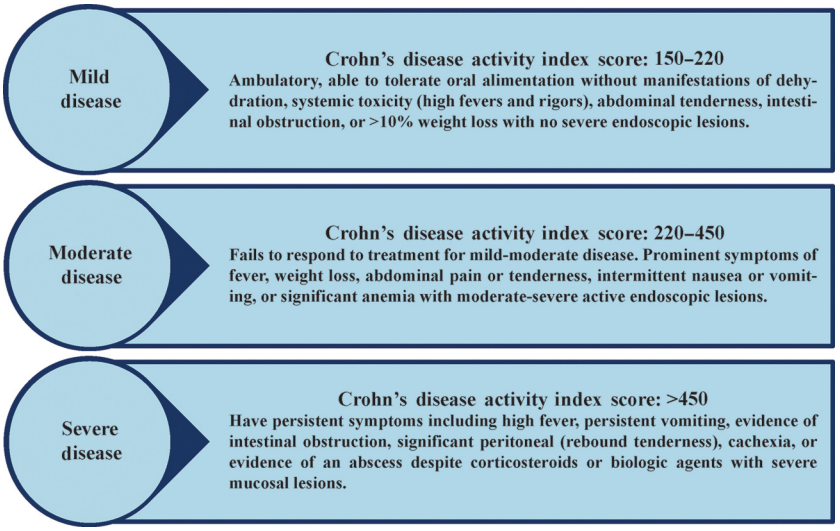

Figure 4 Classification of Crohn's disease on the basis of severity.

et al., 2017; Schmidt et al., 2013). Rectal tacrolimus (ointment) in a dose of 1–1.5 mg twice daily has been proven to be effective in patients resistant to aminosalicylates, corticosteroids, immunosuppressants, and infliximab (Lawrance et al., 2017). If symptoms persist, surgery (colectomy or proctocolectomy) should be considered (Harbord et al., 2017).

Treatment Approaches: Crohn's Disease

The selection of therapy depends on the site, severity (Fig. 4), and prognosis of disease. In addition, previous drug use and the presence of complications are also considered. Patients with extensive disease, young age (<40 years), perianal disease, and those requiring corticosteroids as initial therapy usually show poor prognosis (Miheller et al., 2013). Current practice involves rapid addition of potent agents when the first-line therapy fails to achieve the desired outcome in expected time (accelerated bottom-up approach) (Gomollón et al., 2016). Alternatively, potent agents may be used at an early stage in some patients (top-down approach) (D'Haens et al., 2008; Lichtenstein et al., 2018).

Induction of Remission

The primary aim of remission therapy is to swiftly alleviate the symptoms (Lichtenstein et al., 2018). In general, aminosalicylates and corticosteroids are used in mild or moderate disease, whereas anti-TNF agents either alone or in combination with immunomodulators are preferred in patients with severe disease and/or poor prognosis (Fig. 5) (Terdiman et al., 2013).

Ileocecal Disease

Ileocecal disease is the most common form of CD affecting the terminal ileum and cecum. It can be further divided into mild, moderate, and severe disease.

Mild disease

In mild disease, ileal release budesonide (corticosteroid) is the recommended first-line therapy. Alternatively, oral aminosalicylate (sulfasalazine) may be used. Dietary therapy may be considered in patients who refuse to take medications; however, proper monitoring for disease progression would be required. Anti-TNF agents can be used, but they are not preferred due to their high cost and adverse effects (Lichtenstein et al., 2018).

Moderate disease

Ileal release budesonide or systemic corticosteroids (prednisolone) are recommended as initial therapy in moderate disease (Gomollón et al., 2016; Lichtenstein et al., 2018). Systemic corticosteroids are alternative options; however, they should be sparingly used for remission and their dose must be tapered down (Ho et al., 2006). Patients refractory to corticosteroids should be treated with an anti-TNF agents or combination of a corticosteroid and an immunomodulator (azathioprine or methotrexate) (Gomollón et al., 2016; Lichtenstein et al., 2018; McDonald et al., 2014). Vedolizumab may be considered in patients who fail to respond to systemic corticosteroids and/or anti-TNF agents (Gomollón et al., 2016; Lichtenstein et al., 2018). Whereas, ustekinumab is suggested for patients refractory to corticosteroids, immunomodulators, or anti-TNF agents (Feagan et al., 2016).

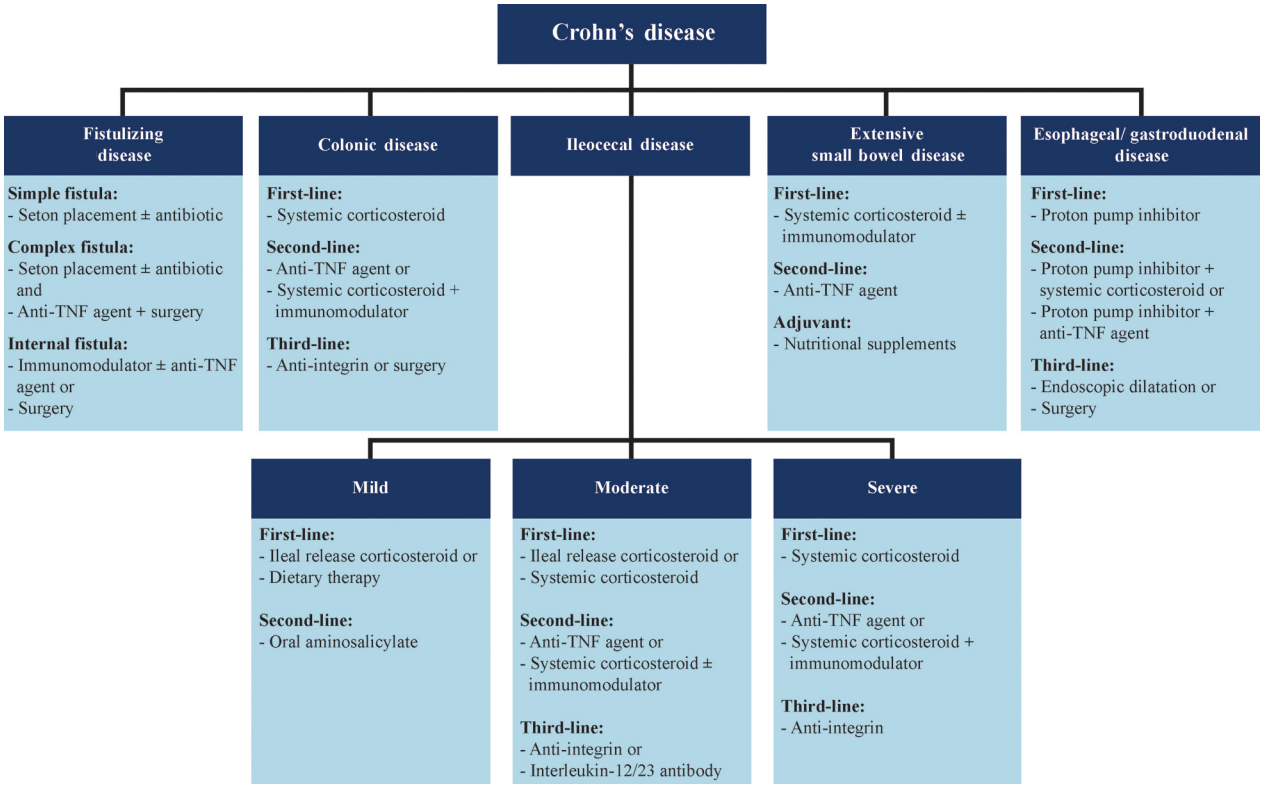

Figure 5 Treatment algorithm for the remission of Crohn's disease.

Severe disease

Systemic corticosteroid (prednisolone or hydrocortisone) is the recommended first-line therapy in severe disease. Alternatively, anti-TNF agents (infliximab) or restarting systemic corticosteroids in combination with immunomodulators (azathioprine) may be used in patients who do not respond to monotherapy with systemic corticosteroids (Gomollón et al., 2016; Lichtenstein et al., 2018). Combination therapy comprising anti-TNF agents and immunomodulators has greater efficacy than either agents alone. Patients with poor prognosis may benefit from early initiation of infliximab and immunomodulator combination therapy (Feagan et al., 2008). Vedolizumab should be used in patients refractory to corticosteroids and/or anti-TNF agents (Gomollón et al., 2016). Whereas, cyclosporine or tacrolimus is ineffective and should not be used (Lichtenstein et al., 2018).

Fistulizing/Perianal Disease

Around one-third of the patients present with fistula predominantly in the perianal region. Treatment of fistulizing disease requires collaborative input from medical and surgical experts. Patients with asymptomatic simple fistula do not require treatment. Whereas, symptomatic simple fistula is initially drained by seton placement followed by treatment with metronidazole or ciprofloxacin (Lichtenstein et al., 2018). Complex fistulizing disease is treated with a combination of surgery and anti-TNF agent (infliximab); however, prior drainage of abscess by seton placement and treatment of infection are needed. Internal fistula (rectovaginal, enterovesical or enteroenteric) is treated with an immunomodulator (azathioprine) either alone or in combination with anti-TNF agent (infliximab). Typically, pharmacological therapy is given prior to surgery in order to improve the patient's condition to enable surgical intervention (Lichtenstein et al., 2018).

Colonic Disease

Systemic corticosteroid (prednisolone) is the recommended first-line therapy for colonic disease. Anti-TNF agents (infliximab) are used in patients refractory to prednisolone. Alternatively, combination therapy comprising a systemic corticosteroid (prednisolone) and an immunomodulator (azathioprine or 6-MP) may be used. Vedolizumab (anti-integrin) or surgery should be considered in patients who do not respond to anti-TNF agents (Gomollón et al., 2016).

Extensive Small Bowel Disease

Extensive small bowel CD is associated with increased inflammation and malabsorption, which often leads to nutritional deficiencies. Systemic corticosteroid is the recommended first-line therapy. Combination therapy with a systemic corticosteroid and an immunomodulator (for steroid-sparing effect) may be considered. Anti-TNF agents should be used in patients refractory to

corticosteroids (Gomollón et al., 2016). Whereas, nutritional supplements are recommended as an adjunctive therapy (Wall et al., 2013).

Esophageal and Gastroduodenal Disease

Mild esophageal and/or gastroduodenal disease should be treated with proton pump inhibitors. A combination of proton pump inhibitor with either systemic corticosteroid or anti-TNF agent is recommended for severe disease. Endoscopic dilatation or surgery may be considered for the treatment of symptomatic strictures (Gomollón et al., 2016).

Maintenance of Remission

The currently approved drugs for CD merely provide symptomatic relief. Once remission has been achieved, maintenance therapy is required in patients who are at risk of recurrence (Gomollón et al., 2016; Lichtenstein et al., 2018). In general, thiopurines (azathioprine, 6-MP), methotrexate, anti-TNF agents (infliximab), and anti-integrins (vedolizumab), either alone or in combination are effective and recommended for the maintenance of remission (Gomollón et al., 2016; Lichtenstein et al., 2018).

For corticosteroid-induced remission, azathioprine, 6-MP, or methotrexate is the recommended first-line agent (Gomollón et al., 2016; Lichtenstein et al., 2018; Terdiman et al., 2013). Dose escalation may be considered in the case of relapse (Gomollón et al., 2016). Alternatively, an anti-TNF agent (infliximab) either alone or in combination with azathioprine/6-MP should be used (Gomollón et al., 2016; Lichtenstein et al., 2018).

For biologics-induced remission, maintenance therapy with the same agent that was used for the induction of remission is recommended (Gomollón et al., 2016). Biological agents including anti-TNF agents (infliximab), anti-integrins (vedolizumab), and interleukin-12/23 antibodies (ustekinumab) are effective options for use as maintenance therapy (Lichtenstein et al., 2018; Terdiman et al., 2013). Furthermore, if remission has been achieved with the combination of anti-TNF agent (infliximab) and immunomodulator (azathioprine), the same combination should be used as maintenance therapy (Gomollón et al., 2016).

In extensive disease, azathioprine or 6-MP is recommended for maintenance of remission. Alternatively, methotrexate may be considered. Anti-TNF agents (infliximab) should be used in patients with aggressive disease and/or poor prognosis (Gomollón et al., 2016).

Postsurgery Maintenance

Postsurgery recurrence significantly increases with the presence of a number of risk factors such as cigarette smoking, associated complications (abscess or fistula), aggressive phenotype, and multiple prior surgeries. Maintenance therapy is recommended in patients with moderate/severe disease or those presented with risk factor(s) (Lichtenstein et al., 2018).

In low-risk patients (moderate/severe disease with no risk factor), azathioprine or 6-MP is recommended as initial maintenance therapy (Doherty et al., 2009; Lichtenstein et al., 2018). Alternatively, mesalamine may be considered in the case of intolerance to azathioprine/6-MP (Ford et al., 2011). Anti-TNF agents (infliximab) should be used in patients refractory to azathioprine/6-MP (Lichtenstein et al., 2018; Sorrentino et al., 2012).

In high-risk patients (with one or more risk factors), an anti-TNF agent (infliximab) is recommended as first-line therapy. It should be initiated within four weeks after surgery (Lichtenstein et al., 2018; Singh et al., 2015). Alternatively, combination therapy with an anti-TNF agent (infliximab) and azathioprine/6-MP may be used that has greater efficacy as compared with either agent alone (Colombel et al., 2010; Renna et al., 2014).

Therapy for Refractory Disease

Several factors such as response to previous therapies, time to relapse, and patient's preferences (affordability, convenience, and adherence) need to be considered prior to selection of therapy for the management of refractory disease. Azathioprine is recommended as initial therapy in patients with an early relapse. Adherence must be checked in the case of poor response to azathioprine. Dose escalation may improve response to azathioprine in patients with better adherence. Infliximab may be used as an alternate option; however, it is preferred in patients with either a moderate/severe disease or those refractory to corticosteroids (Gomollón et al., 2016). Vedolizumab is recommended in patients who fail to respond to azathioprine and infliximab (Sandborn et al., 2013a). Surgery may be considered in patients with localized disease. Whereas, nutritional supplements may be used as an adjuvant therapy in malnourished patients (Gomollón et al., 2016).

Role of Pharmacist

The pharmacists' role in the management of IBD mainly focuses on efforts to rationalize pharmacotherapy, educate patients, improve treatment adherence, minimize cost, and accomplish therapeutic goals.

A study reported inadequate baseline knowledge about disease/medications and poor treatment adherence among patients with IBD. A significant improvement was reported in the disease-related knowledge of patients as well as in their medication adherence following the intervention of clinical pharmacists (Ashok et al., 2017). Another study suggested that medication adherence can be

improved and further sustained through a personalized counseling session led by a pharmacist (Tiao et al., 2017). Pharmacist as a member of the GI team monitors the efficacy and safety of self-injectable biological preparations, provides education to patients regarding their proper use and administration, and optimizes adherence to such preparations (Bhat et al., 2015). A pharmacist-led methotrexate self-injection training program can ensure appropriate and safe use of methotrexate for patients with CD (Clark et al., 2006). A study that assessed the impact of a pharmacist involvement on the prophylaxis of venous thromboembolism (VTE) reported a significant improvement in the rates of VTE prophylaxis (Ra et al., 2013). The availability of various drugs that are costly but used in the management of IBD requires the involvement of pharmacists in both financial and clinical management of patients who are receiving such drugs (Mullican and Francart, 2016). Pharmacist-led evaluation of medication therapy can effectively identify the drug-related problems (DRPs) such as dosage errors, drug without indication, and drug–drug interactions (Cerveny et al., 2007; Chellangi et al., 2015).

Pharmacists' Patient Care Process

A team-based patient-centered care is vital for achieving the desired therapy outcomes for patients in a cost-effective manner. Pharmacists' Patient Care Process (PPCP) is a comprehensive approach as part of pharmacists' collaborative work with other healthcare professionals in the delivery of optimized patient care. The main components of PPCP include collect, assess, plan, implement, and follow-up (monitor/evaluate) (Gonyeau et al., 2018; JCPP, 2014). In PPCP, pharmacists' specific activities for patients with IBD are described in **Fig. 6**.

Patient Education

Inflammatory bowel disease is a chronic medical condition that requires lifelong treatment. Therefore, patient education is an essential component of therapeutic management in order to achieve the desired outcomes. Patient education improves shared decision making, medication use, disease knowledge, and adherence. Education about disease, its therapy, and associated complications should be provided to every patient. The need for continued therapy despite remission of symptoms must be stressed to patients (Lichtenstein et al., 2018). Patients must be informed about the importance and need for preventive therapy in addition to taking adequate dietary supplements (Farraye et al., 2017). The significance of various dietary supplements such as low-residue, elemental, semi-elemental, and defined diets must be covered in patient education (Abegunde et al., 2016; Farraye et al., 2017;

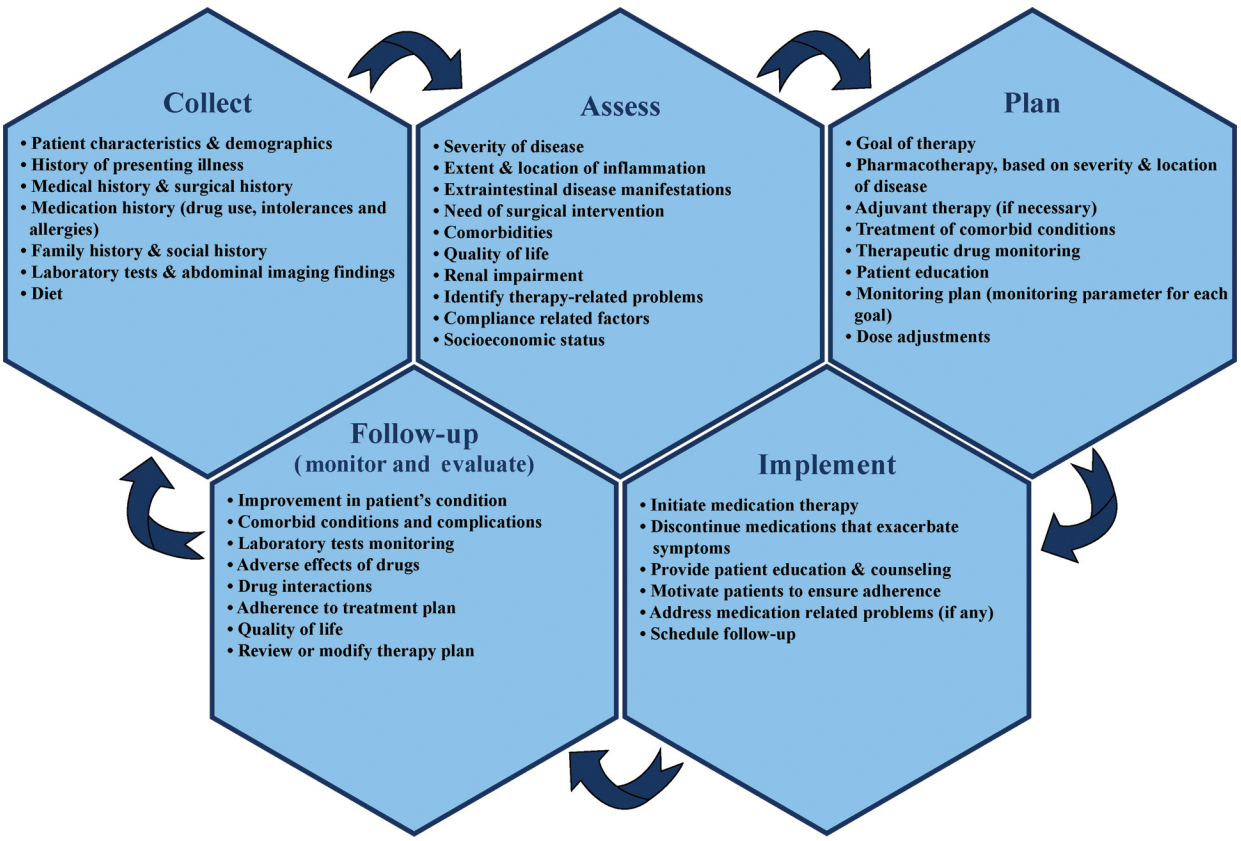

Figure 6 Pharmacists' patient care process for inflammatory bowel disease.

Lichtenstein et al., 2018). Furthermore, information about the safety of drugs in pregnancy or breastfeeding and their effects on fertility should be provided to pregnant patients or those who wish to conceive (Beaulieu and Kane, 2011; Sands et al., 2015). Regular exercise and abstinence from smoking and alcohol should be encouraged. Patients should be advised to seek medical attention if they experience worsening of symptoms such as signs of weight loss, dehydration, fever, abdominal pain, and bloody stools. Moreover, patients must be advised to undergo regular laboratory and other diagnostic tests for the timely identification and rectification of metabolic, hematologic, or other abnormalities.

Treatment Adherence

Treatment adherence is a challenging issue in patients with IBD. Nonadherence to therapy may result in aggravated disease activity, poor response to therapy, increased hospitalization and cost of treatment, and poor patients' quality of life (Herman and Kane, 2015; Lenti and Selinger, 2017; Tae et al., 2016). An estimated one-third of patients with IBD show nonadherence to prescribed therapy (Coenen et al., 2016; Tae et al., 2016). A pooled analysis reported nonadherence to anti-TNF therapy in 17% of patients with IBD (Lopez et al., 2013). Whereas, another study reported nonintentional and intentional nonadherence in around 42% and 57% of patients, respectively (Campos et al., 2016).

Nonadherence to drug therapy is a multifaceted issue that cannot be addressed by focusing on a single aspect only (Lenti and Selinger, 2017; Lopez et al., 2013). Some common predictors of nonadherence include smoking, anxiety or depression, use of syringes, forgetfulness, family and social insecurities, limited knowledge about medicines, and influence of drugs on daily activities (Coenen et al., 2016; Lopez et al., 2013; Spekhorst et al., 2016; Tae et al., 2016). The selection of an appropriate interventional approach should be based on addressing the patient-specific barriers to medicine adherence (Lenti and Selinger, 2017; Lopez et al., 2013). Studies suggest that patient education, simplification of therapeutic regimen, use of reminder systems, and organizational strategies (e.g., pill boxes) are useful for patients with accidental nonadherence. Whereas, addressing motivational issues, teaching skills for problem solving, and addressing problematic patterns of family functioning are beneficial for patients with intentional nonadherence (Chan et al., 2017; Greenley et al., 2013; Herman and Kane, 2015).

Self-Management

Patient's self-management of the disease is another important area for pharmacists to utilize their knowledge and skills. Patients with IBD often experience difficulty in managing various aspects of their disease. Pharmacists can help guide patients and their attendants about various self-management strategies including proper administration of therapy, nutritional supplementation, and management of stress and social relations (Bhat et al., 2015; Tran and Mulligan, 2018; Wong et al., 2011).

Monitoring Therapy Outcomes

The effectiveness of therapy, disease progression, and occurrence of complications should be vigilantly monitored in patients with IBD. Patient reported complaints, patient's history, physical examination, diagnostic tests, and patients' quality of life are all effective tools for the assessment of therapeutic outcomes (El-Matary, 2014). Diagnostic tests including serum transferrin, serum albumin, and markers of inflammation such as ESR and CRP can be used to monitor disease activity. Patients should be monitored for fluid or electrolyte imbalances because of diarrhea. Patients often develop microcytic anemia as a result of malabsorption or chronic blood loss; therefore, proper assessment is recommended. Patients' quality of life can be assessed with the help of an IBD questionnaire that can be used in order to evaluate bowel function, emotional status, systemic symptoms, and social function (Chen et al., 2017).

Therapeutic Drug Monitoring

Several guidelines recommend therapeutic drug monitoring (TDM) of selected therapies in order to ensure maximal efficacy with minimal adverse effects and treatment failure. TDM can also assess patients' adherence or resistance to therapy (Guidi et al., 2018; Hoseyni et al., 2018; Sheasgreen and Nguyen, 2017). In IBD, TDM is typically performed for biological therapies including anti-TNF agents and thiopurines because of loss of efficacy overtime (Hoseyni et al., 2018; Mitrev and Leong, 2017; Restellini et al., 2018; van Hoeve et al., 2018).

Adverse Drug Effects

Adverse drug effects (ADEs) associated with pharmacotherapy of IBD may result in increased morbidity, premature discontinuation of therapy, nonadherence, and poor therapy outcome (Godat et al., 2018; McLean and Cross, 2014). Particular attention should be given to frequent or serious ADEs (**Table 2**).

Aminosalicylates are well-tolerated by most of the patients but they may cause minor GI-related ADEs, arthralgia, anemia, hepatitis, or bone marrow suppression. Among aminosalicylates, sulfasalazine has a higher incidence of ADEs because of systemic absorption of its sulfapyridine moiety. The adverse effects of aminosalicylates can be managed by initiating therapy with a lower dose followed by gradual dose escalation to achieve the desired response (Troncone and Monteleone, 2017).

Table 2 Adverse drug effects associated with pharmacotherapy of inflammatory bowel disease

Drugs	*Dermatological*	*Gastrointestinal*	*Cardiovascular*	*Hematological*	*Immunological*	*Neurological*	*Miscellaneous*
Sulfasalazine	Pruritus, rash, urticaria, *SJS, TEN, skin discoloration, alopecia*	Abdominal pain, vomiting, stomatitis, abnormal LFTs, *fulminant hepatic failure, hepatotoxicity*	Cyanosis, *myocarditis, vasculitis*	Hemolytic anemia, heinz body anemia, leukopenia, *agranulocytosis, aplastic anemia*	Immunoglobulin suppression, *hypersensitivity, SLE*	Dizziness, headache, insomnia, *depression*	**Respiratory:** Cough, *pulmonary fibrosis, pneumonia, dyspnea,* **Others:** Fever, s*epsis*
Mesalamine	Rash, alopecia, urticaria, pruritus, acne, *increased sweating, SJS, facial edema*	Abdominal pain, vomiting, flatulence, abdominal distension, gastroenteritis, GI hemorrhage, hepatotoxicity, e*xacerbation of UC, pancreatitis*	Hypertension, vasodilation, *myocarditis, pericarditis, tachycardia, hypotension,*	*Agranulocytosis, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia*	*Hypersensitivity*	Asthenia, headache	**Respiratory:** Nasopharyngitis, rhinitis **Genitourinary:** *Renal impairment, oligospermia, UTI* **Others:** Arthralgia, *infectious disease*
Balsalazide	Rash, *Erythema nodosum, facial edema*	Abdominal pain, diarrhea, vomiting, flatulence, dyspepsia, xerostomia, stomatitis, exacerbation of UC, *pancreatitis, hepatotoxicity*	*Hypertension, tachycardia, myocarditis, vasculitis*	Anemia	Infectious diseases	Headache, insomnia, *dizziness, depression*	**Respiratory:** Nasopharyngitis, rhinitis, influenza, cough, *pneumonia, pleural effusion* **Genitourinary:** Renal impairment, dysmenorrhea, interstitial nephritis, UTI **Others:** Fever, arthralgia
Budesonide	Acne, rash, eczema, pustular rash, pruritus	Diarrhea, nausea, abdominal pain, flatulence, *pancreatitis, hemorrhoids*	Fluid retention, palpitations, *hypertension, syncope*	Leukocytosis, *anemia*	Oral candidiasis, *anaphylaxis, immunosuppression, angioedema*	Headache, dizziness, insomnia, *smell disturbances*	**Respiratory:** RTIs, sinusitis, *pneumonia* Genitourinary: UTI **Others:** Weight gain, conjunctivitis, *glaucoma, Cushing's syndrome, bone fracture*
Prednisolone	Acne, superinfections, *Kaposi's sarcoma, impaired wound healing*	Superinfections, ulcerative esophagitis, abdominal pain, GI *perforation, pancreatitis*	Fluid retention, hypertension, *CHF, Bradycardia, arrhythmias, hypertrophy, cardiac arrest*	*Leukocytosis*	Opportunistic infections, activation of latent tuberculosis	Headache, psychotic disorder, *seizures*	**Respiratory:** Pulmonary tuberculosis, *hiccups* **Others:** Muscle weakness, osteoporosis, glaucoma, hyperglycemia, *diabetic ketoacidosis*
Hydrocortisone	*Acne, allergic dermatitis, erythema, impaired wound healing, increased sweating, rash*	*Abdominal distention, pancreatitis, peptic ulcer, GI perforation and hemorrhage, elevated LFTs*	*Arrhythmias, CHF, syncope, thromboembolism, thrombophlebitis, vasculitis*	–	Impaired resistance to infections, *Anaphylactoid reaction, anaphylaxis, angioedema*	Psychotic disorder, *depression, mood swings*	**Respiratory:** *Pulmonary tuberculosis* **Others:** Osteoporosis, *Cushing's syndrome, hyperglycemia, cataract, glaucoma*

Azathioprine	*Skin cancer, alopecia*	Nausea, vomiting, *diarrhea, pancreatitis, hepatotoxicity*	*Pericarditis*	Bone marrow suppression, *anemia, thrombocytopenia, pancytopenia*	*Hypersensitivity, malignant lymphoma, T-cell lymphoma*	*Progressive multifocal leukoencephalopathy*	**Respiratory:** *Pulmonary adenocarcinoma* **Others:** *Infectious disease, Neoplastic disease*
6-Mercaptopurine	Rash, *hyperpigmentation, alopecia*	Diarrhea, appetite suppression, vomiting, intestinal ulceration, *hepatic encephalopathy, hepatotoxicity pancreatitis*	–	*Myelosuppression*	*Lymphoproliferative disorder, T-cell lymphoma*	–	**Others:** Fever, hyperuricemia
Methotrexate	Alopecia, photosensitivity, rash, itching, e*rythema, SJS, TEN*	Abdominal pain, diarrhea, stomatitis vomiting, abnormal LFTs, *liver cirrhosis, hepatitis, pancreatitis*	*Thromboembolic disorder, vasculitis*	Thrombocytopenia, leukocytopenia, a*granulocytosis, aplastic anemia, pancytopenia*	Disseminated herpes zoster, *anaphylactoid reaction, malignant lymphoma, opportunistic infection*	Headache, drowsiness, e*ncephalopathy, leukoencephalopathy, seizures, confusion*	**Respiratory:** Bronchitis, nasopharyngitis, *pneumonia* **Genitourinary:** Renal failure, dysuria, hematuria **Others:** Fever, impaired wound healing
Cyclosporine	Hirsutism, acne, brittle fingernails, alopecia, skin ulceration, increased sweating	Gingival hyperplasia, hyperbilirubinemia, *hepatotoxicity*	Hypertension, flushing, arrhythmia cardiac failure, peripheral ischemia	Leukopenia, *thrombocytopenia, anemia*	Hypersensitivity, septicemia, fungal infections, wound and skin infections, viral infections	Headache, neuropathy, depression, insomnia, *progressive multifocal leukoencephalopathy, seizure*	**Respiratory:** Pneumonia, bronchitis, cough, dyspnea, pharyngitis **Genitourinary:** UTI, frequent micturition *nephrotoxicity* **Others:** Muscle cramps, conjunctivitis, abnormal vision, cataract, hyperglycemia, hyperuricemia, *hyperkalemia, hypomagnesemia*
Infliximab	Rash, e*rythema multiforms, SJS, TEN*	Abdominal pain, nausea, *bowel obstruction, hepatotoxicity*	*Acute coronary syndrome, bradyarrhythmia, heart failure, hypertension, myocardial Infarction, systemic vasculitis*	*Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia*	*Anaphylaxis, infusion reactions, malignant lymphoma, sarcoidosis*	Headache, *cerebrovascular accident*	**Respiratory:** Cough, pharyngitis, sinusitis, upper respiratory infection, *pulmonary edema, tuberculosis* **Genitourinary:** *Cervical cancer* **Others:** Fatigue, *cancer, infectious disease, mycosis*
Vedolizumab	Rash, pruritus	Nausea, *hepatitis, elevated bilirubin, abnormal LFTs*	–	–	*Anaphylaxis, infusion reaction*	Headache, *progressive multifocal leukoencephalopathy*	**Respiratory:** Nasopharyngitis, upper RTI, *tuberculosis* **Others:** Fatigue, fever, *cancer, infectious disease, sepsis*
Ustekinumab	Erythema, pruritus, *non-melanoma skin cancer*	Vomiting, diarrhea	–	–	*Anaphylaxis, angioedema*	Headache, *posterior reversible encephalopathy syndrome*	**Genitourinary:** Mycosis, UTI **Respiratory:** Upper RTI, nasopharyngitis, bronchitis, *pneumonia* **Others:** Fatigue, infectious diseases, *cancer*

(*Continued*)

Table 2 Adverse drug effects associated with pharmacotherapy of inflammatory bowel disease (*cont.*)

Drugs	*Dermatological*	*Gastrointestinal*	*Cardiovascular*	*Hematological*	*Immunological*	*Neurological*	*Miscellaneous*
Metronidazole	Pruritus, *SJS, TEN*	Abdominal discomfort, metallic taste, diarrhea, nausea, *hepatotoxicity*	*Flat T-wave, flushing, QT interval prolongation*	*Leukopenia, neutropenia, thrombocytopenia, pancytopenia*	Jarisch-Herxheimer reaction	Dizziness, headache, *aseptic meningitis, encephalopathy, peripheral neuropathy, seizures*	**Respiratory:** Upper RTIs **Genitourinary:** Vaginal candidiasis, vaginal discharge, vaginitis, hemolytic uremic syndrome **Others:** Optic nerve disorder
Ciprofloxacin	Rash, *photosensitivity, SJS, TEN*	Diarrhea, vomiting, *CDD, hepatotoxicity, GI hemorrhage, pancreatitis*	*Aortic aneurysm, cardiorespiratory arrest, prolonged QT interval, myocardial infarction, Torsades de pointes*	*Agranulocytosis, aplastic anemia, bone marrow depression, hemolytic anemia, thrombocytopenia*	*Hypersensitivity*	Headache, irritability, *memory impairment, psychotic disorder, Guillain-Barré syndrome, paranoid disorder*	**Respiratory:** nasopharyngitis **Genitourinary:** Hemorrhagic cystitis, acute renal failure **Others:** Tendons rupture, myasthenia gravis, hypoglycemia

CDD, *Clostridium difficile* diarrhea; CHF, congestive heart failure; GI, gastrointestinal; LFT, liver function test; RTI, respiratory tract infection; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; TEN, toxic epidermal necrolysis; UC, ulcerative colitis; UTI, urinary tract infection.

Note: Serious adverse effects are presented in italics.

Sources: ASHP (2018), Lexicomp (2018), and Micromedex Drugdex (2018).

Short-term use of corticosteroids is well-tolerated. However, their prolonged use is associated with a number of serious ADEs such as osteoporosis, impaired immunity, peptic ulcer, and dysglycemia. Patients receiving long-term corticosteroids therapy should be carefully monitored. Moreover, abrupt discontinuation of corticosteroids is associated with adrenal insufficiency and should therefore be gradually discontinued (Lichtenstein et al., 2018).

Immunomodulators may cause bone marrow depression, hypersensitivity reactions, and secondary infections. Predisposition to development of ADEs may be related to polymorphisms of the enzyme thiopurine methyltransferase, which is partially responsible for activation and metabolism of thiopurines. Anti-TNF agents may cause hypersensitivity reactions, cardiovascular problems, bone marrow suppression, and secondary infections (Farraye et al., 2017).

Drug–Drug Interactions

Patients with IBD often receive multiple drugs simultaneously. Most of these drugs are used for an extended period of time. Moreover, additional therapies are required for the treatment of a variety of comorbid conditions. Therefore, drug–drug interactions are more likely to occur in patients with IBD that may lead to toxicity or impaired therapeutic response (Irving et al., 2008). Patient medication therapy should be reviewed for all possible drug interactions in order to manage them accordingly. Important drug–drug interactions related to pharmacotherapy of IBD, and their adverse outcomes and management are presented in **Table 3**.

Table 3 Drug–drug interactions in inflammatory bowel disease

Interacting drugs	*Adverse outcomes*	*Management/monitoring guidelines*
Mesalamine		
Celecoxib, diclofenac, indomethacin, ibuprofen, naproxen	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Azathioprine, 6-mercaptopurine, thioguanine	Bone marrow suppression	Reduce dose in combination; monitor CBC
Insulin	Hypoglycemia	Monitor glucose levels; adjust insulin dose
Aluminum carbonate/hydroxide/phosphate, magnesium carbonate/hydroxide/trisilicate	Reduced mesalamine therapeutic efficacy	Consider alternate therapy
Sulfasalazine		
Celecoxib, diclofenac, etoricoxib, indomethacin, ibuprofen, naproxen, piroxicam, warfarin	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Azathioprine, 6-mercaptopurine, thioguanine	Bone marrow suppression	Reduce dose in combination; monitor CBC
Methotrexate	Hepatotoxicity	Monitor LFTs; discontinue combination
Insulin	Hypoglycemia	Monitor glucose levels; adjust insulin dose
Cyclosporine, digoxin, warfarin	Reduced interacting drug's efficacy	Increase interacting drug dose when use in combination and monitor its level; in case of warfarin monitor for thrombosis, PT, APTT, and INR
Prednisolone		
Vaccines	Vaccine-induced infection	Avoid concomitant administration, can be used with an interval of two to three months
Amphotericin, hydrochlorothiazide	Electrolyte abnormalities	Monitor electrolytes; consider alternate therapy
Celecoxib, diclofenac, etoricoxib, ibuprofen, indomethacin, ketorolac, naproxen, piroxicam, warfarin	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin	Tendon rupture	Discontinue combination
Ritonavir	Cushing syndrome	Monitor signs of Cushing syndrome
Testosterone	Edema	Monitor signs/symptoms of edema in patients more at risk
Bupropion	Seizures	Use low dose of bupropion
Atracurium, warfarin	Reduced interacting drug's efficacy	Avoid concomitant administration; adjust dose
Phenobarbital, phenytoin, rifampin	Reduced prednisolone efficacy	Adjust dose of corticosteroids
Cyclosporine	Interacting drug's toxicity	Avoid or use with caution; adjust dose if necessary
Contraceptives, fluconazole, ketoconazole	Prednisolone toxicity	Use with caution and decrease dose of corticosteroids
Budesonide		
Celecoxib, diclofenac, indomethacin, ketorolac, mefenamic acid, naproxen, piroxicam	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin	Tendon rupture	Discontinue combination
Ritonavir	Cushing syndrome	Monitor signs of cushing syndrome
Testosterone	Edema	Monitor signs/symptoms of edema in patients more at risk
Bupropion	Seizures	Use low dose of bupropion

(*Continued*)

Table 3 Drug–drug interactions in inflammatory bowel disease (*cont.*)

Interacting drugs	*Adverse outcomes*	*Management/monitoring guidelines*
Clarithromycin, erythromycin, fluconazole, ketoconazole	Budesonide toxicity	Use with caution and decrease dose of corticosteroids
Azathioprine		
Vaccines	Vaccine-induced infection	Consider administration interval of three months
Balsalazide, lisinopril, olsalazine, ramipril, sulfamethoxazole/trimethoprim	Bone marrow suppression	Reduce dose in combination; monitor CBC
Doxorubicin, methotrexate	Hepatotoxicity	Monitor LFTs; discontinue combination
Warfarin	Reduced warfarin efficacy	Avoid concomitant administration; monitor PT, APTT, INR
Allopurinol, febuxostat, sulfamethoxazole/trimethoprim	Azathioprine toxicity	Avoid combination or reduce dose; monitor signs/symptoms of toxicity
Cyclosporine		
Live vaccines	Vaccine-induced infection	Consider administration interval of three months
Atorvastatin, lovastatin, rosuvastatin, simvastatin	Myopathy or rhabdomyolysis	Reduce statins dose; discontinue concomitant administration
Amikacin, aspirin, celecoxib, diclofenac, indomethacin, ketorolac, lisinopril, mefenamic acid, naproxen, piroxicam, ramipril, streptomycin	Nephrotoxicity or electrolyte abnormalities	Monitor RFTs and electrolytes; consider alternative or reduce dose
Furosemide	Gouty arthritis	Monitor signs/symptoms of gouty arthritis; discontinue concomitant administration
Warfarin	Reduced warfarin efficacy	Avoid concomitant administration; monitor PT, APTT, INR
Carbamazepine, cyclophosphamide, famotidine, infliximab, phenobarbital, phenytoin, pyrazinamide, quinine, rifampin, sulfasalazine, warfarin	Reduced cyclosporine efficacy	Avoid concomitant administration; adjust dose if necessary
Alprazolam, colchicine, doxorubicin, methotrexate, morphine, valsartan	Interacting drug's toxicity	Avoid combination or reduce dose; monitor signs/symptoms of toxicity
Amlodipine, aspirin, ceftriaxone, celecoxib, chloroquine, cimetidine, clarithromycin, colchicine, diclofenac, diltiazem, fluconazole, glyburide, indomethacin, ketoconazole, ketorolac, mefenamic acid, metoclopramide, metronidazole, naproxen, piroxicam, rabeprazole, ritonavir, verapamil	Cyclosporine toxicity	Avoid combination or reduce dose; monitor signs/symptoms of toxicity
Infliximab		
Vaccines	Vaccine-induced infection	Avoid concomitant administration, can be administer at an interval of 3 months
Cyclosporine, fentanyl, phenytoin, paclitaxel, theophylline, thioridazine, warfarin	Reduced interacting drug's efficacy	Avoid concomitant administration; monitor drug's efficacy
Adalimumab, anakinra, rituximab, vedolizumab	Increased immunosuppression and risk of infection	Avoid concomitant administration
Vedolizumab		
Biologic agents (vaccines, antibodies, interleukins)	Increased immunosuppression and risk of infection	Avoid concomitant administration
Metronidazole		
QT interval prolonging drugs (amiodarone, cisapride, hydroxychloroquine, saquinavir, tacrolimus, thioridazine)	QT interval prolongation	Discontinue combination; monitor ECG and serum electrolytes
Warfarin	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Cholestyramine, phenytoin	Reduced metronidazole efficacy; phenytoin toxicity	Avoid concomitant administration, can be used with an interval
Cholera vaccine	Reduced immune response to vaccine	Avoid concomitant administration, can be used with an interval
Carbamazepine, cyclosporine, lithium	Interacting drug's toxicity	Adjust interacting drug dose; monitor signs of toxicity
Disulfiram	Psychotic reactions, confusion	Avoid combination, can be used with an interval of 14 days

(*Continued*)

Table 3 Drug–drug interactions in inflammatory bowel disease (*cont.*)

Interacting drugs	*Adverse outcomes*	*Management/monitoring guidelines*
Ciprofloxacin		
QT interval prolonging drugs (amiodarone, amitriptyline, domperidone, droperidol, fluoxetine, ondansetron, saquinavir, thioridazine)	QT interval prolongation	Discontinue combination; monitor ECG and serum electrolytes
Warfarin	Bleeding	Monitor for bleeding signs, PT, APTT, INR; consider alternate therapy
Betamethasone, budesonide, dexamethasone, hydrocortisone, prednisolone	Tendon rupture	Avoid concomitant administration; consider alternate therapy
Simvastatin	Myopathy or rhabdomyolysis	Reduce statins dose; discontinue combination
Gliclazide, glimepiride, glyburide, insulin, metformin, sitagliptin	Hypoglycemia or hyperglycemia	Monitor glucose levels; adjust dose of antidiabetic agents
Iron, sucralfate	Reduced ciprofloxacin efficacy	Avoid concomitant administration, can be used with an interval
Cholera/ typhoid vaccine	Reduced immune response to vaccine	Avoid concomitant administration, can be used with and interval
Doxorubicin, methotrexate, theophylline, tramadol	Interacting drug's toxicity	Adjust interacting drug dose; monitor signs of toxicity

APTT, Activated prothrombin time; CBC, complete blood count; ECG, electrocardiogram; INR, international normalized ratio; LFTs, liver function tests; PT, prothrombin time; RFTs, renal function tests.
Sources: Lexicomp (2018), Micromedex Drugdex (2018), and Preston (2016).

Conclusions

IBD is an idiopathic, debilitating life-long condition that adversely affects the patients' health-related quality of life. The pathogenesis of IBD is multifactorial and is governed by an interplay of the immune system, intestinal microbiota, and various genetic and environmental factors. Monitoring of maintenance therapy for safety and efficacy is essential to ensure prolonged remission and improved patients' quality of life. Pharmacist involvement can promote treatment adherence, medication safety, and effective therapeutic outcomes.

Glossary

Adjuvant therapy Therapy given in addition to the primary therapy in order to maximize effectiveness.
Colostomy It is a surgical procedure performed for the diversion of fecal stream to excrete feces through the abdominal wall.
Fistula An abnormal passage between two organs or an organ and the exterior of the body.
Fulminant Abrupt and extremely intense onset of symptoms.
Refractory The presence of symptoms despite pharmacological therapy.
Relapse The return of symptoms after its apparent cessation.
Remission The period during which the symptoms of a disease subside.
Seton A surgical grade thread or wire passed through the fistula or subcutaneous tissue for drainage of abscess.
Strictures Abnormal narrowing of the small or large intestine due to inflammation and scarring.
Tenesmus Painful spasm of the rectum or bladder with a failed attempt to urinate or defecate.

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Management of Gastrointestinal Disorders and the Pharmacist's Role: Nausea and Vomiting

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Learning Objectives

At the end of this chapter, the reader will be able to:

- Describe the basic concepts and etiopathogenesis of different types of emesis.
- Discuss available pharmacotherapeutic approaches for specific clinical situations.
- Develop a patient-oriented care plan and monitor the therapeutic outcomes.
- Assess and manage the potential adverse drug effects associated with pharmacotherapy of emesis.
- Discuss the role of pharmacist in the effective management of nausea and vomiting.

Introduction

Nausea can be the precursor for vomiting and is defined as a subjectively unpleasant wavelike sensation in the back of the throat or epigastrium. Nausea may also be associated with other symptoms such as pallor, flushing, tachycardia, sweating, excessive salivation, and feeling either hot or cold. Vomiting can be described as the forceful expulsion of stomach contents through the mouth, which is preceded by relaxation of the esophageal sphincter, contraction of the abdominal muscles, descent of the diaphragm, and temporary suspension of breathing (Babic and Browning, 2014; Pleuvry, 2012; Smith et al., 2012).

Etiology and Pathophysiology

Nausea and vomiting are associated to a variety of conditions such as chemotherapy, pregnancy, gastrointestinal (GI) disorders, allergy, or surge. The main causes for nausea and vomiting are listed in **Table 1**.

The sequential process of emesis comprising nausea, retching (rhythmic spasmodic contractions without expulsion of gastric contents), and vomiting is initiated and coordinated by involvement of the central nervous system, the peripheral nervous system, and the GI system (Babic and Browning, 2014; Bashashati and McCallum, 2014).

Table 1 Causes of nausea and vomiting

Gastrointestinal causes	*Non-gastrointestinal causes*	*Drugs/radiations/toxins*
Inflammatory/infectious/allergic conditions	*Cardiovascular diseases*	*Drugs/radiations*
Hepatitis	Myocardial infarction	Radiotherapy
Appendicitis	Cardiomyopathy	Cancer chemotherapy
Cholecystitis	Angina	Antibiotics
Pancreatitis	*Metabolic diseases*	Anticonvulsants
Peptic ulcer disease	Nephrolithiasis	Cardiac antiarrhythmics
Gastroenteritis	Addison's disease	Digoxin
Inflammatory bowel disease	Diabetic ketoacidosis	Oral hypoglycemics
Food protein-induced enterocolitis syndrome	Hereditary fructose intolerance	Oral contraceptives
Gastrointestinal tract obstruction disorders	Galactosemia	Antidepressants
Mesenteric artery syndrome	Thyroid hormone abnormalities	*Drug withdrawal*
Colonic obstruction	*Neurologic diseases*	Benzodiazepines
Pyloric obstruction	Migraine	Opioids
Small bowel obstruction	Vestibular disorders	*Toxins*
Malignancy	Increased intracranial pressure	Ethanol
Functional gastrointestinal disorders	Meningitis	Cyanide
Irritable bowel syndrome	Hemorrhage	Lead
Gastroparesis	*Psychological disorders*	Iron
Gastrointestinal reflux	Anxiety	Carbon monoxide
Rumination syndrome	Anorexia and bulimia nervosa	Food poisoning
Cyclic vomiting syndrome	*Postoperative vomiting*	
Gastroesophageal reflux disease	*Pregnancy-induced vomiting*	
Hirschsprung disease	Vomiting up to first trimester	
Malrotation	Hyperemesis gravidarum	

Sources: Hasler, W.L., 2018. Nausea, vomiting, and indigestion. In: Jameson, J.L., Fauci, A.S., Kasper, D.L. et al. (Eds.), Harrison's Principles of Internal Medicine. 20th ed. The McGraw-Hill Companies Inc, USA (Hasler, 2018); Herrell, H.E., 2014. Nausea and vomiting of pregnancy. Am. Fam. Physician 89, 965–970 (Herrell, 2014); Hesketh, P.J., 2008. Chemotherapy-induced nausea and vomiting. N. Engl. J. Med. 358, 2482–2494 (Hesketh, 2008); Quigley, E. M., Hasler, W.L., Parkman, H.P., 2001. AGA technical review on nausea and vomiting. Gastroenterology 120, 263–286 (Quigley et al., 2001); Singh, P., Yoon, S.S., Kuo, B., 2016. Nausea: a review of pathophysiology and therapeutics. Therap. Adv. Gastroenterol. 9, 98–112 (Singh et al., 2016); Veiga-Gil, L., Pueyo, J., Lopez-Olaondo, L., 2017. Postoperative nausea and vomiting: physiopathology, risk factors, prophylaxis and treatment. Rev. Esp. Anestesiol. Reanim 64, 223–232 (Veiga-Gil et al., 2017)

The vomiting center (VC) located in the medulla oblongata of the brain, coordinates emesis by receiving afferent signals from sensory organs, and sending efferent signals to effector organs. Neurotransmitter receptors play an important role in the process of emesis regulation and therefore are the main targets of pharmacotherapy (Shinpo et al., 2012). These include serotonin ($5HT_3$), dopamine (D_2), histamine (H_1), neurokinin-1 (NK_1), and cholinergic (muscarinic M_1) receptors. These neurotransmitter receptors are inhibited for the control of nausea and vomiting (Bashashati and McCallum, 2014; Flake et al., 2004; Navari, 2015; Quigley et al., 2001).

A number of afferent signals might be responsible for initiating an emetic response. The chemoreceptor trigger zone (CTZ) present in the brainstem just outside the blood brain barrier, senses toxins, and noxious substances in the blood or cerebrospinal fluid and triggers an emetic response by sending neurotransmitters (serotonin, dopamine, and NK_1) to the VC and the nucleus tractus solitarius (NTS) (Pleuvry, 2012).

The GI system initiates an emetic response when the enterochromaffin cells of the GI mucosa are damaged by exposure to either chemotherapy, radiation, anesthetics, or mechanical irritation. Serotonin is released, which in turn stimulates vagal afferent signals as well as directly acts on the VC and the NTS (Bashashati and McCallum, 2014).

The cerebral cortex and the limbic system stimulate the emetic center in response to emotional states such as anxiety, pain, and conditioned responses (anticipatory nausea and vomiting). The neurotransmitters involved in this pathway are not clearly known (Pleuvry, 2012). Vestibular system disorders (vertigo and motion sickness) stimulate the VC by releasing acetylcholine and histamine (Babic and Browning, 2014; Smith et al., 2012).

Clinical Features

Emesis is caused by many disorders; therefore, its clinical presentation varies. The patient either experiences a simple, self-limiting episode that subsides by itself or suffers persistent debilitating vomiting that necessitates antiemetic therapy. Simple emesis may present as abdominal pain/cramps, pale skin, heartburn, vertigo, tinnitus, headache, and fever (Balaban and Yates, 2017; Koch and Hasler, 2017). Whereas, persistent vomiting may cause dehydration with electrolyte imbalance, malnutrition, weight loss, dental

caries, dental erosions, and aspiration pneumonia, thus significantly affecting patient's quality of life and their ability of self-care. Rarely, persistent vomiting may lead to esophageal tear, which is either partial (Mallory Weiss) or complete (Boerhaave syndrome) (Hasler, 2018; Koch and Hasler, 2017).

Diagnosis

Patients who present with nausea and vomiting are initially assessed for the nature of symptoms (onset, severity and duration), triggering factors, dietary intake, hydration status, current medical conditions, medications used, and surgical status. Furthermore, the underlying etiology must be identified for tailoring therapy.

Taking a full patient history can help identify the underlying cause of emesis. Acute emesis is often associated with drugs, toxins, and infections. Whereas, delayed emesis occurs as a result of chronic diseases such as GI obstruction. Physical examination further strengthens the diagnosis and findings of the patient's history (Keeley, 2015; Singh et al., 2016). Orthostatic hypotension and reduced skin turgor are signs of dehydration. Abdominal tenderness can be an indication of inflammation, whereas presence of fecal blood may indicate GI mucosal injury or tumor (Koch and Hasler, 2017).

Differential diagnosis through selected screening tests might be necessary in some patients particularly in patients with persistent emesis. Laboratory tests will be helpful to identify hypokalemia, azotemia, or metabolic alkalosis that might occur due to loss of gastric content. Endoscopy or computed tomographic (CT) imaging is helpful in identifying gastric and intestinal obstruction (Keeley, 2015; Singh et al., 2016). Abnormal pancreatic and liver biochemistries indicate pancreaticobiliary disease. Central nervous system causes are best evaluated with either head CT imaging or magnetic resonance imaging (MRI). Similarly, for every suspected underlying etiology, its specific differential diagnostic tests should be performed (Koch and Hasler, 2017; Quigley et al., 2001).

Nonpharmacological Management

Various nonpharmacological approaches comprising dietary, physical, and psychological strategies may be used in the management of nausea and vomiting. Dietary modifications such as avoiding or decreasing the consumption of foods or beverages that trigger emesis, eating smaller meals, avoiding spicy or fried foods, and preferably eating bland foods such as BRAT (bananas, rice, apple sauce and toast) help improve the condition (Koch and Hasler, 2017; Stern et al., 2011). Ginger is also effective in the treatment of emesis related to pregnancy, surgery, and motion sickness (Ernst and Pittler, 2000; Saberi et al., 2013; Sheikhi et al., 2015). An example of physical strategy is attaining a stable position that relieves motion sickness. Psychological strategies include relaxation, biofeedback, hypnosis, cognitive distraction, optimism, guided imagery, acupuncture, yoga, and systemic desensitization (Cheong et al., 2013; Kamen et al., 2014; Sheikhi et al., 2015).

Pharmacological Management: General Approaches

Prevention or complete elimination of nausea and vomiting with no or minimal adverse effects is the desired goal of pharmacotherapy. A number of important issues need to be considered that include correction of fluid, electrolyte, or nutritional imbalances; identification and elimination of the underlying cause where possible; and suppression or elimination of the symptoms (Quigley et al., 2001).

A simple episode of nausea and vomiting may be self-limiting. If the condition does not improve and symptoms persist, pharmacotherapy with antiemetics is needed. A single agent or combination therapy (agents from different pharmacological classes of antiemetics) is initiated depending upon the severity and complexity of presenting condition (Flake et al., 2004; Quigley et al., 2001; Singh et al., 2016). Besides the effectiveness of pharmacotherapy, economic impact should also be considered especially in the case of long-term management such as nausea and vomiting induced by chemotherapy, pregnancy, or surgery (Haiderali et al., 2011; Piwko et al., 2013).

Antiemetic Drugs

Antiemetic drugs mainly produce their effect by antagonizing the neurotransmitters that are involved in the regulation of emesis. The main classes of antiemetic drugs include serotonin $5HT_3$ receptor antagonists ($5HT_3$RAs), neurokinin-1 receptor antagonists (NK_1RAs), dopamine D_2 receptor antagonists, and antihistamines/anticholinergics (**Fig. 1**) (Kenward et al., 2015; Pleuvry, 2012; Singh et al., 2016). Selection of an appropriate antiemetic(s) depends on certain factors such as the underlying cause; frequency, duration, and severity of emetic episodes; ability of patient to use certain dosage form; and response to previously used antiemetic medications (Flake et al., 2004; Quigley et al., 2001).

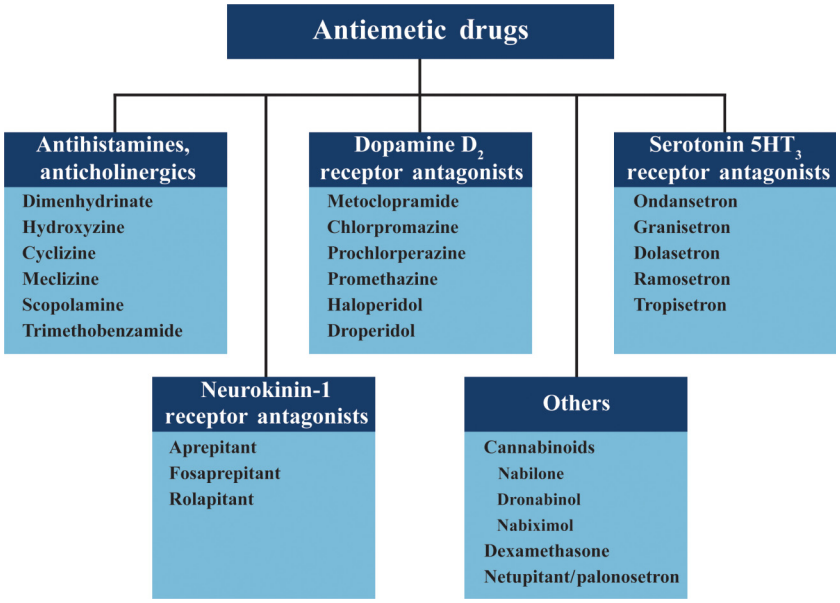

Figure 1 Classes of antiemetic drugs.

Specific Clinical Situations

The following sections describe the management of nausea and vomiting in specific clinical situations such as chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), radiotherapy-induced nausea and vomiting (RINV), nausea and vomiting of pregnancy (NVP), and motion sickness.

Chemotherapy-Induced Nausea and Vomiting

CINV is one of the major causes of nonadherence, increased anxiety and depression, and poor quality of life in cancer patients (Navari, 2015). CINV has been categorized into five different types: acute, delayed, anticipatory, breakthrough, and refractory (**Fig. 2**) (Jordan et al., 2014; Navari and Aapro, 2016).

Even though milestones have been achieved in the management of acute CINV; anticipatory and delayed CINV still remains a major problem to be managed. Of the patients who experience nausea and vomiting during earlier chemotherapy sessions, 30% have reportedly experienced nausea, whereas 20% have experienced vomiting during subsequent chemotherapy sessions (Mustian et al., 2011). CINV can be prevented in up to 70%–80% of the patients with appropriate use of prophylactic antiemetics (Jordan et al., 2014; Tageja and Groninger, 2016).

Chemotherapeutic agents differ in their emetogenic potential. They are classified into four different groups based on their emetogenicity: high, moderate, low, and minimal that possess an incidence risk of emesis in >90%, 30%–90%, 10%–30%, and <10% of patients, respectively (**Fig. 3**) (Grunberg et al., 2005; Navari and Aapro, 2016). Antiemetic regimens are selected on the basis of emetogenicity of chemotherapeutic agents (Jordan et al., 2014).

Acute and Delayed Chemotherapy-Induced Nausea and Vomiting

Pharmacotherapy of acute and delayed CINV is summarized in **Table 2**. CINV should preferably be controlled through prophylaxis. The prophylaxis of acute CINV is initiated prior to the start of chemotherapy and continued up to 24 h, whereas prophylaxis of delayed CINV is continued till fourth day following administration of chemotherapy (Berger et al., 2017; Jordan et al., 2014).

In patients receiving high emetogenic chemotherapy, acute CINV is managed with a combination of a $5HT_3$RA, dexamethasone and aprepitant/fosaprepitant (NK_1RAs) within first 24 h of chemotherapy. For delayed CINV, dexamethasone and aprepitant/fosaprepitant (NK_1RAs) are recommended in combination (**Table 2**) (Jordan et al., 2014; Navari and Aapro, 2016).

Patients undergoing moderately emetogenic chemotherapy are recommended a combination of a $5HT_3$RA (preferably palonosetron) and dexamethasone for acute CINV. Addition of aprepitant to this combination is recommended in selected patients. Whereas for delayed CINV, dexamethasone is the drug of choice. Alternatively, aprepitant can also be used provided that it had been used in prophylaxis of acute CINV (Jordan et al., 2014) (**Table 2**).

Patients receiving low emetogenic chemotherapy can be effectively managed with a single agent such as a low-dose corticosteroid. Antiemetic prophylaxis is usually not required in the case of minimal emetogenic chemotherapy (Jordan et al., 2014).

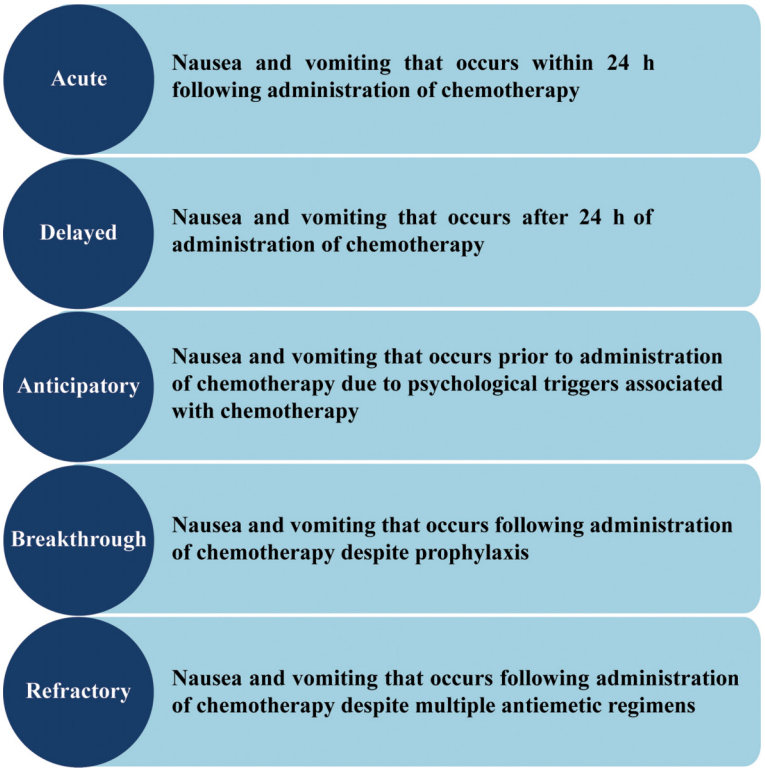

Figure 2 Types of chemotherapy-induced nausea and vomiting.

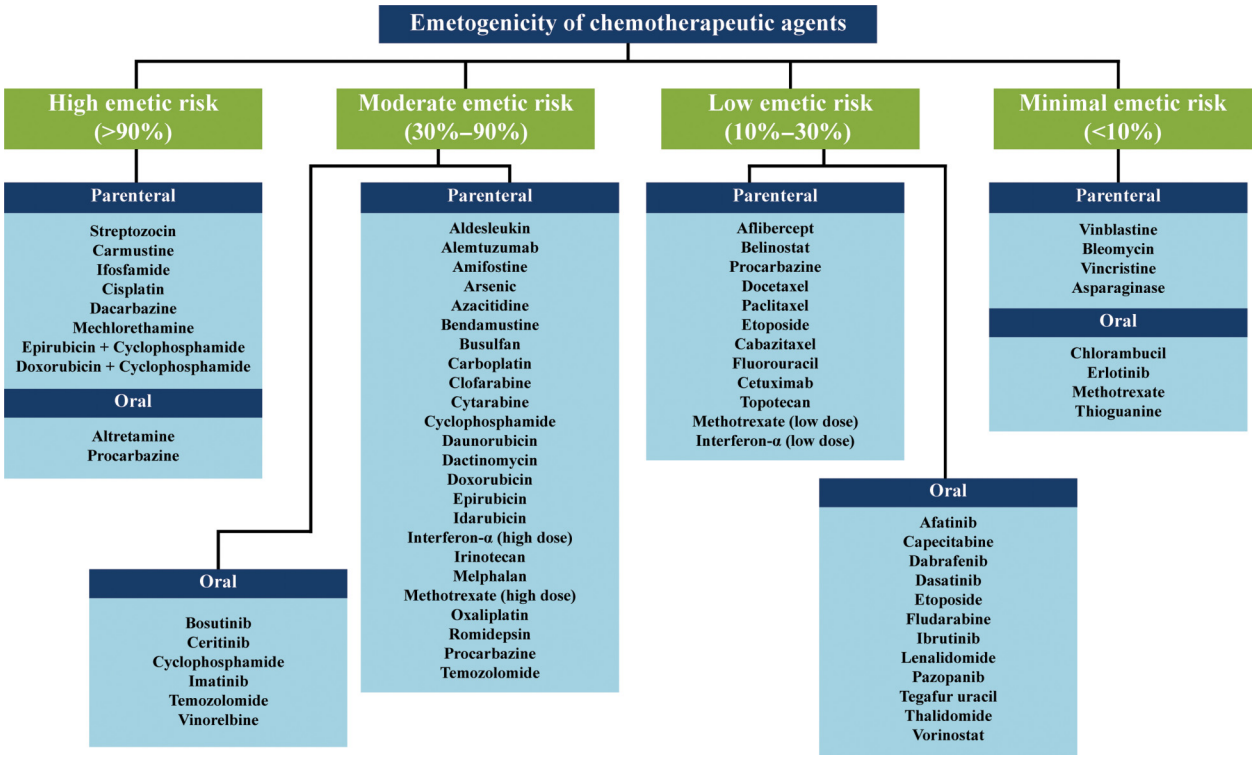

Figure 3 Emetogenicity of chemotherapeutic agents. Note: Incidence risk is mentioned in round brackets.

Table 2 Pharmacotherapy of chemotherapy-induced nausea and vomiting

NCCN recommendations		*ASCO recommendations*		*MASCC/ESMO recommendations*	
Acute phase	*Delayed phase*	*Acute phase*	*Delayed phase*	*Acute phase*	*Delayed phase*
High emetogenic chemotherapeutic agents					
Before chemotherapy: NK_1RA + $5HT_3RA$ + dexamethasone; or olanzapine + palonosetron + dexamethasone; or NK_1RA + $5HT_3RA$ + dexamethasone + olanzapine	Based on day 1 regimen, delayed phase therapy varies accordingly	Before chemotherapy: NK_1RA + $5HT_3RA$ + dexamethasone + olanzapine	Continue olanzapine on days 2–4, add dexamethasone on days 2–4 for high emetic risk	$5HT_3RA$ + NK_1RA + dexamethasone	Dexamethasone; or if aprepitant 125 mg for acute: metoclopramide + dexamethasone; or aprepitant + dexamethasone
Moderate emetogenic chemotherapeutic agents					
Before chemotherapy: $5HT_3RA$ + dexamethasone; or olanzapine + palonosetron + dexamethasone; or NK_1RA + $5HT_3RA$ + dexamethasone	Based on day 1 regimen, delayed phase therapy varies accordingly	Treated with carboplatin area under the curve (AUC) ≥4 mg/mL/min: NK_1RA + $5HT_3RA$ + dexamethasone Other moderate-risk regimens: $5HT_3RA$ + dexamethasone on day 1	Dexamethasone on days 2–3	Carboplatin regimens: $5HT_3RA$ + dexamethasone + NK_1RA Excluding carboplatin-based: $5HT_3RA$ + dexamethasone	Carboplatin regimens: none Excluding carboplatin based: if aprepitant 125 mg used for acute: use aprepitant in delayed
Low emetogenic chemotherapeutic agents					
Start before chemotherapy: dexamethasone; or metoclopramide PO/IV; or prochlorperazine; or oral $5HT_3RA$	–	Acute: $5HT_3RA$ or dexamethasone	–	Dexamethasone or $5HT_3RA$ or dopamine D_2 receptor antagonist	No routine prophylaxis
Minimal emetogenic chemotherapeutic agents					
No routine prophylaxis	–	No routine prophylaxis	–	No routine prophylaxis	–

$5HT_3RA$, serotonin $5HT_3$ receptor antagonist; *ASCO*, American Society of Clinical Oncology; *AUC*, area under the curve; *IV*, intravenous; *MASCC/ESMO*, Multinational Association for Supportive Care in Cancer/European Society for Medical Oncology; *NCCN*, National Comprehensive Cancer Network; *NK_1RA*, neurokinin-1 receptor antagonist; *PO*, per os (by mouth).

Source: Berger, M.J., Ettinger, D.S., Aston, J., et al., 2017. NCCN Guidelines Insights: Antiemesis, Version 2.2017. J. Natl. Compr. Canc. Netw. 15, 883–893 (Berger et al., 2017); Hesketh, P.J., Kris, M.G., Basch, E., et al., 2017. Antiemetics: American society of clinical oncology clinical practice guideline update. J. Clin. Oncol. 35, 3240–3261 (Hesketh et al., 2017); Roila, F., Molassiotis, A., Herrstedt, J., et al., 2016. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann. Oncol. 27, 119–133 (Roila et al., 2016).

Other Types of Chemotherapy-Induced Nausea and Vomiting

For the management of breakthrough and refractory CINV, repeated administration of the same agent that was already used prophylactically is hardly effective (Navari and Aapro, 2016). Other options should be considered such as a dopamine receptor antagonist (e.g., metoclopramide), a benzodiazepine, or a neuroleptic agent (e.g., olanzapine) (Jordan et al., 2014).

Anticipatory nausea and vomiting is usually managed through prophylaxis, which includes nonpharmacological approaches such as behavioral therapy, hypnosis, and acupuncture/acupressure, and pharmacological therapy with benzodiazepines. These prophylactic approaches might lose their efficacy over the course of time. For treatment of anticipatory nausea and vomiting, either oral alprazolam 0.5–1 mg or oral lorazepam 0.5–2 mg are recommended, starting the evening prior to chemotherapy (Navari and Aapro, 2016).

Postoperative Nausea and Vomiting

PONV is experienced by 20%–30% of patients undergoing surgery and generally occurs within 24 h of anesthesia administration (Wiesmann et al., 2015). PONV decreases patient's comfort and satisfaction, and can cause/prolong hospitalization, stress on the surgical closure, hematomas, dehydration, electrolyte imbalances, and aspiration pneumonitis. A number of risk factors related to patient, anesthesia, and surgery predispose patient to PONV (Wiesmann et al., 2015).

All patients undergoing surgery do not experience PONV; therefore, prophylaxis is not a rational approach in every patient. For this purpose, a risk scoring system has been suggested based on four factors: female gender, history of PONV/motion sickness, non-smoker, and use of opioid during surgery (Stoicea et al., 2015). Each of these risk factors increases the incidence risk by around 20% (Wiesmann et al., 2015). This tool is very useful for the identification of high-risk patients in order to apply various antiemetic strategies accordingly (Weilbach et al., 2006).

Management strategies involve reduction of baseline risk and use of antiemetic drugs for the prophylaxis and treatment of PONV. Baseline risk can be minimized using local instead of systemic anesthesia; adequate hydration; intraoperative supplemental oxygen; and using less emetogenic induction agents, anesthetic agents, and analgesics.

Antiemetic drugs used for the management of PONV include $5HT_3$RAs, NK_1RAs, corticosteroids, droperidol, haloperidol, antihistamines, and anticholinergics (Stoicea et al., 2015; Wiesmann et al., 2015). As prophylactic therapy for PONV, various antiemetic drugs are used at specified timings as shown in **Table 3**. A combination therapy, involving drugs from different classes, is recommended for high-risk patients (Wilhelm et al., 2007).

Rescue therapy is recommended for patient experiencing PONV even after receiving prophylactic therapy. In this therapy, an agent should be administered from a pharmacologic class other than that already used for prophylaxis. In cases where no prophylactic therapy was given initially, any of the following may be used: ondansetron (or other $5HT_3$RAs), dexamethasone, droperidol, and promethazine (Gan et al., 2014).

Radiotherapy-Induced Nausea and Vomiting

RINV occurs in around 50%–80% of patients undergoing radiotherapy (Li et al., 2017). The incidence of RINV depends on various factors such as the site of irradiation, the dosing, fractionation, irradiated volume, and radiotherapy techniques. The incidence risk is very high in patients receiving a total body irradiation (~90%) and those receiving radiations to the upper abdominal area (50%–80%). Whereas radiotherapy of other body parts have a decreased incidence risk (Feyer et al., 2015). RINV significantly affects the quality of life (Poon et al., 2016). Nausea seems to impact the patient more directly, whereas vomiting affects those closest to the patient (Yee et al., 2018). Clinical practice guidelines have classified radiotherapy receiving patients into four groups with respect to incidence risk of RINV: at high risk are the patients receiving total-body or -nodal irradiation (TBI/TNI); moderate risk occurs in patients receiving upper body or abdomen and hemibody radiotherapy; low risk exists in patients receiving cranial, craniospinal, head and neck, lower thorax, and pelvic radiotherapy; and patients undergoing extremities and breasts irradiation are at minimal risk (Feyer et al., 2015; Ruhlmann et al., 2017).

Prophylactic therapy is administered to patients who are at high or moderate risk of RINV. For patients at high emetic risk, prophylaxis with a combination of a $5HT_3$RA and dexamethasone is recommended (**Table 4**) (Li et al., 2017). In patients with moderate emetic risk, prophylaxis with a $5HT_3$RA is usually recommended; however, the use of dexamethasone is optional. In patients with low emetic risk, a $5HT_3$RA agent is used either as prophylaxis or as rescue therapy (Li et al., 2017). In patients with minimal emetic risk, no prophylaxis is administered rather a rescue therapy may be opted among dexamethasone, dopamine receptor antagonists, or $5HT_3$RAs. Limited data are available on recommendations of rescue therapy; however, $5HT_3$RAs are considered effective as antiemetic treatment of RINV (Feyer et al., 2015; Ruhlmann et al., 2017).

Nausea and Vomiting of Pregnancy

NVP affects a majority (70%–80%) of pregnant women. The symptoms occur predominantly during the first trimester, but some women may experience symptoms throughout the entire pregnancy (Bustos et al., 2017; Lee and Saha, 2011). The exact etiology of NVP is not known, but it is widely agreed that a variety of factors including physiological, hormonal, psychological, genetic, and cultural components are involved (Furneaux et al., 2001). The severity of symptoms for NVP ranges from mild to moderate nausea and vomiting, but a small percentage of women develop a severe form of NVP called hyperemesis gravidarum (HG). If not treated,

Table 3 Pharmacotherapy of postoperative nausea and vomiting

Class of drugs	*Drug*	*Remarks*	*Adult dose for prophylaxis*	*Pediatric dose (IV) of prophylaxis*	*Timing of prophylaxis dose*	*Treatment or rescue dose*
$5HT_3$RAs	Ondansetron	Gold standard	4 mg IV, 8 mg OD	50–100 mcg/kg up to 4 mg	At the end of surgery	1 mg IV every 8 h
	Palonosetron	Prolonged half-life	0.075 mg IV	–	Immediately before induction	0.075 mg IV single dose
	Granisetron	Might not be equally effective in ultra-metabolizers of CYP2D6 pathway	0.35–3 mg IV	40 μg/kg up to 0.6 mg	At the end of surgery	0.1 mg
NK_1RA	Aprepitant	As effective as ondansetron in achieving complete response	40 mg orally	Not labeled for use in pediatrics	Within 3 h prior to induction	None
Corticosteroid	Dexamethasone	Monitor glucose levels in diabetic patients	4–5 mg IV	150 mcg/kg up to 5 mg	At induction	2–4 mg IV
Butyrophenones (Dopamine D_2 receptor antagonists)	Droperidol	High risk of QTIP/TdP	0.625–1.25 mg IV	10–15 mcg/kg up to 1.25 mg	At the end of surgery	0.625–1.25 mg IV or IM every 4–6 h
	Haloperidol	High risk of QTIP/TdP	0.5–2mg (IM or IV)	Not mentioned	Not specified	–
Antihistamines-Anticholinergics	Promethazine	Contraindicated in children less than 2 years	6.25–12.5 mg IV	Not mentioned	Not specified	12.5–25 mg IV or IM every 4–6 h
	Dimenhydrinate	Adequate hydration is recommended	1 mg/kg IV	0.5 mg/kg up to 25 mg	Not specified	–
	Scopolamine	Monotherapy not affective in prophylaxis	Transdermal patch	Not mentioned	Prior evening or 4 h before surgery	–

$5HT_3RA$, serotonin $5HT_3$ receptor antagonist; *CYP2D6*, cytochrome P450 2D6; *IM*, intramuscular; *IV*, intravenous; *NK_1RA*, neurokinin-1 receptor antagonist; *OD*, once daily; *QTIP*, QT interval prolongation; *TdP*, torsades de pointes.

Source: Cao, X., White, P.F., Ma, H., 2017. An update on the management of postoperative nausea and vomiting. J. Anesth. 31, 617–626 (Cao et al., 2017); Jokinen, J., Smith, A.F., Roewer, N., Eberhart, L.H., Kranke, P., 2012. Management of postoperative nausea and vomiting: how to deal with refractory PONV. Anesthesiol. Clin. 30, 481–493 (Jokinen et al., 2012); Lexicomp (Ed.), 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc, USA (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018); Wiesmann, T., Kranke, P., Eberhart, L., 2015. Postoperative nausea and vomiting - a narrative review of pathophysiology, pharmacotherapy and clinical management strategies. Expert Opin. Pharmacother. 16, 1069–1077 (Wiesmann et al., 2015).

Table 4 Pharmacotherapy of radiotherapy-induced nausea and vomiting

	High emetic risk	*Moderate emetic risk*	*Low emetic risk*	*Minimal emetic risk*
MASCO/ESMO	Prophylaxis with a $5HT_3RA$ + dexamethasone	Prophylaxis with a $5HT_3RA$ and/or dexamethasone (dexamethasone for days 1–5)	Prophylaxis or rescue with a $5HT_3RA$	Rescue with a $5HT_3RA$
ASCO	Prophylaxis with a $5HT_3RA$ and/or dexamethasone. Give prior to each fraction and for at least 24 h after radiotherapy	Prophylaxis with a $5HT_3RA$ prior to each fraction	Prophylaxis or rescue with a $5HT_3RA$. Once initiated, administer prior to each fraction	Rescue with a dopamine D_2 receptor antagonist or a $5HT_3RA$. Once initiated, administer prior to each remaining fraction
NCCN	Granisetron 2 mg PO OD and/or dexamethasone 4 mg PO OD prior to each fraction; or ondansetron 8 mg PO BD-TID and/or dexamethasone 4 mg PO OD prior to each fraction	Granisetron 2 mg PO OD and/or dexamethasone 4 mg PO OD prior to each fraction; or ondansetron 8 mg PO BD and/or dexamethasone 4 mg PO OD prior to each fraction	–	–

$5HT_3RA$, serotonin $5HT_3$ receptor antagonists; *ASCO*, American Society of Clinical Oncology; *BD*, twice daily; *MASCC/ESMO*, Multinational Association for Supportive Care in Cancer/European Society of Medical Oncology; *NCCN*, National Comprehensive Cancer Network; *OD*, once daily; *PO*, per os (by mouth); *TID*, three-times daily.

Source: Berger, M.J., Ettinger, D.S., Aston, J., et al., 2017. NCCN Guidelines Insights: Antiemesis, Version 2.2017. J. Natl. Compr. Canc. Netw. 15, 883–893 (Berger et al., 2017); Hesketh, P.J., Kris, M.G., Basch, E., et al., 2017. Antiemetics: American society of clinical oncology clinical practice guideline update. J. Clin. Oncol. 35, 3240–3261 (Hesketh et al., 2017); Roila, F., Molassiotis, A., Herrstedt, J., et al., 2016. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann. Oncol. 27, 119–133 (Roila et al., 2016); Ruhlmann, C.H., Jahn, F., Jordan, K., et al., 2017. 2016 updated MASCC/ESMO consensus recommendations: prevention of radiotherapy-induced nausea and vomiting. Support Care Cancer 25, 309–316 (Ruhlmann et al., 2017)

HG may result in significant maternal morbidity and adverse birth outcomes (Bustos et al., 2017; Lee and Saha, 2011). NVP significantly affects the quality of life of the pregnant woman and imparts a negative impact on employment, household duties, parenting, and family relationships (Bustos et al., 2017). In addition, NVP also exerts a large economic burden on patients, caregivers, and society. The estimated total economic burden of NVP was $1.77 billion in the United States in 2012 (Piwko et al., 2013).

Management of NVP involves dietary changes, intravenous fluid rehydration (including electrolytes and vitamins), and pharmacological treatment. Dietary changes include eating smaller and more frequent meals and avoiding foods, odors, or supplements that trigger nausea, especially fatty or spicy foods and iron tablets. Some other strategies that might help include drinking fluids between meals or eating bland, dry, and high-protein foods. Ginger and acupuncture are also shown to be effective (Herrell, 2014; Saberi et al., 2013).

In the case of persistent nausea and vomiting, drug therapy is recommended. However, the teratogenic potential of each drug should be considered. Approximately 10% of women with nausea and vomiting in pregnancy require medication. The American College of Obstetricians and Gynecologists recommends a combination of vitamin B6 (10–25 mg every 8 h) and doxylamine (25 mg at bed time and 12.5 mg each in the morning and afternoon) as first-line therapy in NVP (ACOG, 2018). This combination has been associated with a 70% reduction in nausea and vomiting with no reports of teratogenicity. Patients that are refractory to this combination can successively be treated with any of the following options: dopamine receptor antagonists (e.g., metoclopramide and various phenothiazines), antihistamines (e.g., dimenhydrinate and diphenhydramine), or serotonin $5HT_3RA$ (e.g., ondansetron) (ACOG, 2018). Metoclopramide is rarely associated with tardive dyskinesia. However, the risk increases with prolonged use and the total cumulative dose. Therefore, the treatment duration should not exceed 12 weeks (Herrell, 2014; Wijemanne et al., 2016). Corticosteroids, such as methyl prednisolone, have shown beneficial results in patients of HG (ACOG, 2018). The use of methyl prednisolone is associated with a three- to four-fold higher risk for cleft lip with or without cleft palate, thus its use should be avoided till first 10 weeks of gestation (Herrell, 2014). Severe NVP can cause dehydration and lead to increased level of ketones. This can be treated with IV fluid replenishment and multivitamins, especially thiamine. Antiemetics can be administered intravenously, if needed. However, follow-up measurement of urinary ketones and electrolytes will be required. Women with continued vomiting even after therapy should be hospitalized (ACOG, 2018).

Motion Sickness

Motion sickness is a syndrome that occurs as a result of exposure to certain types of motion. It is believed to be caused by conflict between the vestibular, visual, and other proprioceptive systems (Brainard and Gresham, 2014). Although vomiting is a typical presentation of motion sickness, it is often preceded by stomach awareness, malaise, drowsiness, and irritability. Management involves nonpharmacological (behavioral) and pharmacological strategies. Patients should be educated about the situations that might lead to motion sickness and strategies to minimize the amount of unpleasant motion. Scopolamine is recommended as a first-line drug for prevention of motion sickness (Spinks and Wasiak, 2011). Its transdermal patch is administered several hours before the anticipated motion exposure. In the case of poor response with usual dose, the dose can be doubled (Bar et al., 2009). First-generation antihistamines (cyclizine, meclizine, dimenhydrinate, etc.) are also effective. However, they often have sedative and

other side effects. Nonsedating antihistamines and ondansetron are not effective in the prevention and treatment of motion sickness (Brainard and Gresham, 2014).

Role of Pharmacist

Pharmacists are important members of the multidisciplinary health-care team and are experts in medicines. Their active involvement is needed in order to rationalize medication use and achieve the desired patient outcomes. For this purpose, pharmacists have a huge role to play in the pharmacotherapy of nausea and vomiting.

Pharmacists contribute to improving patients' health by providing pharmacotherapy-related patient-care services. In this connection, Pharmacists' Patient Care Process (PPCP) is a contemporary and comprehensive approach to patient care. In PPCP, pharmacists use a patient-centered model of care and work in collaboration with other members of multidisciplinary health-care team (Gonyeau et al., 2018; JCPP, 2014; Jupp et al., 2016). The following are the main components of PPCP: collect, assess, plan, implement, and follow-up (monitor/evaluate). PPCP for nausea and vomiting is illustrated in Fig. 4.

Pharmacists provide comprehensive patient education and counseling, which is one of the main strategies used for the management of nausea and vomiting. A study has demonstrated that education provided by pharmacists resulted in proper use of antiemetic drugs and led to improved control of chemotherapy-induced nausea with reduction in the cost for antiemetics by 16% (Iihara et al., 2012).

Many patients are persistently affected by nausea and vomiting. They suffer, not only physically and mentally but also financially. In such situations, treatment adherence becomes a major concern. The pharmacist role is to evaluate patients by identifying all considerable factors such as patient's health literacy, the convenience or complexity of the prescribed regimen, and pinpointing the factors that may affect adherence. Patients should be properly educated, and all issues that might lead to nonadherence should be addressed (McCullough, 2017).

Patients should be provided with accurate information regarding the condition and other therapy-related issues such as its outcome, potential harms, cost, duration, and proper administration. Patient education regarding the appropriate use of medications with special emphasis on adherence to antiemetic therapy should be provided. Adequate verbal and written information should be provided to each patient about the timing of drug administration, its duration, and possible adverse effects and their management (Tilleman et al., 2018). Other issues can also be addressed while educating a patient, which may have an impact on

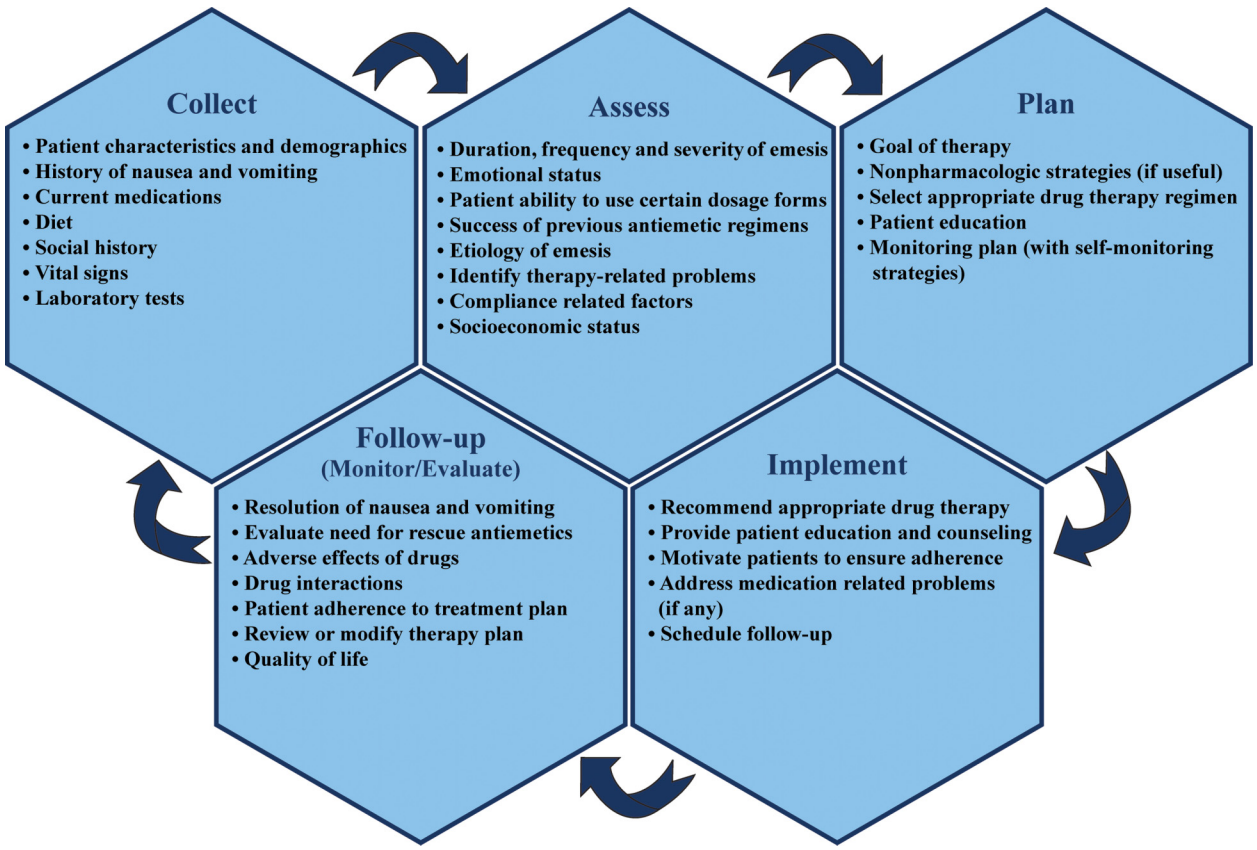

Figure 4 Pharmacists' patients care process for nausea and vomiting.

the condition such as dietary and lifestyle modifications; avoiding foods that may trigger emesis; eating soft bland foods; taking adequate amount of water; use of ginger; and psychological strategies.

Monitoring of therapy outcome is another important activity undertaken by pharmacists. Prevention or complete elimination of nausea and vomiting with no or minimal adverse effects are the desired outcomes of pharmacotherapy of nausea and vomiting. A patient receiving antiemetic therapy should be evaluated for resolution of symptoms and decrease in severity of nausea and number of emetic episodes per day. Moreover, patient evaluation for fluid and electrolyte imbalance is necessary. Therefore, parameters such as change in weight, estimated fluid loss, acid–base balance, and serum electrolytes should be regularly measured. Patient should also be evaluated for improvement of the underlying cause of nausea and vomiting. Physical assessment involving evaluation of mucous membrane and skin turgor should also be performed. Patients undergoing chemotherapy should be assessed after each chemotherapy session as most of the patients experience emetic episodes on the third day of the chemotherapy session. Documenting the experiences can help the health-care providers to modify the next management plan (Gravatt et al., 2017).

Antiemetic therapy is associated with many adverse drug effects (ADEs); therefore, their monitoring and management are also among the prime responsibilities of pharmacists (Husband and Worsley, 2007; Iihara et al., 2012). ADEs unceasingly place patients at risk and are a major source of health-care mishaps. They are not unexpected in the highly complex antiemetic therapy. ADEs deteriorate a patient's health-related quality of life, which already is poor in patients receiving antiemetic therapy as emesis itself is an adverse outcome of a number of underlying etiologies. Some of the frequently occurring ADEs associated with antiemetic therapy are discussed as follows (**Table 5** for more details). Antihistamine-anticholinergic class of drugs work by blocking H_1 receptors in the brain and muscarinic receptor M_1 both peripherally and centrally, which not only increase its efficacy but also its adverse effects. The commonly associated adverse effects with these drugs include sedation, xerostomia, dilated pupils, blurred vision, decreased GI motility/secretions, and urinary retention (ACOG, 2018; Veiga-Gil et al., 2017). Serotonin $5HT_3$RAs are fairly safer drugs and pose a risk of mild ADEs that include headache, constipation, diarrhea, and transient elevation of liver enzymes. Rarely, they may cause QT interval prolongation (ACOG, 2018; Veiga-Gil et al., 2017). The short-term use of dexamethasone is well-tolerated in most patients. Despite that, its use is associated with adverse effects such as hypertension, depression, conjunctivitis and steroid-related hyperglycemia. Diabetic patients are more prone to the steroid-related hyperglycemia; therefore, they should be advised to regularly monitor their glucose level (Wiesmann et al., 2015). Aprepitant is usually a well-tolerated drug and is associated with mild side effects such as fatigue, hiccups, headache, and diarrhea (Navari and Aapro, 2016). Stevens–Johnson syndrome is a rare but severe adverse effect associated with the use of aprepitant. Apart from these well-known and widely used pharmacologic agents, drugs from other classes have been used as antiemetics. Their ADEs are listed in **Table 5**. Moreover, a variety of drug interactions (DIs) are also possible in

Table 5 Adverse drug effects associated with pharmacotherapy of nausea and vomiting

Drugs	*Cardiovascular*	*Gastrointestinal*	*Neurological/psychiatric*	*Others*
Dimenhydrinate	–	Nausea, vomiting, epigastric distress, xerostomia	Sedation	Genitourinary: urinary retention
Hydroxyzine	*QTIP*	Xerostomia	Sedation	Dermatologic: *injection site reaction*
Meclizine	–	Xerostomia	Sedation	Immunologic: a*naphylactoid reaction* Ophthalmic: *blurred vision*
Scopolamine	*Tachyarrhythmia*	Xerostomia	*Confusion, hallucinations*	Dermatologic: *dry skin* Ophthalmic: mydriasis Genitourinary: urinary retention
Trimethobenzamide	–	*Hepatotoxicity, jaundice*	Dizziness, sedation, *coma, disoriented, extrapyramidal signs, seizure, depressed mood*	Ophthalmic: blurred vision
Diphenhydramine	–	Xerostomia	Dizziness, dyskinesia, sedation	Respiratory: dryness of nasopharyngeal mucosa, thick sputum Immunologic: *anaphylaxis*
Dolasetron	Bradyarrhythmia, *cardiac arrest, myocardial ischemia, QTIP, syncope, TdP, ventricular arrhythmia*	Diarrhea, *pancreatitis*	Dizziness, headache	Immunologic: *anaphylaxis,* Others: fatigue, *serotonin syndrome*
Granisetron	*QTIP*	–	Asthenia, headache, sedation	Immunologic: *hypersensitivity reactions* Other: fever
Ondansetron	*ECG abnormalities, QTIP, TdP*	Constipation, diarrhea	Headache	Respiratory: hypoxia Other: fatigue, malaise, *serotonin syndrome*
Palonosetron	Bradyarrhythmia, *QTIP*	Constipation	Headache, *seizure*	Immunologic: *anaphylaxis, hypersensitivity reactions* Other*: serotonin syndrome*

(*Continued*)

Table 5 Adverse drug effects associated with pharmacotherapy of nausea and vomiting (*cont.*)

Drugs	*Cardiovascular*	*Gastrointestinal*	*Neurological/psychiatric*	*Others*
Aprepitant	Hypotension	Abdominal pain, constipation, diarrhea, indigestion, loss of appetite, hepatotoxicity	Asthenia, dizziness, headache	Dermatologic: *SJS* Respiratory: cough, hiccups Hematologic: anemia, neutropenia Others: dehydration, fatigue
Fosaprepitant	–	Diarrhea	Asthenia	Dermatologic: *SJS* Hematologic: *neutropenia,* Immunologic: *hypersensitivity reaction, infusion reaction* Others: *fatigue*
Rolapitant	–	Loss of appetite	Dizziness	Respiratory: cough, hiccups Hematologic: neutropenia
Chlorpromazine	Orthostatic hypotension, tachycardia, *QTIP*	Nausea, xerostomia, *obstipation, paralytic ileus, jaundice*	Akathisia, dizziness, parkinsonism, sedation, tardive dyskinesia	Dermatologic: *erythroderma* Endocrine/metabolic: ineffective thermoregulation, hyperthermia Hematologic: *agranulocytosis, aplastic anemia, leukopenia*
Prochlorperazine	*QTIP*	–	*Tardive dyskinesia, NMS*	
Promethazine	*QTIP*	Nausea and vomiting, xerostomia, *jaundice*	CNS depression, dizziness, extrapyramidal disease, convulsion, sedation, *NMS*	Dermatologic: dermatitis, phototoxicity, urticaria, *injection site reaction* Respiratory: *apnea* Hematologic: *agranulocytosis, leukopenia, thrombocytopenia*
Metoclopramide	–	Nausea, vomiting	Asthenia, headache, sedation, *NMS, tardive dyskinesia*	Endocrine/metabolic: fluid retention Other: fatigue
Dexamethasone	Hypertension, *cardiomyopathy*	*Pancreatitis*	Depression, euphoria	Respiratory: tuberculosis Endocrine/metabolic: Cushing's syndrome, growth retardation, *hyperglycemia* Ophthalmic: abnormal vision, cataract, conjunctivitis, *conjunctival hemorrhage, glaucoma, uveitis* Musculoskeletal: *osteoporosis* Immunologic: *infectious disease*
Haloperidol	Hypotension, *QTIP, sudden cardiac death, TdP*	Constipation, xerostomia, *paralytic ileus*	Akathisia, extrapyramidal disease, sedation, *dystonia, NMS, seizure, tardive dyskinesia*	Ophthalmic: blurred vision Hematologic: *agranulocytosis* Reproductive: *priapism*
Droperidol	Hypotension, tachycardia, *cardiac arrest, QTIP, TdP, ventricular tachycardia*	–	Sedation, anxiety, dysphoric mood, restlessness, *NMS*	Immunologic: *anaphylaxis*
Dronabinol	Palpitations, tachyarrhythmia, vasodilation, *hypotension*	Abdominal pain, nausea, vomiting, xerostomia	Amnesia, ataxia, confusion, dizziness, sedation, anxiety, euphoria, hallucinations, d*epression, mania, schizophrenia*	Dermatologic: flushing Immunologic: *hypersensitivity reactions*
Nabilone	Hypotension	Xerostomia	Asthenia, ataxia, sedation, headache, poor concentration, vertigo, euphoria, *psychotic disorder*	Ophthalmic: visual disturbance
Olanzapine	Orthostatic hypotension, *sudden cardiac death*	*Acute hemorrhagic pancreatitis*	Personality disorder, *akathisia, asthenia, dizziness, sedation, tremors, cerebrovascular disease, dystonia, seizure, status epilepticus,* s*uicidal intent*	Respiratory: *pulmonary embolism* Endocrine/metabolic: hypercholesterolemia, hyperglycemia, hyperprolactinemia, increased appetite, weight gain, *hyperglycemic hyperosmolar state* Immunologic: *eosinophilia*

CNS, central nervous system; *ECG*, electrocardiogram; *NMS*, neuroleptic malignant syndrome; *QTIP*, QT interval prolongation; *SJS*, Stevens–Johnson syndrome; *TdP*, torsades de pointes. Note: Serious adverse effects are presented in italics.

Source: ASHP, 2018. Drug Information Monographs. AHFS DI Essentials. American Society of Health-System Pharmacists, Inc. Available from: https://www.drugs.com/monograph/ (ASHP, 2018); Lexicomp (Ed.), 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc, USA (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available from: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018)

patients with nausea and vomiting as they are usually exposed to polypharmacy (Umar, 2018). Antiemetic drugs are frequently used simultaneously with many other drugs for underlying problems and comorbidities. Therefore, patients' drug therapy may be associated with DIs leading to adverse outcomes. DIs are considered preventable causes of morbidity and mortality. Pharmacists should screen every patient's therapy for DIs in order to manage them accordingly.

Extensive literature is available regarding the role of the pharmacist in the pharmacotherapy of nausea and vomiting. Various studies have reported a significant impact of pharmacists on optimizing patient outcomes and improving medication safety. According to a systematic review, pharmacist interventions can improve outcome measures such as rates of nausea and vomiting control, medication adherence, and patient satisfaction (Colombo et al., 2017). A study found that pharmaceutical consultations substantially improve the outcome of antiemetic therapy, management of adverse effects, and patient satisfaction (Monfort et al., 2015). Impact of a clinical pharmacist-led guidance team was assessed in a prospective, multicenter, double-arm, controlled study. Clinical pharmacist produced a significant impact on various outcome parameters including reduction in the incidence of drug-induced nausea ($P = 0.028$) and vomiting ($P = 0.035$) (Chen et al., 2014).

Interprofessional collaboration is of great value in the management of nausea and vomiting. With the changes in scope of practice, more pharmacists proactively and collaboratively involve in direct patient care services in both inpatient and ambulatory settings (Jupp et al., 2016). Literature supports that collaborative disease therapy management can improve therapy outcomes, enhance medication adherence and medication safety, and minimize health-care expenditures (Jackson et al., 2018; Jupp et al., 2016). A study found that implementation of collaborative disease therapy management for CINV has shown favorable results, in which, the pharmacists have made a substantial number of clinical interventions and provided patient education to patients undergoing chemotherapy (Jackson et al., 2018). A successful reduction in the cost of antiemetic therapy was reported as result of a treatment algorithm developed by a team comprising pharmacists, oncologists, and oncology nurses (Berard and Mahoney, 1995). Another study showed that oncology pharmacists' collaboration with medical oncologists improved the management of CINV. Pharmacists successfully identified areas related to the use of antiemetics that needed refinement (Chan et al., 2008). As many cases of nausea and vomiting are drug induced, therefore proper monitoring of drug therapy will be helpful to detect such cases. Pharmacist–physician joint monitoring of chemotherapy was found very effective in identifying cases with adverse drug effects (Holle et al., 2016).

Various guidelines are available for the appropriate management of nausea and vomiting. These guidelines provide evidence-based standardized approaches. A key role of pharmacists is to ensure that treatments are consistent with these guidelines (Tilleman et al., 2018; Wood et al., 2015). A study has demonstrated that adherence to antiemetic guidelines resulted in significant reduction in the incidence of nausea/vomiting and side effects, and improvement of the patient's quality of life (Abunahlah et al., 2016). An educational intervention involving emphasis on the current guidelines was also found very effective to decrease markedly the incidence of PONV in a population of adult surgical patients (Sigaut et al., 2010). A randomized trial assessed the impact of pharmacist intervention involving evaluation of drug-use based on hospital guidelines. Pharmacist significantly contributed to promoting appropriate drug-use and controlling unnecessary hospital costs (Dranitsaris et al., 1995). Moreover, pharmacists significantly enhance care of the patients with CINV by making formulary considerations using patient-centered and evidence-based treatment (McCullough, 2017).

Pharmacists' contribution to pharmacotherapy of nausea and vomiting has been reported by many other studies as follows: supportive care provided by pharmacists in community- and hospital-pharmacies (Jansen and Ortland, 2017); pharmacist prescribing of antiemetic agents for nausea and vomiting with improved compliance to treatment-algorithm, drug safety, and patients/professionals acceptance (Martin and Norwood, 1988); evaluation of quality of life in patients with nausea and vomiting (de Souza et al., 2015); community pharmacists' roles/services (Albassam and Awad, 2018; Maesschalck, 2011); role of hospital pharmacist in the management of nausea and vomiting (Breton et al., 2011); and outpatient approach to nausea and vomiting (Prunty and Prunty, 2013).

Glossary

Akathisia A movement disorder characterized by a feeling of inner restlessness and inability to stay still.
Asthenia Loss of strength and energy.
Emetogenicity The potential of an agent to cause nausea and/or vomiting.
Extrapyramidal signs Forms of abnormal body movements that are caused by blockade of normal dopamine functions in the brain.
Neuroleptic malignant syndrome A life-threatening idiosyncratic reaction to antipsychotic drugs (neuroleptics) characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction.
Radiotherapy Therapy using ionizing radiation, generally as part of cancer treatment to control or kill malignant cells.
Retching Spasmodic movements of thoracic and abdominal muscles without emesis; also called dry heaves.
Stevens-Johnson syndrome (SJS) A severe inflammatory eruption of the skin and mucous membranes, which usually occurs as an allergic reaction to drugs or other substances.
Tardive dyskinesia A disorder associated with the use of neuroleptic drugs that results in involuntary, repetitive body movements.

Torsades de pointes (TdP) A specific form of polymorphic ventricular tachycardia characterized by rapid, irregular QRS complexes, which appear to be twisting around the ECG (electrocardiogram) baseline.
Xerostomia An abnormal dryness of mouth due to insufficient secretions.

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Management of Gastrointestinal Disorders and the Pharmacist's Role: Peptic Ulcer Disease

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Learning Objectives

At the end of this chapter, the reader will be able to:

- Develop a basic understanding of the epidemiology and pathophysiologic of peptic ulcer disease (PUD).
- Describe the main clinical features and complications of PUD.
- Discuss various pharmacological approaches available for PUD and the rationale for their use.
- Design a patient-specific care plan to ensure effective therapeutic outcomes.
- Educate patient about the proper administration of medications.
- Identify and manage adverse drug effects and drug interactions associated with pharmacotherapy of PUD.

Introduction

Peptic ulcer disease (PUD) refers to defects or breaks in the inner lining of the stomach and/or duodenum that penetrates through the muscularis mucosa leading to inflammation of the underlying tissue. *Helicobacter pylori* (*H. pylori*) infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common causes of PUD.

Epidemiology

Peptic ulcer disease remains a relatively common condition worldwide (Sung et al., 2009). Its overall incidence has changed over the past few decades (Azhari et al., 2018; Sung et al., 2009). The global annual incidence of PUD ranges from 0.10% to 0.19% based on physician diagnosis and 0.03% to 0.17% based on hospitalization data (Sung et al., 2009). According to a recent systematic review, the incidence of PUD varies in different parts of the world (Europe, Asia, and North America), with the highest in Spain (141.8 per 100,000 persons) and the lowest in the United Kingdom (23.9 per 100,000 persons) (Azhari et al., 2018). The incidence of PUD is related to gender and age. Males and older persons are more susceptible to PUD than females and younger persons, respectively (Garrow and Delegge, 2010). The prevalence of PUD is also variable, which exceeds its incidence mainly because of recurrence. The 1-year global prevalence is 0.12%–1.5% for physician-diagnosed PUD and 0.10%–0.19% for PUD diagnosed during hospitalizations (Sung et al., 2009). In a large population-based study in the United States, the estimated prevalence of peptic ulcers is 8.4% (Garrow and Delegge, 2010). Similarly, a large endoscopic study of a population sample from Sweden reported a prevalence of 4% (2% gastric and 2% duodenal ulcers) (Aro et al., 2006).

Etiology

Infection with *H. pylori* and use of NSAIDs are the most common causes of PUD. Among NSAIDs, the risk of ulcer is highest with full doses of nonselective NSAIDs, followed by low-dose aspirin and cyclooxygenase-2 (Cox-2)-selective NSAIDs (Masclee et al., 2014). Duodenal ulcer is almost always (>90%) associated with *H. pylori* infection, whereas gastric ulceration is associated with both *H. pylori* infection and the use of NSAIDs (Dovjak, 2017). Other less common causes of peptic ulcer include Zollinger–Ellison syndrome, cigarette smoking, stress, chronic illnesses, infections other than *H. pylori*, radiations, and concomitant administration of anticoagulants, selective serotonin reuptake inhibitors or corticosteroids with NSAIDs. The risk of PUD increases with old age (>60 years), previous history of ulcer, and alcohol consumption (**Table 1**). Individuals with multiple risk factors are at a higher risk for peptic ulcer-related bleeding (Nagata et al., 2015; Sostres et al., 2015; Venerito et al., 2018). Lately, the prevalence of idiopathic ulcer (*H. pylori* and NSAID-negative peptic ulcer) has increased, accounting for up to 10%–30% of PUD cases. In such patients, the less common causes of ulcer must be considered (Charpignon et al., 2013; Iijima et al., 2014). The ulcerogenic potential of diet and nutrition such as spicy food, carbonated drinks, coffee, tea, milk, and beer is uncertain; however, they may cause dyspepsia.

Pathophysiology

Peptic ulcers develop as a result of imbalance between aggressive factors (acid and pepsin) and defensive factors (synthesis of prostaglandins, ischemia), irrespective of the causative agent. *H. pylori* infection causes gastritis in almost all infected individuals, but only a fraction of them (~10%) actually develop PUD. The incidence of PUD depends on a myriad of host and bacterial factors. Host-related factors include genetic predisposition, duration of infection, smoking, and the use of NSAID. The most notable bacterial factors are the expression of CagA (cytotoxin-associated gene-A) and VacA (vacuolating toxin) virulence factors (proteins) (Amieva and Peek, 2016). The CagA protein disrupts various epithelial cell signaling processes involved in cell replication and cell death, whereas the VacA gene protein introduces a large pore-forming protein in the epithelial cell membrane that results in an increased efflux of micronutrients and apoptosis (Costa et al., 2009). Bacterial surface proteins (Hop and BabA proteins) facilitate bacterial adhesion and act as a chemotactic for neutrophils and monocytes, which further augments cellular injury. Additionally, *H. pylori* infection alters the secretion of gastrin (hypersecretion of gastrin in duodenal ulcer) mainly because of the reduced number of somatostatin secreting antral "D" cells and the stimulation of gastrin release by cytokines during active inflammation, that result in hyperchlorhydria. In gastric ulcers, hypochlorhydria may allow the growth of other bacteria that may cause chronic inflammation.

NSAIDs cause ulcers by local irritation as well as systemic inhibition of prostaglandins synthesis that are essential for mucosal integrity and repair (Bhatt et al., 2008). All NSAIDs including aspirin are weak acids. They remain unionized in the acidic pH of the stomach and diffuse into the gastric epithelium. In the epithelial cells, the neutral pH ionizes NSAIDs resulting in irritation and inflammation, which may subsequently cause epithelial injury. Systemically, NSAIDs inhibit the cyclooxygenase (Cox) enzymes involved in the synthesis of prostaglandins. The Cox-1 enzyme synthesizes protective prostaglandins that regulate normal physiologic processes and is present in the stomach, kidney, intestine, and platelets. While, the inducible Cox-2 enzyme is generated during acute inflammation and synthesizes prostaglandins involved in inflammation, fever, and pain (Bhatt et al., 2008). The nonselective NSAIDs inhibit both the Cox-1 and Cox-2 isoforms. They have a higher risk of gastrointestinal (GI) toxicity as compared to the Cox-2-selective NSAIDs, which only inhibit the Cox-2 enzyme. NSAIDs can also cause mucosal injury through the production of proinflammatory mediators such as tumor necrosis factors and leukotrienes.

Cigarette smoking not only induces ulcers but also impairs ulcer healing and increases the risk of ulcer complications. The exact mechanism of smoking-induced ulcer is unknown. The association of genetic factors and ulcers remains unclear, however a higher incidence of ulcers has been reported in first degree relatives and patients with blood group "O" (Malfertheiner et al., 2009).

Table 1 Risk factors for peptic ulcer disease

Patient's characteristic
• Old age (>60 years)
Infections
• *Helicobacter pylori* • Cytomegalovirus (particularly in AIDS and transplant patients) • Herpes simplex virus (particularly in AIDS and transplant patients) • Helicobacter heilmannii
Medications
• NSAIDs (including Cox-2-selective NSAIDs and low-dose aspirin) • Anti-coagulants (alone or in combination with NSAIDs) • Corticosteroids (in combination with NSAIDs) • Selective serotonin reuptake inhibitors (in combination with NSAIDs) • Bisphosphonates • Potassium chloride • Chemotherapy • Iron preparations
Diseases
• Zollinger–Ellison syndrome • Stress (burns, multiorgan failure, CNS trauma) • Crohn's disease • Chronic kidney disease • Chronic heart failure • Arthritis • Coronary artery disease • Liver cirrhosis • Chronic obstructive pulmonary disease • Pancreatitis • Lymphoma • Bile reflux disease
Environmental and diet
• Cigarette smoking • Nicotine • Alcohol • Spicy food • Carbonated drinks • Caffeinated drinks
Miscellaneous
• Hereditary • Radiations • Ischemia

AIDS, acquired immune deficiency syndrome; *CNS*, central nervous system; *Cox*, cyclooxygenase; *NSAIDs*, nonsteroidal anti-inflammatory drugs.
Sources: González-Pérez, A., Sáez, M. E., Johansson, S., Nagy, P., Rodríguez, L.A.G., 2014. Risk factors associated with uncomplicated peptic ulcer and changes in medication use after diagnosis. PLOS ONE 9, e101768 (González-Pérez et al., 2014); Drini, M., 2017. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. Aust. Prescr. 40, 91–93 (Drini, 2017); Lanas, A., Chan, F.K.L., 2017. Peptic ulcer disease. Lancet 390, 613–624 (Lanas and Chan, 2017); Lee, S.P., Sung, I.K., Kim, J.H., et al., 2017. Risk Factors for the Presence of Symptoms in Peptic Ulcer Disease. Clin. Endosc. 50, 578–584 (Lee et al., 2017).

Clinical Features

The clinical features of PUD vary with the severity of the disease. Patients may present with mild epigastric discomfort to life-threatening complications. Epigastric pain is the most frequent presentation of ulcer, but it is nonspecific and might be present in patients with other GI conditions including nonulcer dyspepsia. The patient may point at the site of pain with one finger commonly known as the pointing sign. Generally, the pain is expressed as a burning, gnawing, aching sensation and is localized to the epigastrium. In complicated cases, it may radiate toward the back or lower abdomen. Severe nocturnal pain that awakens the

patient may also be reported by some patients (Lanas and Chan, 2017; Narayanan et al., 2018). In duodenal ulcers, food intake often diminishes pain that recurs after 1–3 h, whereas food intake worsens pain in gastric ulcers. Dyspepsia, an uncomfortable feeling may be present in some patients, but it is common with other GI conditions as well. Moreover, patients may experience dyspepsia, following intake of NSAIDs, spicy food, or milk.

Peptic ulcer-related bleeding is a serious complication. Bleeding may be occult, which can only be ascertained following fecal occult blood test, or it may present as melena or hematemesis. Chronic bleeding may result in anemia, while significant acute blood loss can cause shock (Budimir et al., 2017; Lanas and Chan, 2017; Venerito et al., 2018). Mild epigastric tenderness may be observed with deep palpitations in patients with noncomplicated ulcers whereas, severe "board-like" abdominal tenderness is suggestive of perforation. Moreover, early satiety, nausea, vomiting, pain precipitating with meals, weight loss, and bloating indicate gastric obstruction.

Diagnosis

The main objective of diagnosis is to ascertain the cause of ulcer and to rule out gastric malignancy. The patient's history, being quick and easy, provides important information about the severity and potential cause(s) of PUD. Information regarding the use of NSAIDs, prior history of PUD, failure of *H. pylori* therapy, smoking, and age guides the selection of the appropriate diagnostic procedure and treatment. In physical examination, epigastric tenderness may be found between the umbilicus and the xiphoid process that less commonly radiates to the back.

Routine laboratory tests such as full blood count and fecal occult blood test may assist in the evaluation of bleeding ulcers, while rare specialized tests such as fasting serum gastrin concentration and gastric acid analysis may be performed for patients who are unresponsive to therapy or suspected to have Zollinger–Ellison syndrome.

Endoscopy is the gold-standard method for investigating the upper GI tract and ulcers. It permits direct inspection, photographic documentation, tissue biopsy, and employment of therapeutic interventions (e.g., epinephrine injection and placement of hemostatic clips). Endoscopy is recommended for high-risk patients, particularly elderly patients having alarm features (e.g., weight loss, bleeding, vomiting, dysphagia) and patients who do not respond to therapy. For patients who undergo endoscopy, biopsies should be taken and tested for the presence of *H. pylori* infection and malignancy (Chey et al., 2017).

Barium radiography is a less expensive and widely available method of ulcer detection. It is used as an alternate method to endoscopy. In this technique, the patients receive a barium meal that improves ulcer detection.

Detection of *H. pylori* infection is recommended in all patients having active ulcers, prior history of PUD (except successful eradication), and individuals starting chronic NSAIDs therapy. A number of invasive and noninvasive methods have been developed for the detection of *H. pylori* (**Table 2**). The accuracy and sensitivity of invasive tests (except histology) are greatly affected with the use of antibiotics, bismuth salts, and proton pump inhibitors (PPIs); therefore, they should be withdrawn at least 4 weeks (2 weeks for PPIs) before performing these tests (Chey et al., 2017).

Treatment

The main goals of PUD treatment include symptomatic relief, eradication of *H. pylori* infection, healing the ulcer, and preventing ulcer complications and recurrence. Various non-pharmacological and pharmacological options may be used. In non-pharmacological treatment, diet and lifestyle modifications are recommended. Although no specific diet promotes or augments ulcer healing, intake of spicy food and carbonated or caffeinated beverages may increase gastric acid secretion or cause dyspepsia. Therefore, they should be avoided or used in moderation. Regular small meals are encouraged and late-night snacks are better avoided because they increase nocturnal acid secretion. Moreover, cigarette smoking and the use of NSAIDs should be avoided. Pharmacological treatment includes various regimens for the eradication of *H. pylori* related ulcers and the treatment and prevention of NSAIDs-related ulcers (Chey et al., 2017; Lanza et al., 2009).

Treatment of *H. pylori*-induced Ulcer

H. pylori eradication therapy aims to completely eliminate *H. pylori* infection and heal the ulcer by selecting a cost-effective drug regimen. The type and duration of therapy, antibiotic resistance, and patient adherence are key factors responsible for the success of treatment. In the following sections, various treatment options and their selection criteria are discussed. Drugs doses, precautions, use in pregnancy and lactation, and renal/hepatic dose adjustments are presented in **Tables 3 and 4**.

Treatment Options

Therapy against *H. pylori* infection comprises multiple drugs (**Fig. 1**) in order to achieve successful eradication and minimize the emergence of resistance (Chey et al., 2017).

Triple therapy: The conventional triple therapy is a combination of a PPI and two antibiotics (metronidazole with clarithromycin or amoxicillin) and is recommended for a duration of 10–14 days (Chey et al., 2017; Fallone et al., 2016; Luther et al., 2010). Triple

Table 2 Diagnostic approaches for the detection of *Helicobacter pylori*

Tests	*Description*	*Sensitivity*	*Specificity*	*Merits*	*Demerits*	*Guidelines recommendations*
Invasive endoscopic tests (requires tissue biopsy)						
Rapid urease test	Change in color (pH sensitive indicator) is detected because of ammonia production due to urease enzyme	80%–95%	95%–100%	Test of choice; easy to perform on biopsy sample; rapid	Potential false-negative result with drugs; expensive; reduced accuracy in ulcer; 13-carbon test requires expensive mass spectrometer	Sensitivity can be improved with increasing number of biopsy samples
Histology	Microbial examination using various stains	>90%	>95%	Test of choice to rule out malignancy; permits classification of gastritis	Takes several days; expensive; requires skilled expert	Performed to exclude gastric malignancy
Culture	Culture of biopsy particularly for antibiotic susceptibility	Variable	100%	Enables antibiotic susceptibility testing	Time consuming; expensive; technically demanding	Limited to patients who fail initial treatment
Polymerase chain reaction	Detection of *H. pylori* DNA in gastric tissue	High	High	High specificity and sensitivity	High rates of false-positive or -negative; positive DNA does not correlate with the presence of organism	–
Noninvasive tests (does not require tissue biopsy)						
Urea breath test	*H. pylori*'s urease enzyme converts ingested radiolabeled urea into ammonia and carbon dioxide, the latter is exhaled and detected in breath	>90%	>90%	Determines active *H. pylori* infection; simple; rapid; recommended for confirmation of eradication	Exposure to low-dose radiations with 14-carbon test; potential false-negative with drugs; results take around two days	Test of choice
Fecal antigen test	Detects *H. pylori* antigen in stool by enzyme immunoassay using polyclonal antibody	>90%	>90%	Identifies active *H. pylori* infection, comparable to urea breath test; inexpensive; convenient	Potential false-negative with drugs	Alternate for initial screening and eradication confirmation to urea breath test; convenient in children; some individuals may be reluctant to obtain stool samples
Office-based antibody serologic test	Detects IgG antibodies against *H. pylori* in blood using strips	>80%	>90%	Quick (under 15 min); inexpensive; convenient; not affected by drugs; widely available	Qualitative; cannot differentiate between active or previous infection; less sensitive and specific than laboratory-based test; not recommended for eradication confirmation	Not recommended for initial screening except in patients with no prior history of ulcer
Laboratory-based antibody serologic test	Detects IgG antibodies against *H. pylori* in serum using ELISA and latex agglutination techniques	>80%	>90%	Quantitative; more accurate than office-based serologic test; inexpensive; convenient; not affected by drugs	Cannot differentiate between active or previous infection; less sensitive and specific than invasive tests; not recommended for eradication confirmation	May be performed in patients with no prior history of ulcer

DNA, deoxyribonucleic acid; *ELISA*, enzyme-linked immunosorbent assay; *H. pylori*, *Helicobacter pylori*; *IgG*, immunoglobulin G.

Source: Calvet, X., Lehours, P., Lario, S., Megraud, F., 2010. Diagnosis of Helicobacter pylori infection. Helicobacter 15, 7–13 (Calvet et al., 2010); Malfertheiner, P., Megraud, F., O'morain, C., et al., 2016. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut 66, 6–30 (Malfertheiner et al., 2016); Chey, W.D., Leontiadis, G.I., Howden, C.W., Moss, S.F., 2017. ACG clinical guideline: treatment of Helicobacter pylori infection. Am. J. Gastroenterol. 112, 212–239 (Chey et al., 2017).

Table 3 Recommended drugs' doses and precautions

Therapeutic class	*Drug*	*Adult dosage*	*Cautions*
Proton pump inhibitors	Omeprazole	Oral 20–40 mg once or twice daily for 4–8 weeks[a]	Avoid in patients with known hypersensitivity. May induce CDAD, CLE, SLE, fundic gland polyps, osteoporosis, hypomagnesemia, vitamin B_{12} deficiency, acute interstitial nephritis and hepatic toxicity
	Esomeprazole	Oral 20–40 mg once or twice daily for up to 6 months[a]	
	Pantoprazole	Oral 40–80 mg once or twice daily for 4–8 weeks[a]	
	Rabeprazole	Oral 20 mg once or twice daily for up to 4 weeks[a]	
	Lansoprazole	Oral 30–60 mg once or twice daily for up to 8 weeks[a]	
Histamine-2 receptor antagonists	Ranitidine	Oral 150 mg twice daily	Avoid in patients with known hypersensitivity. May induce vitamin B_{12} deficiency, hepatotoxicity, acute porphyria, confusion in elderly patients, prolongation of QT interval and gynecomastia (cimetidine)
	Famotidine	Oral 40 mg once daily at night for up to 8 weeks	
	Cimetidine	Oral 800 mg once daily at night or 400 mg twice daily or 300 mg four times daily	
Anti-infective agents	Clarithromycin	Oral 500 mg twice daily in combination with other drugs	Avoid in patients with known hypersensitivity, cholestatic jaundice, cardiac arrhythmia. May induce SJS, TEN, prolongation of QT interval, hepatotoxicity, CDAD and exacerbation of myasthenia gravis
	Amoxicillin	Oral 1 g twice daily in combination with other drugs	Avoid in patients with known hypersensitivity. May induce anaphylaxis and CDAD
	Metronidazole	Oral 500 mg thrice daily as triple or quadruple regimen or Oral 500 mg twice daily as non-bismuth quadruple regimen	Avoid in patients with known hypersensitivity, first-trimester, concomitant intake of disulfiram or alcohol. May induce seizures, encephalopathy, peripheral neuropathy, CDAD, hepatotoxicity and blood abnormalities
	Tetracycline	Oral 500 mg four times daily in combination with other drugs	Avoid in patients with known hypersensitivity, hepatic impairment, second and third trimester. May induce photosensitivity, intracranial hypertension, retardation of bone growth and teeth discoloration
	Levofloxacin	Oral 500 mg once daily in combination with other drugs	Avoid in patients with known hypersensitivity. May induce anaphylaxis, blood abnormalities, renal toxicity, phototoxicity, hypoglycemia, CDAD, prolongation of QT interval and torsade de pointes
	Furazolidone	Oral 200 mg twice daily in combination with other drugs	Avoid in infants, with concomitant intake of disulfiram and patients with known hypersensitivity. May induce hemolytic anemia in G6PD deficient patients
	Rifabutin	Oral 150–300 mg twice daily in combination with other drugs	Avoid in patients with known hypersensitivity. May induce blood abnormalities, ocular inflammation, arthralgia and brown-orange discoloration of body fluids
Mucosal protectants	Misoprostol	Oral 200 mcg four times daily for 4 weeks	Avoid in patients with known hypersensitivity. May induce diarrhea, anaphylaxis, chills and teratogenicity
	Bismuth subsalicylate	Oral 300 mg four times daily in combination with other drugs	Avoid in patients with known hypersensitivity, diarrhea, gastrointestinal bleeding, children with chicken pox and influenza. May induce black discoloration of tongue
	Sucralfate	Oral 300 mg four times daily in combination with other drugs; Oral 1 g four times daily for stress ulcer	Avoid in patients with known hypersensitivity. May induce hyperglycemia in diabetics or alter drugs absorption

CDAD, *Clostridium difficile* associated diarrhea; *CLE*, cutaneous lupus erythematosus; *G6PD*, glucose-6 phosphate dehydrogenase; *SJS*, Stevens–Johnson syndrome; *SLE*, systemic lupus erythematosus; *TEN*, toxic epidermal necrolysis.

[a]Twice daily dosing is prescribed for shorter duration of therapy in treating *H. pylori* infection and the duration often varies with specific regimen.

Source: ASHP, 2018. Drug Information Monographs. AHFS DI Essentials. American Society of Health-System Pharmacists, Inc. Available from: https://www.drugs.com/monograph (ASHP, 2018); Lexicomp, 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc., U.S. (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available from: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018).

therapy containing amoxicillin should be avoided in individuals with an allergy to β-lactam antibiotics (Chey et al., 2017). *H. pylori* strains resistant to clarithromycin can significantly affect the efficacy of clarithromycin-based triple therapy; thus, they are not recommended in areas with a high prevalence (>15%) of clarithromycin resistance. Alternatively, levofloxacin-based triple therapy may be used (Chey et al., 2017; Fallone et al., 2016; Luther et al., 2010).

Bismuth quadruple therapy: The bismuth quadruple therapy is a combination of bismuth, PPI, and two antibiotics (e.g., metronidazole with tetracycline, amoxicillin, or clarithromycin) (Chey et al., 2017). It is recommended for a duration of 14 days and is preferred over the triple therapy especially in areas with high clarithromycin resistance (Chey et al., 2017; Fallone et al., 2016; Venerito et al., 2013). The addition of bismuth can increase eradication rates by 30%–40% (Dore et al., 2016; Zhang et al., 2015b). Adherence, however, is a major issue with this therapy due to the increased number of drugs and a complex dosing schedule.

Table 4 Drugs use in pregnancy and lactation and dose adjustment

			Dose adjustment	
Drug	*Pregnancy*	*Lactation*	*Kidney impairment*	*Liver impairment*
Omeprazole	Uncertain risk	Uncertain risk	Not necessary	Reduce dose to 10 mg OD for maintenance therapy
Esomeprazole	Uncertain risk	Uncertain risk	Not necessary	Maximum daily dose of 20 mg in severe hepatic impairment
Pantoprazole	Uncertain risk	Uncertain risk	Not necessary	Not necessary
Rabeprazole	Uncertain risk	Uncertain risk	Not necessary	Severe hepatic impairment, use with caution
Lansoprazole	Uncertain risk	Uncertain risk	Not necessary	Severe hepatic impairment, maximum 15 mg daily
Ranitidine	Uncertain risk	Uncertain risk	CrCl <50 mL/min: Reduce the usual dose by half	Not necessary
Famotidine	Uncertain risk	Uncertain risk	CrCl <50 mL/min: 150 mg Oral OD	Not necessary
Cimetidine	Uncertain risk	Minimal risk	CrCl < 30 mL/min: 300 mg Oral BD	Severe hepatic impairment, reduce the usual dose by half
Clarithromycin	Minimal risk	Uncertain risk	CrCl <30 mL/min: Reduce the usual dose by half	Not necessary
Amoxicillin	Uncertain risk	Minimal risk	CrCl < 30 mL/min: Avoid extended release formulations; Use immediate release formulation 250–500 mg BD	Not necessary
Metronidazole	Established risk	Uncertain risk	Not necessary	Severe hepatic impairment, reduce the usual dose by half
Tetracycline	Established risk	Minimal risk	CrCl <50 mL/min: Extend dose interval: administer every 12–24 h	Not necessary
Levofloxacin	Minimal risk	Uncertain risk	CrCl <50 mL/min: Reduced the usual dose by half	Not necessary
Furazolidone	Minimal risk	Uncertain risk	–	–
Rifabutin	Uncertain risk	Uncertain risk	CrCl <30 mL/min: Reduce the usual dose by half	Not necessary
Misoprostol	Established risk	Uncertain risk	Caution is advised	Not necessary
Bismuth subsalicylate	Minimal risk (1st and 2nd trimester); established risk (3rd trimester)	Established risk	Not necessary	Not necessary
Sucralfate	Uncertain risk	Uncertain risk	Not necessary	Not necessary

BD, twice daily; *Crcl*, creatinine clearance; *OD*, once daily.

Source: ASHP, 2018. Drug Information Monographs. AHFS DI Essentials. American Society of Health-System Pharmacists, Inc. Available from: https://www.drugs.com/monograph (ASHP, 2018); Lexicomp, 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc., U.S. (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available from: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018)

Adherence can be improved by utilizing a fixed-dose combination formulation, pharmacist-assisted blister packaging, and proper patient education (Gisbert, 2011; Graham and Dore, 2016; Malfertheiner et al., 2011).

Nonbismuth quadruple therapy: A number of nonbismuth quadruple therapies have been used for *H. pylori* eradication. The nonbismuth quadruple therapies comprise a PPI and three antibiotics used for varying duration (Liu et al., 2018; Malfertheiner et al., 2016). Nonbismuth quadruple therapies are costly, complex, and have low adherence. The concomitant therapy contains a PPI and three antibiotics (clarithromycin, amoxicillin, and metronidazole), administered for a duration of 10–14 days (Gisbert and Calvet, 2012b). Concomitant therapy is superior to other non-bismuth therapies in terms of efficacy and compliance (Molina-Infante et al., 2012). Optimized concomitant therapy with a high dose of PPI may achieve higher eradication rates (Molina-Infante et al., 2015). The sequential therapy includes a PPI and amoxicillin, administered for 5–7 days, followed by clarithromycin and metronidazole for an additional 5–7 days (Chey et al., 2017). In hybrid therapy, a PPI and amoxicillin are administered for initial 5–7 days, followed by a combination of PPI, amoxicillin, clarithromycin, and metronidazole for an additional 5–7 days (Chey et al., 2017).

Rescue therapy: Rescue therapy or salvage therapy is a type of therapy given after the failure of standard therapies. Some notable examples of rescue therapies for PUD include levofloxacin containing triple therapy with a PPI, levofloxacin, and amoxicillin; or quadruple therapy with a PPI, bismuth, levofloxacin, and amoxicillin. Their use for 10–14 days effectively achieves eradication in sensitive strains. Alternately, furazolidone or rifabutin may be used as rescue therapy for sensitive strains (Fallone et al., 2016; Liao et al., 2013; Liou et al., 2010).

Use of acid suppression agents in H. pylori regimens: PPIs (e.g., omeprazole, esomeprazole, pantoprazole, and rabeprazole) are an integral part of all eradication therapies. The primary aim of administering a PPI is to inhibit or reduce gastric acid secretion in order

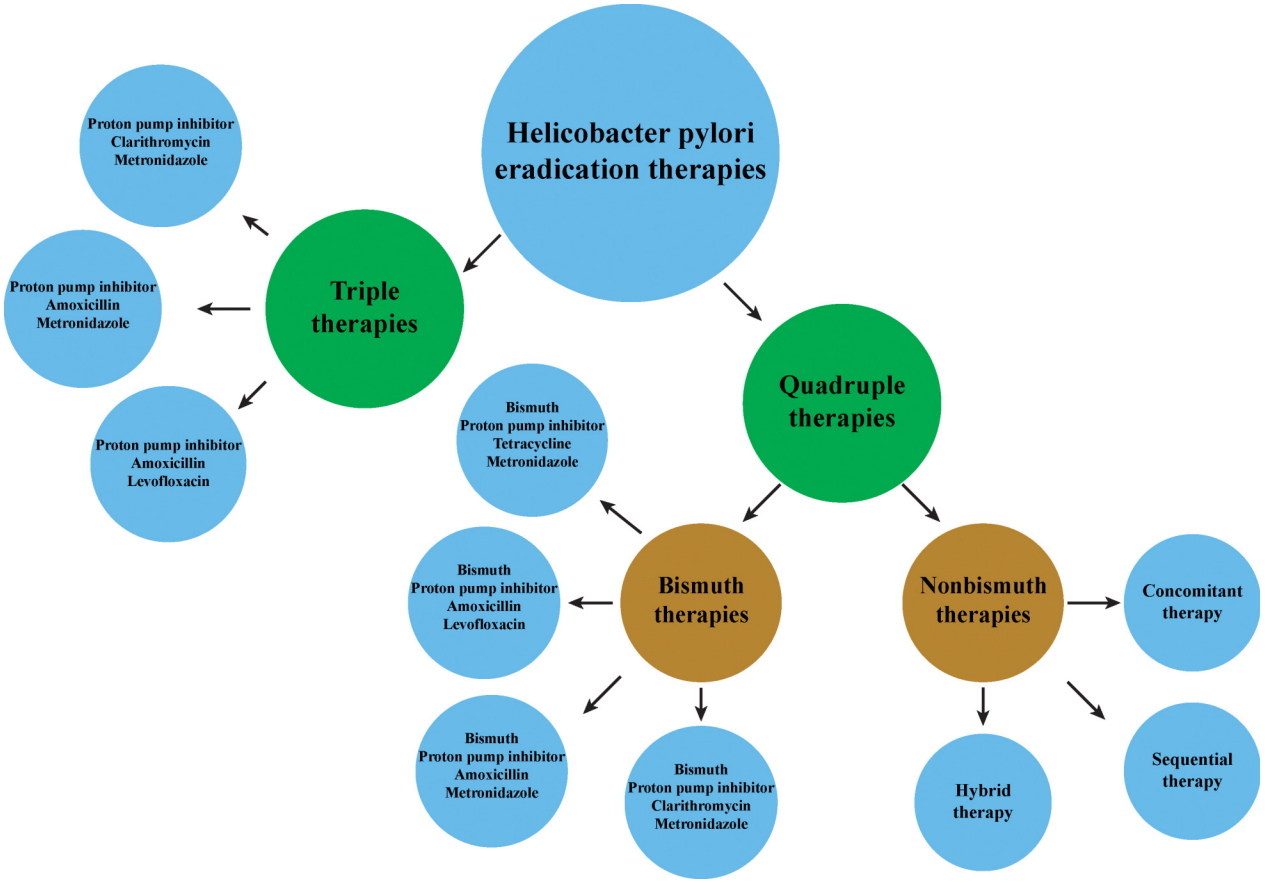

Figure 1 Various therapeutic regimens for the eradication of *Helicobacter pylori* infection.

to promote bacterial growth (*H. pylori*), thus predisposing them to the action of antibiotics. Moreover, PPIs reduce acid-induced mucosal injury. The appropriate selection and optimum efficacy of PPI are influenced by the CYP2C19 genotype. Higher doses of PPIs may be required in fast metabolizers (Kuo et al., 2014; Lee et al., 2014). Alternatively, a novel potassium competitive acid blocker (vonoprazan) may be used (Murakami et al., 2016).

Probiotic adjuvant therapy: Lately, the use of probiotics as an adjuvant therapy has gained popularity. Probiotics such as the lactobacillus, bifidobacterium, and saccharomyces genus have been reported by some studies to improve eradication rates and reduce the incidence of adverse effects (Jung et al., 2018; Losurdo et al., 2018; Zhang et al., 2015a).

Treatment Selection Criteria

The selection of an appropriate therapeutic regimen for a particular patient is mainly based on recent antibiotic use and resistance patterns (Fig. 2). Other factors include contraindication/intolerance, availability, cost, and patient adherence (Chey et al., 2017; Malfertheiner et al., 2016). In general, resistance against tetracycline and amoxicillin is low. Resistance against metronidazole can be overcome by increasing its dose. Resistance against clarithromycin, levofloxacin, and rifabutin can significantly alter their therapeutic outcome (Graham and Fischbach, 2010).

Low-clarithromycin resistance: In areas where the prevalence of clarithromycin resistance is low (<15%) or when patient has no recent exposure to clarithromycin, clarithromycin triple therapy is recommended as first-line treatment for 10–14 days (Fallone et al., 2016). Alternatively, amoxicillin may be used in combination with metronidazole in areas where resistance to metronidazole is low (<15%). The addition of bismuth to clarithromycin triple therapy can increase eradication by 30%–40%. As far as the use of amoxicillin is concerned, it is an important component of eradication regimens due to lower resistance. However, it should be avoided in patients who are allergic to penicillin. If first-line therapy fails, repeated use of clarithromycin should be avoided. The recommended second-line empirical therapy is bismuth quadruple therapy for a duration of 14 days (Chey et al., 2017; Fallone et al., 2016). If second-line therapy fails, the selection of third-line rescue therapy must be based on findings of the antibiotic susceptibility test (Lim et al., 2016; Liu et al., 2018; Malfertheiner et al., 2016; Sugano et al., 2015). Levofloxacin-based triple or quadruple therapy is recommended for susceptible strains. If resistance against levofloxacin is high, bismuth-based therapy containing furazolidone or rifabutin is used (Fallone et al., 2016; Gisbert and Calvet, 2012a; Liao et al., 2013; Liou et al., 2010).

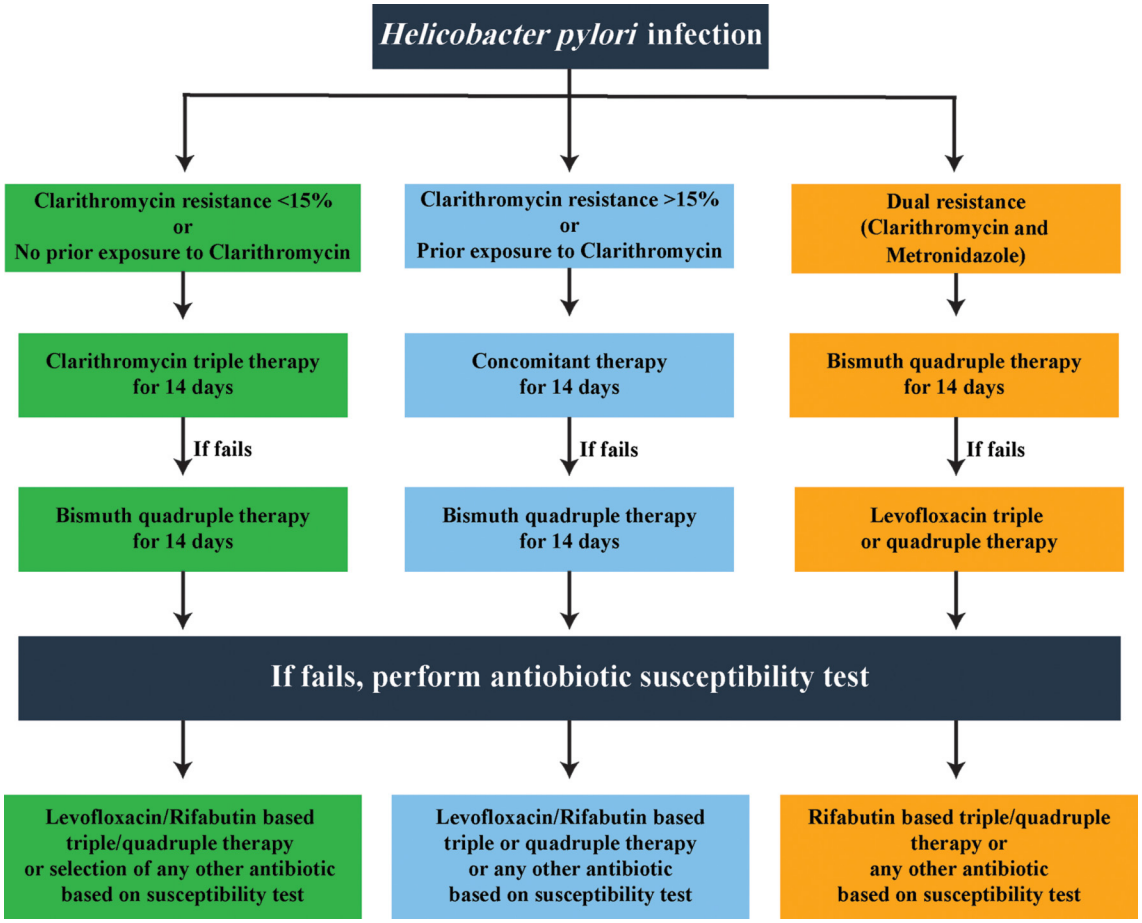

Figure 2 Treatment algorithm for the eradication of *Helicobacter pylori* infection.

High clarithromycin resistance: In patients with recent exposure to clarithromycin or areas where clarithromycin resistance is high (>15%), but metronidazole resistance is low (<15%), nonbismuth quadruple therapy (especially the concomitant therapy) is recommended for a duration of 14 days. If first-line therapy fails, bismuth quadruple therapy for a duration of 14 days should be used (Chey et al., 2017; Chung et al., 2011; Lee et al., 2011). Following failure of second-line therapy, selection of appropriate antibiotic must be based on antibiotic susceptibility test. Levofloxacin-based triple or quadruple therapy is recommended for susceptible strains (Chuah et al., 2012; Fallone et al., 2016; Marin et al., 2013). In the case of levofloxacin resistance, furazolidone- or rifabutin-containing regimen may be used following the susceptibility test.

High clarithromycin and metronidazole resistance: In areas where resistance to both clarithromycin and metronidazole is high (dual resistance), bismuth quadruple therapy for a duration of 14 days is the recommended first-line treatment (Fallone et al., 2016; Luther et al., 2010; Malfertheiner et al., 2016). If bismuth quadruple therapy fails, clarithromycin triple therapy should be avoided as second-line therapy. Levofloxacin-based triple or quadruple therapy is the recommended second-line therapy in such cases (Fallone et al., 2016; Marin et al., 2013). If second-line treatment fails or resistance to levofloxacin is high, a bismuth quadruple therapy containing susceptible antibiotics such as furazolidone or rifabutin, determined by antibiotic susceptibility testing, should be used (Fallone et al., 2016; Gisbert and Calvet, 2012a).

Treatment of NSAID-Induced Ulcers

Patients must be tested for *H. pylori* infection because NSAID-associated ulcers may be *H. pylori* positive. Eradication is generally recommended in *H. pylori* positive cases. In patients with confirmed NSAID-induced ulcers, nonselective NSAIDs should be discontinued (when possible). A standard 4–8 weeks' therapy preferably with a PPI can achieve satisfactory ulcer healing. They can also be substituted with sucralfate or histamine-2 receptor antagonists (H_2RAs) such as ranitidine or famotidine. Ulcer healing may be impaired if use of NSAIDs is continued. In such situations, the following measures may be considered such as reducing the NSAID dose, switching to acetaminophen or non-acetylated salicylate or a Cox-2-selective NSAID, and co-therapy with a PPI. If co-therapy with a PPI/H_2RAs is employed, they need to be used for a longer duration of around 8–12 weeks (Melcarne et al., 2016; Satoh et al., 2016).

Prevention of NSAID-Induced Ulcers

Generally, NSAIDs are not recommended in patients who are at risk for GI toxicity. Long-term NSAID treatment may be needed in some situations such as chronic rheumatological conditions; therefore, prevention of the NSAID-associated ulcer and GI complications should be considered. Ulcer preventive therapy with a PPI or misoprostol or high dose H_2RA is recommended for patients using nonselective NSAIDs (e.g., aspirin, diclofenac, and naproxen). Alternatively, selective Cox-2 NSAID (celecoxib) may be used that are safer and are less likely to cause ulcers (Melcarne et al., 2016; Satoh et al., 2016).

Ulcer preventive therapy is very useful if the risk of ulcer and GI toxicity is high (**Table 1**). It may not be needed in low-risk situations. However, some guidelines recommend preventive therapy in all individuals taking nonselective NSAIDs irrespective of ulcer risk. PPIs are the therapy of choice for the prevention of NSAID-induced ulcer or ulcer complications (Satoh et al., 2016; Yang et al., 2017). Alternatively, misoprostol or high-dose H_2RA may be used. Misoprostol has comparable efficacy to PPI but they have poor patient compliance and increased incidence of adverse effects (e.g., abdominal pain and diarrhea). High-dose H_2RA (ranitidine or famotidine) may be used effectively for the prevention of ulcer; however, their low doses are ineffective (Melcarne et al., 2016; Scally et al., 2018; Scheiman, 2016).

Cox-2-selective NSAIDs have significantly lower risk of GI adverse effects, whereas they have similar anti-inflammatory activity like nonselective NSAIDs. The risk of ulcer with Cox-2-selective NSAIDs appears similar to that associated with combination of a nonselective NSAID and PPI. While co-therapy of PPI with Cox-2-selective NSAIDs further decreases the risk of ulcers. A Cox-2-selective NSAID alone or in combination with PPI may be the preferred option in order to prevent ulcer or ulcer complications. The risk for cardiovascular events is considerably higher with Cox-2-selective NSAIDs; therefore, caution is advised (Melcarne et al., 2016; Scheiman, 2016).

Maintenance Therapy

Chronic acid-suppression (maintenance) therapy for the prevention of ulcer or ulcer complications is recommended for patients with a history of ulcer complications, frequent recurrence, heavy smoking, and NSAID use. PPIs at lowest effective doses are the preferred therapy. Alternatively, misoprostol may be used, but they often cause diarrhea (Satoh et al., 2016).

Idiopathic Ulcers

The increasing occurrence of idiopathic ulcers (i.e., *H. pylori*-negative and NSAID-negative ulcers) is a growing concern. The exact cause of idiopathic ulcers remains unknown, but several studies have reported hypersecretion of gastrin and gastric acid as the main cause. Despite no significant reduction in the incidence of bleeding or mortality with acid suppression therapy, guidelines recommend the use of PPIs for the management of idiopathic ulcers (Satoh et al., 2016; Wong et al., 2012).

Personalized Pharmacotherapy

Genetic polymorphism of the CYP2C19 isoform can cause significant difference in the metabolism of PPIs. For instance, almost all Asians are poor metabolizers of PPIs and thus require a low dose of PPIs. In contrast, majority of Caucasians are rapid metabolizers of PPIs and require higher doses. Prior knowledge of CYP2C19 genotype may help adjust the dose of PPIs, thus reducing the chances of treatment failure (Kuo et al., 2014). Moreover, increased drug plasma concentration in poor metabolizers may increase the risk of adverse events (Ma and Lu, 2011). Obese individuals may require higher doses of antibiotics (due to drug accumulation in fat tissues) in order to achieve optimum concentration at the gastric mucosal level. In addition, allergy to a specific antibiotic may prohibit its use in some patients. Patients with genetic predisposition, such as family history of ulcer or blood type "O," have a higher risk of ulcer and may require ulcer preventive therapy.

Role of Pharmacist

Patient care is an integrated collaborative process and pharmaceutical care is an essential component of patient care. In this regard, a pharmacist has a variety of roles and professional responsibilities in the pharmacotherapy of PUD. Some notable pharmacist's activities include development of a patient care plan, selection of an appropriate therapy, prevention of irrational drug use, patient education and counseling, monitoring of therapeutic outcome, dose adjustments, and identification/management of adverse drug reactions and drug interactions.

Successful and safe therapy always requires the active involvement of a pharmacist. According to the American Society of Health-System Pharmacists (ASHP), pharmacists are key to ensure that patients use prescribed regimens appropriately so that the clinical outcomes of associated PUD are optimal (ASHP, 2001). Many studies are available regarding the pharmacist's specific role in PUD as discussed below. Most of these have mainly targeted stress-ulcer prophylaxis. Pharmacist-managed programs involving educational intervention and medication reconciliation on patient-care rounds and at hospital discharge have shown a significant decrease in irrational drug use during hospitalization and upon discharge along with substantial cost savings (Buckley et al., 2015; Hatch et al., 2010). In intensive care settings, pharmacist-based quality improvement programs, educational initiatives and interactions

with physicians during ward rounds successfully reduce inappropriate drug use with a significant economic impact (Hammond et al., 2017; Masood et al., 2018). In nonintensive care settings, studies report that pharmacist-led educational sessions have shown to improve the appropriateness of prescribing by family practice resident physicians, resulting in minimization of patient risk and cost savings (Agee et al., 2015). Interprofessional collaboration among clinical pharmacists and hospital services can significantly reduce inappropriate drug use (Belfield et al., 2017). Standard treatment guidelines improve rational drug use. The pharmacist has a vital role in improving adherence with these guidelines (Rafinazari et al., 2016; Sanders et al., 2012). In specialized settings such as nephrology, the active involvement of a clinical pharmacist as a team member significantly contributes to reducing inappropriate prescribing of antiulcer drugs and their related cost (Mousavi et al., 2013). In the community pharmacy setting, the pharmacist can provide a verity of services about antiulcer medications such as PPIs. They can guide patients about the proper administration of medications, prescription refills, over-the-counter medications, treatment of minor ailments, physician referrals, and informed self-care decisions (Armstrong and Nakhla, 2016; Boardman and Heeley, 2015). A pharmacist-managed *H. pylori* clinic is also described by some studies (Morreale, 1995; Ravnan et al., 2002). A variety of services can be provided in these clinics to ambulatory patients such as overall patient assessment, screening for the presence of *H. pylori*, treatment of positive cases, adjustment of acid-suppressive drug regimens, patient education, and monitoring of adverse drug effects and therapeutic outcomes. The studies have shown that pharmacist-managed telephone-based clinics are also very effective to improve the overall outcome of *H. pylori* eradication therapy (Morreale, 1995; Ravnan et al., 2002).

Pharmacists' Patient Care Process

Pharmacists in collaboration with other healthcare professionals can optimize pharmacotherapy of PUD and improve therapeutic outcomes. These activities can be better described by applying the Pharmacists' Patient Care Process (PPCP), developed by the Joint Commission of Pharmacy Practitioners (Gonyeau et al., 2018). The main components of PPCP include the following: collect, assess, plan, implement, and follow-up (monitor and evaluate). Throughout this process, the pharmacist needs to collaborate, document, and communicate with physicians, other pharmacists, and other health care professionals for the purpose of providing safe, effective, and coordinated care. For PUD, specific pharmacists' activities related to each component of PPCP are presented in **Fig. 3**.

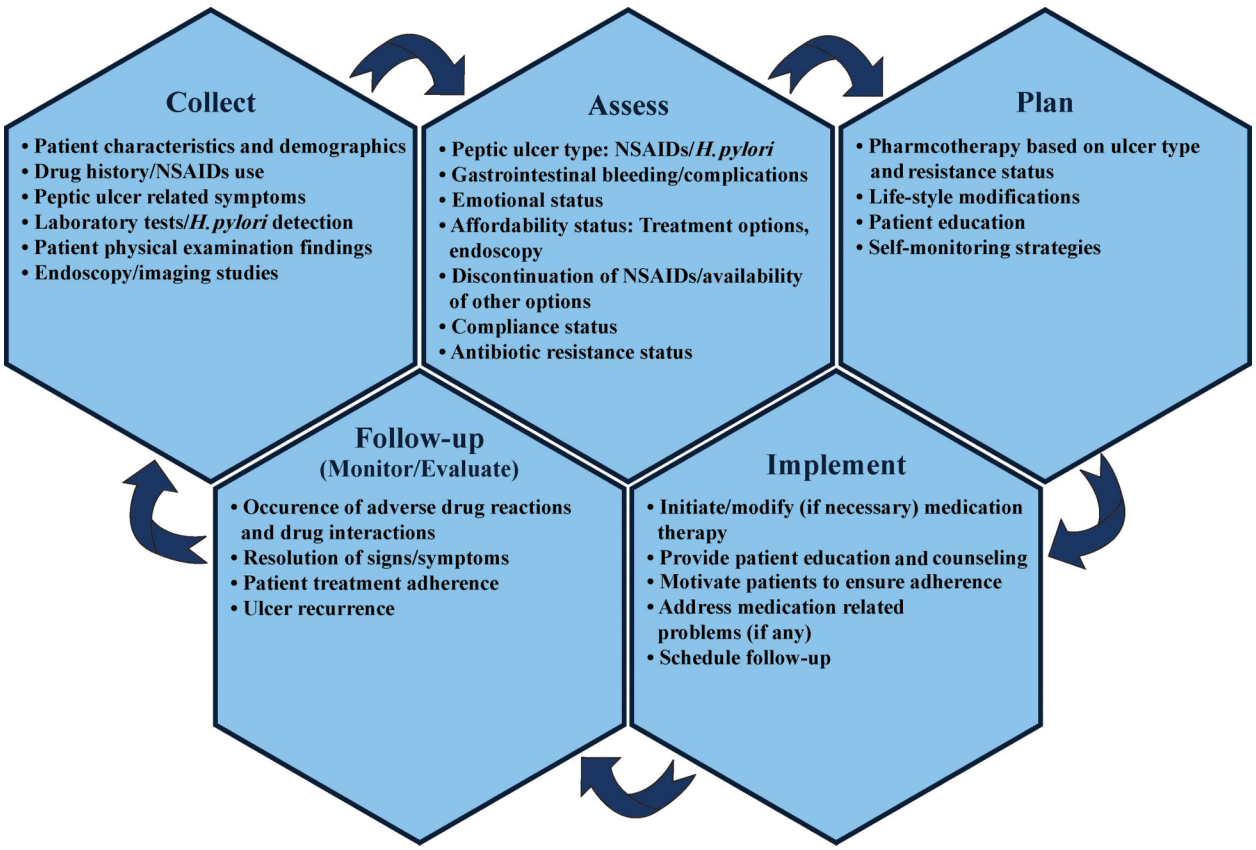

Figure 3 Pharmacists' patient care process for peptic ulcer disease.

Patient Education

Pharmacist-led patient education is one of the important interventions that contribute to improve medication adherence (Blom and Krass, 2011; Kini and Ho, 2018). Patient education should cover various areas related to pharmacological and non-pharmacological management. Appropriate administration of prescribed medicine is essential in order to minimize treatment failure and antibiotic resistance. Adherence to eradication therapy is a major challenge due to an increased number of drugs and frequent dosing. Patients must be educated to complete the treatment course even if symptoms disappear, seek pharmacist's advice when purchasing over-the-counter analgesics, and avoid over the counter NSAIDs and aspirin (paracetamol-based products are preferred). If NSAID therapy is necessary, then they should be administered with or after meals to reduce the risk of dyspepsia. Patients need to be well informed about the optimum time of administration of PPIs, the dose, and duration. PPIs should be administered 30–60 min before breakfast (if prescribed once daily) and dinner (if prescribed twice daily) along with other drugs. In the case of bismuth quadruple therapy, all medicines should be taken with meals except the PPI (Chey et al., 2017). Pregnant women should be warned against the use of misoprostol (Auffret et al., 2016). Patients need to be informed about the most common and/or serious potential adverse effects of therapy (**Table 5**). Drugs commonly employed for the treatment of ulcers may interact with other drugs (**Table 6**) when coadministered, thereby increasing the risk of adverse effects or treatment failure. Patients must be informed to avoid contraindicated and serious drug interacting combinations (**Table 6**). Patients should be advised to visit physicians if they develop blood in stools, black tarry stools, vomiting or abdominal pain. Patients with dyspepsia or reflux-like symptoms should be advised to take antacids and raise the head of the bed to improve nocturnal symptoms. Patients should be advised to avoid cigarette smoking, alcohol, spicy food, carbonated or caffeinated beverages, and NSAIDs (Bear et al., 2017).

Monitoring of Therapy Outcomes

The outcome of therapy in patients with uncomplicated ulcers is assessed through symptomatic relief, while patients having complicated or refractory ulcers may undergo *H. pylori* testing or endoscopy. At present, monitoring of ulcer healing following successful treatment through endoscopy is not recommended by most of the guidelines. However, monitoring the outcome has increased significantly, particularly in patients treated for *H. pylori*-associated ulcer due to the increasing prevalence of resistance and treatment failure. *H. pylori* infected individuals should be evaluated for eradication at least 4 weeks after completion of therapy (Lim et al., 2013). The urea breath test and fecal antigen test are the preferred noninvasive tests for confirmation of successful eradication. Monitoring is needed for persistent or recurrent symptoms of ulcer after completion of eradication therapy to ascertain the cause of treatment failure (resistance or nonadherence). Ulcer complications, particularly bleeding should be monitored as well (Laursen et al., 2012).

Adverse Drug Effects

Although PPIs are effective and safe, their use may be associated with headache, abdominal pain, nausea, and diarrhea. The use of antibiotics may cause nausea, diarrhea, abdominal pain, and oral or vaginal candidiasis (in women). Clarithromycin and metronidazole may cause taste disturbances. Metronidazole may cause disulfiram-like reactions in individuals who consume alcohol. Thus, alcohol must be avoided in patients prescribed metronidazole. Tetracycline causes photosensitivity and tooth discoloration (Drucker and Rosen, 2011; Vennila et al., 2014). Bismuth may cause dark discoloration of the tongue or stool. A detailed overview of adverse drug reactions associated with drugs used for the management of PUD is given in **Table 5**.

Drug Interactions

Drugs used for the management of PUD are associated with a variety of drug interactions (**Table 6**). PPIs increase the gastric pH, thereby affecting the absorption and bioavailability of a number of orally administered drugs such as ketoconazole and digoxin. PPIs also alter the absorption of a number of antiviral drugs including those used for the treatment of human immune virus infection (HIV), which may result in treatment failure. Therefore, caution is advised about the use of PPIs in HIV-positive individuals. PPIs and clarithromycin are potent inhibitors of the CYP2C19 enzyme, which may result in increased plasma levels and toxicity of a number of drugs such as warfarin, phenytoin, and diazepam. Rabeprazole may be prescribed if other drugs that are substrates of the CYP2C19 are coadministered. Similarly, antibiotics when coadministered with other drugs may also interact and result in treatment failure or drug-related adverse events. Important drug–drug interactions, their adverse outcomes, and management are given in **Table 6**.

Conclusions

A number of pharmacological approaches are available for the management of the disease. A thorough patient's assessment is needed in order to select appropriate therapy. Pharmacist involvement is vital for effective management of PUD. Some of the main pharmacist's roles include the development of a care plan, patient education, monitoring of therapeutic outcomes, dosing adjustment, and the management of adverse drug reactions and drug interactions.

Table 5 Adverse effects of drugs used for the management of peptic ulcer disease

Drugs	*Dermatological*	*Gastrointestinal*	*Genitourinary*	*Neurological*	*Others*
Omeprazole	Rash, *CLE, erythema multiforms, SJS, TEN*	*Gastritis, pancreatitis, CDD*, abdominal pain, constipation, diarrhea, flatulence, nausea, acid regurgitation, vomiting, *hepatic encephalopathy, hepatic necrosis, liver failure*	*Acute interstitial nephritis*	Asthenia, dizziness, headache	Hematologic: *Hemolytic anemia* Musculoskeletal: *Bone fracture, rhabdomyolysis* Respiratory: Upper respiratory tract infection Others: *Hypomagnesemia, angioedema*, fever
Esomeprazole	*CLE, erythema multiforms, SJS, TEN*	Abdominal pain, constipation, diarrhea, flatulence, nausea, xerostomia, *CDD, fundic gland polyposis of stomach*	*Acute interstitial nephritis*	Headache, somnolescence	Musculoskeletal: *Bone fracture, rhabdomyolysis* Others: *Anaphylaxis, angioedema, hypomagnesemia, cyanocobalamin deficiency*
Pantoprazole	*CLE, SJS, TEN*	Abdominal pain, diarrhea, flatulence, *atrophic gastritis, CDD, fundic gland polyposis of stomach*	*Acute interstitial nephritis*	Headache	Hematologic: *Thrombocytopenia* Musculoskeletal: *Bone fracture, rhabdomyolysis*
Rabeprazole	*CLE, erythema multiforms, SJS, TEN*	Abdominal pain, diarrhea, nausea, vomiting, *CDD, fundic gland polyposis of stomach*	*Acute interstitial nephritis*	Headache	Musculoskeletal: *Bone fracture, rhabdomyolysis* Others: *Anaphylaxis, SLE*
Lansoprazole	*CLE, erythema multiforms, SJS, TEN*	Abdominal pain, diarrhea, nausea, vomiting, *CDD, fundic gland polyposis of stomach, pancreatitis*	*Acute interstitial nephritis*	Headache	Musculoskeletal: *Bone fracture, rhabdomyolysis* Others: *Hypomagnesemia, anaphylaxis*
Ranitidine	*SJS, TEN*	Abdominal pain, constipation, diarrhea, *necrotizing enterocolitis in fetus, pancreatitis, cholestatic hepatitis, liver failure, abnormal LFT's*	–	Headache	Cardiovascular: *Bradyarrhythmia* Hematologic: *Agranulocytosis, aplastic anemia, pancytopenia, thrombocytopenia*
Famotidine	*SJS, TEN*	Constipation, diarrhea, *necrotizing enterocolitis in fetus*	–	Dizziness, headache, *seizure*	Musculoskeletal: *Rhabdomyolysis* Others: *Anaphylaxis, angioedema, pneumonia*
Cimetidine	–	*Gastric cancer, necrotizing enterocolitis in fetus, pancreatitis*	–	Psychotic disorder	Gynecomastia
Clarithromycin	*SJS, TEN, Henoch-Schonlein purpura*	Abdominal pain, diarrhea, taste alteration, indigestion, nausea, vomiting, CDD, *hepatitis, liver failure*		Headache, *cerebrovascular disease*	Cardiovascular: *Cardiovascular death, prolonged QT interval* Others: *Anaphylaxis, drug-induced eosinophilia and systemic symptoms, all cause death*
Amoxicillin	Rash, *erythema multiforms, SJS, TEN*	Diarrhea, nausea, vomiting, *CDD*	*Mycotic vulvovaginitis*	Headache	*Anaphylaxis*
Metronidazole	*SJS, TEN*	Abdominal discomfort, altered taste, diarrhea, nausea, *hepatotoxicity, hepatic failure*	Genital candidiasis, vaginal discharge, vaginal irritation, vaginitis, *hemolytic uremic syndrome*	Dizziness, headache, *seizure, aseptic meningitis, encephalopathy, peripheral neuropathy*	Hematologic: *Leukopenia* Others: Jarisch–Herxheimer reaction, *disorder of optic nerve, ototoxicity*
Tetracycline	Phototoxicity	–	–	*Bulging fontanelle, pseudotumor cerebri*	Tooth discoloration, *acidosis, azotemia, raised serum blood urea nitrogen*

(*Continued*)

Table 5 Adverse effects of drugs used for the management of peptic ulcer disease (*cont.*)

Drugs	*Dermatological*	*Gastrointestinal*	*Genitourinary*	*Neurological*	*Others*
Levofloxacin	*Erythema multiforms, SJS*	Diarrhea, nausea, *hepatitis, liver failure*	*Acute renal failure*	Dizziness, headache, insomnia, *disorientation, disturbed attention, Guillain-Barre syndrome, memory impairment, peripheral neuropathy, raised ICP, seizure, delirium, depression, hallucinations, paranoid disorder, suicidal psychotic disorder*	Cardiovascular: *Aortic aneurysm, cardiac arrest, prolonged QT interval, torsade de pointes, ventricular tachycardia* Hematologic: *Aplastic anemia, pancytopenia, thrombocytopenia purpura* Musculoskeletal: *Exacerbation of myasthenia gravis, tendon rupture, tendinitis* Others: Hypersensitivity reaction, anaphylaxis, retinal detachment, *hypoglycemia*
Furazolidone	Rash, *erythema multiforms*	Abdominal pain, diarrhea, GI bleeding, nausea, vomiting, hepatotoxicity, jaundice	Abnormal urinalysis, discolored urine, nephritis, oliguria	Dizziness, headache, insomnia, neuropathy, neurotoxicity, somnolescence, vertigo, giddiness, hypomania, agitation, psychotic disorder	Cardiovascular: Hypertension Hematologic: Agranulocytosis, anemia, raised eosinophil count, hemolysis, hemolytic anemia, leukopenia Others: Hypersensitivity reaction, disulfiram-like reaction, malaise, serum sickness, dyspnea, pulmonary eosinophilia, hypoglycemia
Rifabutin	Rash	CDD, altered taste	Discolored urine	Ocular discoloration, uveitis	Hematologic: *Neutropenia, thrombocytopenia* Others: *SLE*
Misoprostol	–	Abdominal pain, diarrhea, *gastrointestinal hemorrhage*	*Uterus rupture*	–	Cardiovascular: *Cardiac dysrhythmia, chest pain, myocardial infarction* Hematologic: Anemia, thromboembolic disorder Others: *Anaphylaxis, deafness, toxic shock syndrome, abortion related clostridial infection*
Bismuth subsalicylate	Rash, skin discoloration	Dark stool, black hairy tongue, nausea, diarrhea, gastralgia, constipation, GI bleeding, melena, hepatotoxicity	Nephrotoxicity	*Neurotoxicity*, headache, dizziness, encephalopathy, tinnitus	Cardiovascular: Mild hypotension Hematologic: Elevated hemoglobin Others: Anaphylaxis, hypercalcemia
Sucralfate	–	Constipation, *bezoar*	–	–	Aluminum toxicity in patients with renal failure, hyperglycemia

CDD, *Clostridium difficile* associated diarrhea; *CLE*, cutaneous lupus erythematosus; *GI*, gastrointestinal; *ICP*, intracranial pressure; *LFTs*, liver function tests; *SJS*, Stevens–Johnson syndrome; *SLE*, systemic lupus erythematosus; *TEN*, toxic epidermal necrolysis.

Note: Serious adverse effects are presented in italics.

Source: ASHP, 2018. Drug Information Monographs. AHFS DI Essentials. American Society of Health-System Pharmacists, Inc. Available from: https://www.drugs.com/monograph (ASHP, 2018); Lexicomp, 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc., U.S. (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available from: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018)

Table 6 Important drug interactions

Interacting drugs	*Potential adverse outcome*	*Remarks*
Omeprazole, esomeprazole, pantoprazole, rabeprazole and lansoprazole		
Cilostazol	May result in cilostazole toxicity	Consider reducing the dose of cilostazole
Citalopram	Increased risk of QT interval prolongation	Monitor patients for ECG changes and discontinue citalopram in patients with QTc interval >500 ms
Clopidogrel	Diminished efficacy of clopidogrel	Consider administration of rabeprazole or pantoprazole
Ketoconazole	Diminished efficacy of ketoconazole	Consider administration of ketoconazole with acidic beverage and monitor antifungal activity
Rilpivirine	Diminished efficacy of rilpivirine	Avoid concomitant use of both drugs
Saquinavir	May result in saquinavir toxicity	Monitor patients for GI symptoms, QT interval prolongation and DVT
Clarithromycin		
Cisapride	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs
Fluconazole	Increased risk of QT interval prolongation and torsade de pointes	Avoid concomitant use of both drugs
Ketoconazole	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs or monitor patients for ECG changes
Simvastatin	Increased risk of myopathy or rhabdomyolysis	Consider reducing the dose of simvastatin or administer fluvastatin
Ziprasidone	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs
Amoxicillin		
Tetracyclines	Diminished efficacy of amoxicillin	Avoid concomitant use of both drugs
Venlafaxine	Increased risk of serotonin syndrome	Monitor for tremors, muscle rigidity, tachycardia, diaphoresis, diarrhea, agitation or delirium. Avoid concomitant administration of both drugs
Warfarin	Increased risk of bleeding	Consider monitoring of INR and corresponding dose adjustment
Metronidazole		
Hydroxychloroquine	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs or monitor patients for ECG changes
Mebendazole	Increased risk of Stevens–Johnson syndrome or toxic epidermal necrolysis	Avoid concomitant administration of both drugs
Saquinavir	Increased risk of QT interval prolongation	Monitor patients for ECG changes and discontinue one or both drugs in patients with QT interval >480 ms
Warfarin	Increased risk of bleeding	Monitor INR or prothrombin time and sign/symptoms of bleeding
Tetracycline		
Cholera vaccine	Diminished efficacy of cholera vaccine	Avoid concomitant use of both drugs
Digoxin	Increased risk of digoxin toxicity	Monitor digoxin serum concentration with corresponding dose adjustment
Methoxyflurane	Increased to renal toxicity including fatality	Avoid concomitant administration of both drugs
Penicillin	Diminished efficacy of amoxicillin	Better to avoid concomitant use of both drugs
Levofloxacin		
Cisapride	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs or monitor patients for ECG changes
Fluoxetine	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs or monitor patients for ECG changes
Hydroxychloroquine	Increased risk of QT interval prolongation	Avoid concomitant use of both drugs or monitor patients for ECG changes
Theophylline	Increased risk of theophylline toxicity	Monitor theophylline concentration and make appropriate dose adjustment
Warfarin	Increased risk of bleeding	Consider monitoring of INR, no dose reduction of warfarin is required
Furazolidone		
Carbamazepine	Increased risk of serotonin syndrome	Monitor for tremors, muscle rigidity, tachycardia, diaphoresis, diarrhea, agitation or delirium. Avoid concomitant administration of both drugs
Fluoxetine	Increased risk of serotonin syndrome	Monitor for tremors, muscle rigidity, tachycardia, diaphoresis, diarrhea, agitation or delirium. Avoid concomitant administration of both drugs
Levodopa	Increased risk of significant hypertension	Avoid concomitant use of both drugs
Metoclopramide	Increased risk of significant hypertension	Avoid concomitant use of both drugs
Tramadol	Increased risk of serotonin syndrome or opioid toxicity	Avoid concomitant use of both drugs

(*Continued*)

Table 6 Important drug interactions (*cont.*)

Interacting drugs	*Potential adverse outcome*	*Remarks*
Rifabutin		
Artemether/lumefantrine	Diminished efficacy of artemether/lumefantrine	Avoid concomitant use of both drugs
Clarithromycin	Diminished efficacy of clarithromycin and increased risk of rifabutin adverse effects including uveitis	Consider decreasing rifabutin dose and monitoring for ocular inflammation
Hormonal contraceptives	Diminished efficacy of hormonal contraceptives	Consider alternate method of conception
Tramadol	Diminished efficacy of tramadol	Consider increasing the dose of tramadol
Voriconazole	Increased plasma concentration of rifabutin and decreased voriconazole plasma concentration	Avoid concomitant use of both drugs
Misoprostol		
Antacids	Diminished efficacy of misoprostol	Monitor for diarrhea, particularly with magnesium containing antacids. Consider reducing misoprostol dose or discontinue antacid
Phenylbutazone	May cause headache, dizziness and ataxia	If adverse effects occurs consider another NSAID
Bismuth subsalicylate		
NSAIDs	Increased risk of bleeding due to salicylate	Avoid concomitant use of both drugs
Sucralfate		
Digoxin	Diminished efficacy of digoxin	Consider increasing the dose of digoxin by 20%–40%
Ketoconazole	Diminished efficacy of ketoconazole	Avoid concomitant use of both drugs. Consider antifungal efficacy of ketoconazole

DVT, deep vein thrombosis; *ECG*, electrocardiogram; *INR*, international normalized ratio; *ms*, millisecond; *NSAIDs*, nonsteroidal anti-inflammatory drugs.
Source: ASHP, 2018. Drug Information Monographs. AHFS DI Essentials. American Society of Health-System Pharmacists, Inc. Available from: https://www.drugs.com/monograph (ASHP, 2018); Lexicomp, 2018. Drug Information Handbook. 26th ed. Wolters Kluwer Clinical Drug Information, Inc., U.S. (Lexicomp, 2018); Micromedex Drugdex, 2018. IBM Watson Health, Greenwood Village, Colorado, USA. Available from: https://www.micromedexsolutions.com/ (Micromedex Drugdex, 2018)

Glossary of Terms

Duodenal bulb It is the portion of the duodenum closest to the stomach.
Gastric metaplasia Transformation of the intestinal epithelial cells into an epithelium that resembles gastric epithelium.
***Helicobacter pylori* eradication therapy** Multidrug therapy comprising an acid-suppressing agent and at least two antibiotics intended to completely eliminate *Helicobacter pylori* infection.
Hyperchlorhydria A state of increased gastric acid level due to increased secretion of gastric acid.
Idiopathic ulcer Peptic ulcer disease in which the cause of ulceration is unknown.
Maintenance therapy Long-term acid suppression therapy in order to prevent the recurrence of peptic ulcer or its complications.
Melena Dark sticky feces containing partially digested blood.
Occult bleeding Bleeding that is not visible to the patient or physician.
Penetration A type of peptic ulcer complication in which ulceration develops a hole in the gastrointestinal lining and affects another organ.
Perforation A complication of peptic ulcer in which a hole develops in the lining of the gastrointestinal tract typically in the stomach or duodenum that opens into the peritoneal cavity.
Quadruple therapy A multidrug regimen comprising a proton pump inhibitor with three antibiotics; or a proton pump inhibitor with two antibiotics and bismuth salt.
Refractory ulcer Peptic ulcer that does not heal after 8–12 weeks of standard treatment.
Triple therapy A multidrug treatment regimen comprising a proton pump inhibitor with two antibiotics intended for the eradication of *Helicobacter pylori* infection.
Virulence The ability of *Helicobacter pylori* to infect a host.
Xiphoid process The cartilage at the lower end of the sternum.
Zollinger–Ellison syndrome A condition of abnormal production of gastrin that results in increased production of gastric acid.

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Management of Renal Disorders and the Pharmacist's Role: Acute Kidney Injury

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Learning Objectives

- Categorize AKI as pre-renal, intrinsic, or post-renal based on patient history, laboratory values and results of physical examination.
- Identify risk factors for AKI.
- Formulate preventive strategies to decrease the risk of developing AKI in high risk populations.
- Formulate a therapeutic plan to manage AKI.
- Identify medications/medications classes including herbal medicines associated with AKI.

Key concepts

- Acute Kidney Injury (AKI) is a common condition and is associated with high morbidity and mortality.
- AKI has been traditionally categorized based on three types of injury; pre-renal: renal hypoperfusion; intrinsic: structural damage to the kidney; and post-renal: obstruction within the urinary tract.

- There is no compelling evidence for any drugs to prevent or reverse AKI and the most effective strategies to prevent AKI include: maintaining adequate hydration and avoiding nephrotoxic medications; whilst supportive therapies such as renal replacement therapy, nutritional support, avoiding nephrotoxins, blood pressure, fluid and electrolyte management remain the mainstay of treatment.
- Dosing of drugs during AKI remain challenging as serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) are unreliable. Therapeutic drug monitoring is recommended for drugs with narrow therapeutic index or predominantly renally cleared medications.
- Hospital and community pharmacists can play huge role in AKI management. Pharmacists can help prevent AKI by assessing risk, optimizing drug therapy, adjusting drug dosages related to kidney function, monitoring of drugs and response to treatment, patient and other health care professionals' education and medication reconciliation.

Introduction

Acute Kidney Injury (AKI), is a common, harmful, potentially treatable disorder that is often under-recognized and is increasing in incidence globally (KDIGO, 2012). AKI manifests as an abrupt decline (hours to days) in glomerular filtration rate (GFR) and results in an accumulation of nitrogenous waste products such as blood urea nitrogen (BUN), serum creatinine (SCr), and commonly, a reduction in urine output (NICE, 2013). It is not a single disease entity, but a broad clinical syndrome encompassing various etiologies (specific kidney diseases, extra renal causes, etc.). The manifestations and clinical consequences of AKI can be quite similar regardless of the etiology. AKI is the new consensus term for acute renal failure (ARF) (NICE, 2013). The change in terminology is to standardize the definition of the syndrome as well as recognize that even small rises in serum creatinine are associated with important clinical consequences including increased risk of death (KDIGO, 2012; NICE, 2013).

However, despite the standardization in the definition and staging, progress in understanding the underlying pathophysiology, AKI continues to be associated with poor outcomes and remains a major unmet medical need without any pharmacological treatments that directly reverses the injury (Australian Institute of Health and Welfare, 2015; Lameire et al., 2013). AKI is strongly associated with serious short- and long-term complications, in particular increased mortality and morbidity, the development of chronic kidney disease (CKD) and high financial health care costs (Australian Institute of Health and Welfare, 2015; Lameire et al., 2013). Although AKI is increasingly being seen in primary care in people without any acute illness, it is much more common in the setting of acute or critical illness. It affects approximately 20% of hospitalized patients (older adults and critically ill being particularly affected) of whom 10% require renal replacement therapy (RRT) (Bellomo et al., 2012; Lameire et al., 2013).

Hence there is a need to increase an awareness of the condition among health care professionals (including primary care professionals) as early recognition along with supportive therapy is the focus of the management for those with AKI. Individuals at risk of an AKI, for example those with CKD, need to have their hemodynamic status closely monitored with exposure to nephrotoxins minimized (Bellomo et al., 2012). Assessments of individuals should include medical and surgical history, physical examination, medication use and laboratory tests. Pharmacists have an important role to play when it comes to AKI, both in terms of prevention and treatment, that is, reducing risk and avoidable harm, medication optimization in AKI, advising about drug dosing, and identifying and monitoring drugs that can cause kidney damage.

In this chapter, the definition and classification, incidence, clinical features, and etiologies of AKI are presented. Methods to recognize AKI, preventative strategies for patients at risk and management strategies for established AKI, and the role of pharmacist in AKI identification and management will also discussed.

Definition and Classification of Acute Kidney Injury

In recent years, there has been a paradigm shift in the understanding of AKI. Initially described and defined as a complete loss of kidney function (acute kidney failure (ARF)), it is now widely recognized that lesser degrees of kidney impairment have significant consequences (KDIGO, 2012; NICE, 2013). The significant re-examination of the definitions used in recent years is to recognize that AKI represents a heterogenous clinical syndrome with multiple causes rather than a specific disease and to encompass the entire spectrum of the syndrome from minor changes in kidney function to kidney failure which can influence prognosis and management (KDIGO, 2012; NICE, 2013).

The acute dialysis quality initiative first defined AKI with the RIFLE criteria (risk, injury, failure, loss, end stage) in 2004. The acute kidney injury network (AKIN) later supported the RIFLE criteria with minor modifications (Bellomo et al., 2004a; Mehta et al., 2007). **Table 1** lists an overview of all classification systems. The kidney disease: improving global outcomes (KDIGO) clinical practice guidelines working group in 2012 merged the two definitions in a recent guideline update and proposes a staging system that is extended to include pediatric patients (younger than 18 years) (KDIGO, 2012). AKI is now defined as an increase in SCr of $\geq$26.5 μmmol/L within 48 h of observation or 1.5 times baseline or greater, which is known to have occurred within 7 days, or a reduction in the urine volume below 0.5 mL/kg/h for 6 h (**Table 1**) (KDIGO, 2012).

All three staging systems have been validated across different patient populations with the staging correlated with mortality, cost, and length of stay. The KDIGO classification has shown to identify more patients with AKI and more predictive of

Table 1 RIFLE, AKIN and KDIGO Classification Schemes for AKI (KDIGO, 2012; NICE, 2013; Bellomo et al., 2012)

RIFLE category	*SCr and GFR criteria*	*Urine output criteria*
Risk	SCr increase to 1.5-fold or GFR decrease >25% from baseline	Urine output <0.5 mL/kg/h for ≥6 h
Injury	SCr increase to twofold or GFR decrease >50% from baseline	Urine output <0.5 mL/kg/h for ≥12 h
Failure	SCr increase to twofold or GFR decrease >75% from baseline, or SCr ≥4 mg/dL (≥354 μmmol/L) with an acute increase of at least 0.5 mg/dL (44 μmmol/L)	Anuria for ≥12 h
Loss	Complete loss of function (RRT) for >4 weeks	
ESKD	RRT >3 months	
AKIN criteria	*SCr criteria*	*Urine output criteria*
Stage 1	Increase in SCr of ≥0.3 mg/dL (≥26.4 μmmol/L) within 48 h; or increase 1.5–1.9 times from baseline	Urine output <0.5 mL/kg/h for ≥6 h
Stage 2	Increase in SCr 2.0–2.9 times from baseline	Urine output <0.5 mL/kg/h for ≥12 h
Stage 3	Increase in SCr ≥3.0 times from baseline or SCr ≥4.0 mg/dL (≥354 μmmol/L) or RRT treatment	Urine output <0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h
KDIGO criteria	*SCr criteria*	*Urine output criteria*
Stage 1	Increase in SCr of ≥0.3 mg/dL (≥26.4 μmmol/L) within 48 h; or increase 1.5–1.9 times from baseline	Urine output <0.5 mL/kg/h for 6–12 h
Stage 2	Increase in SCr 2.0–2.9 times from baseline	Urine output <0.5 mL/kg/h for ≥12 h
Stage 3	Increase in SCr ≥ 3.0 times from baseline or SCr ≥4.0 mg/dL (≥354 μmmol/L) or RRT treatment or in if <18 years decrease in eGFR to <35 mL/min/1.73 m^2	Urine output <0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

in-hospital mortality than RIFLE and AKIN classification (Fujii et al., 2014; Luo et al., 2014; Zeng et al., 2014). However, despite the significant contributions of these definitions towards the definition and management of AKI, they have limitations. All three staging systems suffer from the same inherent weakness as they rely on SCr and urine output to identify AKI and several factors can affect SCr and urine output. Firstly, there is a lag time for the increase in SCr which usually takes 24–48 h to increase following injury. Secondly, although urine output reduction occurs earlier it is a very nonspecific marker as it depends upon several factors. Furthermore, patients with AKI can have a 24 h urine output less than 50 mL (anuric), less than 500 mL/day (oliguric) or more than 500 mL/day (nonoliguric) (Bellomo et al., 2012). Lastly, the definitions depend on a reference value to describe 'baseline' renal function. Ideally, this value should reflect the patient's steady state kidney function just before the episode of AKI. However, this SCr value may not be available for all patients at the time of diagnosis and various surrogate estimates are frequently used (such as back calculating a baseline SCr using an assumed normal eGFR of 75 mL/min/1.73 m^2 in cases of missing data). This method needs to be interpreted with caution as it can overestimate incidence of AKI (Siew et al., 2010; Zavada et al., 2010). Hence, significant research is currently underway with new biomarkers (such as Cystatin C) for AKI to replace or complement SCr. In addition to diagnosing AKI earlier, these markers may also provide information about the etiology of AKI (Koyner, 2012; Spahillari et al., 2012).

Epidemiology

The incidence of AKI is increasing worldwide (Evans et al., 2017; Lameire et al., 2013; Mesropian et al., 2016; Siew and Davenport, 2015; Waikar et al., 2006). The epidemiology of AKI varies widely depending upon the patient population studied and the criteria used to evaluate the patients. Differences in data capture, AKI awareness, monitoring, recognition, and clinical practice make comparisons between health care settings and periods difficult.

AKI occurs much more commonly in the hospital as compared to the community setting (Evans et al., 2017). Community-acquired AKI has an incidence of approximately 1%. Most of these patients develop AKI on the background of CKD and is referred as "acute" on chronic renal impairment (Wonnacott et al., 2014). Pre-renal AKI accounts for most of these cases (~70%), followed by obstructive uropathy and intrinsic AKI due to various etiologies (~17% and 11%, respectively) (Meola et al., 2016). In contrast, hospital-acquired AKI has an incidence ranging from about 4% to 7.2% with pre-renal and intrinsic AKI from nephrotoxic medications accounting for most cases (Liangos et al., 2006). The incidence of AKI is much higher in patients who are critically ill ranging from 30% to 60% with high mortality rates reported especially among those who require RRT (~50%) (Bellomo et al., 2012; Goldberg and Dennen, 2008; Hoste et al., 2015). Common risk factors for AKI are listed in **Table 2** (KDIGO, 2012). The high incidence and substantial morbidity and mortality of AKI demand a logical approach to its early diagnosis, prompt recognition and management of its complications (Wonnacott et al., 2014).

Table 2 Risk factors for AKI (KDIGO, 2012)

Exposure:
- Critical illness
- Sepsis
- Circulatory shock
- Burns
- Trauma
- Cardiac surgery
- Major non-cardiac surgery
- Nephrotoxic medications (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], aminoglycosides)
- Iodinated contrast media

Susceptibility factors
- Volume depletion
- Older age
- Female sex
- Black race
- Chronic kidney disease
- Other chronic disease (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anemia

Etiology

Once AKI is discovered it is important to determine the underlying cause of AKI because the initial evaluation and management is tailored to the particular cause. AKI most frequently results of tubular and vascular factors and can be divided into three broad categories based upon the anatomical location of the injury associated with the precipitating factors. The terms "pre-renal", "intrinsic" and "post-renal" have been traditionally used to narrow the differential diagnosis of AKI (Glassock et al., 2001). Pre-renal AKI results from decreased renal perfusion in the setting of undamaged parenchymal tissue; Intrinsic AKI, results from structural damage to the kidney and is considered under different anatomical components of the kidney (vascular supply, glomerular, tubular, and interstitial disease); and post-renal AKI results from obstruction of urine downflow from the kidney (Glassock et al., 2001).

Pre-renal AKI

Pre-renal AKI caused by an under perfusion of an otherwise normal kidney. It is a normal physiological response to hypotension or hypovolaemia, resulting in intense renal conservation of sodium and water at the expense of a decreased GFR. The hallmark of pre-renal AKI is that renal function is reversible with appropriate therapy and once underlying cause is corrected. Pre-renal AKI represents the most common form of AKI cases (Badr and Ichikawa, 1988).

Impaired renal perfusion with a resultant fall in glomerular capillary filtration pressure is the most common cause of pre-renal AKI. The kidneys are usually adept at regulating their blood supply over a variety of perfusion pressures, and such regulation is highly effective in healthy individuals. However, a marked reduction in renal perfusion may overwhelm autoregulation and precipitate an acute fall in GFR (Badr and Ichikawa, 1988). It is important to note that with lesser degrees of renal hypoperfusion, glomerular filtration pressures and GFR are maintained by afferent arteriolar vasodilation (mediated by vasodilatory prostaglandins) and efferent arteriolar vasoconstriction (mediated by angiotensin II).

In this setting AKI, may be precipitated by drugs that impair afferent arteriolar dilation or efferent arteriolar vasoconstriction (nonsteroidal antiinflammatory drugs [NSAIDs] and ACEI or ARBs, respectively) (Ungprasert et al., 2015; Zhang et al., 2006). Some common causes for pre-renal AKI are presented in **Table 3**. These include extracellular fluid volume depletion resulting from renal losses (diuretics, osmotic diuresis in hyperglycemia) or extrarenal losses (gastrointestinal losses) fluid sequestration in liver failure or other edematous states, or inadequate perfusion pressure caused by heart failure. Treatment is imperative, as failure to restore the renal blood flow can lead to intrinsic renal AKI with tubular cell injury (Glassock et al., 2001).

Intrinsic AKI

Intrinsic AKI results from direct damage to the kidney, it involves the renal parenchyma and is categorized based on the injured structures within the kidney; vasculature, glomeruli, tubules, and interstitial (Bellomo et al., 2012). **Table 4** lists some of the causes that can damage the renal parenchyma and lead to intrinsic AKI.

Table 3 Common causes for pre-renal AKI (Workeneh and Batuman, 2018)

- *Volume depletion:*
  - Renal losses (diuretics, osmotic diuresis in hyperglycemia)
  - Gastrointestinal losses-vomiting, diarrhea
  - Cutaneous losses-burns, Steven–Johnson syndrome
  - Hemorrhage
  - Pancreatitis
- *Decreased cardiac output:*
  - Heart failure
  - Pulmonary embolism
  - Acute myocardial infarction
  - Sever valvular disease
  - Abdominal compartment syndrome (tense ascites)
- *Systemic vasodilation:*
  - Sepsis
  - Anaphylaxis
  - Anesthetics
  - Drug overdose
- *Afferent arteriolar vasoconstriction:*
  - Hypercalcemia
  - *Drugs** - NSAIDs, amphotericin B, calcineurin inhibitors, radiocontrast agents*
  - Hepatorenal syndrome
- *Diseases that decrease effective arterial blood volume:*
  - Hypovolemia
  - Heart failure
  - Liver failure
  - Sepsis

Table 4 Causes of intrinsic AKI (Basile et al., 2012; Brivet et al., 1996; Praga and Gonzalez, 2010; Waikar et al., 2006)

- *Vascular*
  - Atheroemboli,
  - Malignant hypertension,
  - Scleroderma crisis,
  - Renal artery or vein thrombosis,
  - Trauma,
  - Microangiopathy [thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS)]
- *Glomerular*
  - Nephritic
    - Goodpasture's syndrome,
    - Lupus nephritis,
    - Acute post infectious glomerular nephritis
  - Nephrotic
    - Focal segmental glomerulosclerosis (FSGS)
    - Minimal change disease
- *Tubular*
  - Ischemic ATN
    - Hemorrhage,
    - Sepsis,
    - Shock,
    - Trauma,
    - Hypotension,
    - Pre-renal azoetemia
  - Nephrotoxic ATN[a] (aminoglycosides, radiocontrast, amphotericin B[a])
  - Endogenous toxins
    - Hemoglobinuria,
    - Myoglobinuria
- *Interstitial*
  - Drugs[a] (Penicillin antibiotics, omeprazole[a])
  - Infection (Staphylococcal, Streptococcal)
  - Systemic Disease (Sjögren syndrome, systemic lupus nephritis)

[a]Drug induced kidney disease is discussed in detail in Table 10.

Post-renal AKI

Post-renal AKI or obstructive nephropathy accounts for less than 5% of all cases of AKI and may develop as a result of obstruction at any level with the urine collection system (Lameire et al., 2013). This results in an increased pressure within the renal collecting systems and resulting in a reduced GFR, reduced tubular reabsorption of sodium and water, and also acquire renal tubular acidosis, and other abnormalities of tubular function. Bladder outlet obstruction is the most common cause of obstructive nephropathy, and

Table 5 Causes of obstructive nephropathy (Workeneh and Batuman, 2018)

- *Bladder outflow obstruction*
  - Benign prostatic hypertrophy
  - Prostate cancer
  - Infiltrative bladder cancer
  - Neurogenic bladder
- *Ureteric obstruction*
  - Bilateral stone disease
  - Crystal deposition (urate, sulphonamides, acyclovir, cisplatin, indinavir**)
  - Pelvic tumors
  - Papillary necrosis
  - Retroperitoneal fibrosis
  - Radiation fibrosis
  - Renal calculi
  - Urethral strictures

is often a result of a prostatic process (hypertrophy, cancer, or infection) (Basile et al., 2012). Blockage can also occur at the ureters secondary to blood clots or nephrolithiasis or due to crystal precipitation by some medications; however, these are relatively uncommon (Workeneh and Batuman, 2018). **Table 5** lists some of the causes for obstructive nephropathy. Most causes of post-renal AKI are amenable to therapy, and the prognosis is generally good depending upon the underlying disease (Workeneh and Batuman, 2018).

Clinical Presentation and Diagnosis

The initial signs or symptoms of AKI are highly variable and dependent on the underlying etiology. Early recognition and cause identification are critical, as they directly affect the outcome of AKI. One of the first steps in the diagnostic process is to determine whether the change in renal function is acute, chronic or acute in a patient with known CKD (acute on chronic renal failure) (Bellomo et al., 2012). Early or mild AKI may be asymptomatic. Frequent presenting symptoms include weakness, anorexia, generalized malaise, and nausea. Patients should be evaluated for their change in fluid and electrolyte status. Patients may exhibit signs of hypovolemia or hypervolemia. Signs of hypovolemia may include tachycardia, orthostatic hypotension, dry mucous membranes, decreased skin turgor, cool extremities, and sunken eyes. Signs of hypervolemia may include edema and weight gain. Reduced urine output may present as anuria (<50 mL/24 h) or oliguria (50–500 mL/24 h) in hospitalized patients, although some patients may be nonoliguric (>500 mL/24 h) (Workeneh and Batuman, 2018). Some additional signs of AKI include; confusion or altered mental status, fever, signs of uremic encephalopathy (asterixis, stupor, papilledema, or coma), arrhythmias (due to electrolyte imbalances and acidosis), rash (indicative of AKI as a result of an allergic reaction), uremic odor, pruritis, flank pain, fasciculations, muscle cramps, pericardial effusion or pericardial rub (pericarditis), distended bladder or enlarged prostate (post-renal cause). Livedo reticularis or blue toe syndrome, indicative of AKI caused by atheroembolism. The classic triad of fever, rash and eosinophilia suggest allergic interstitial nephritis and should prompt a review of medications. However, the triad occurs uncommonly (Workeneh and Batuman, 2018).

Laboratory studies, complemented by history and physical examination, form the foundation for the diagnosis. An elevated SCr and decreased urine output are primary indicators for AKI (**Table 1**). Laboratory tests for diagnosis and initial evaluation include: serum chemistry, urine chemistry and sediment analysis assessment to ascertain concentration: albuminuria and total proteinuria; and the presence or absence of hematuria, pyuria, renal tubular epithelial cells, granular and cellular casts (Bellomo et al., 2012). Renal ultrasonography of the kidneys may be warranted if obstruction is suspected. Additional tests may be required to assess complications, systemic diseases or diseases in other organ systems, and hemodynamic status in critically ill patients (Workeneh and Batuman, 2018).

Albuminuria is preferred over total protein for the evaluation of kidney diseases, is a marker of glomerular damage and frequently occurs in parenchymal kidney diseases other than ATN (KDIGO, 2012; NICE, 2013). Increased red or white blood cells in the urine may indicate urinary tract lesion while the presence of renal tubular epithelial cells or granular or cellular casts in the sediment indicates localized lesion in the kidney. Renal ultrasonography is the preferred imaging study (>90% sensitivity) as it is not associated with radiation exposure or contrast administration, may be performed to assess the size and shape of the kidney and to determine if there is any obstruction (Bellomo et al., 2004a, 2012; Carrero et al., 2017; KDIGO, 2012; NICE, 2013). Tests for urine concentration may help distinguish between decreased kidney perfusion from ATN. The glomerular filtrate is isotonic with plasma; concentration of the urine requires intact tubular function. Concentration of the urine in the setting of AKI indicates decreased kidney perfusion and preserved tubular function. Absence of urine concentration indicates decreased kidney perfusion and preserved tubular function.

Table 6 Characteristics of different types of AKI (Burke, 2016)

	Pre-renal	*Intrinsic (ATN and AIN)*	*Post-renal*
History and clinical presentation	Volume depletion CHF Drugs: NSAIDs, ACEI and ARBs	Prolonged pre-renal state Nephrotoxins (Aminoglycosides, contrast) Vasculitis Glomerulonephritis	Kidney stones BPH cancer
Physical examination	Hypotension Dehydration Ascites	Rash, fever (with AIN)	Distended bladder Enlarged prostate
Serum BUN/SCr ratio	>20:1	15:1	15:1
Urine sodium	<20 mEq/L	>40 mEq/L	>40 mEq/L
FENa	<1%	>2%	>2%
Urine osmolality	High urine osmolality	Low urine osmolality	Low urine osmolality
Urine sediment	Normal	Muddy brown granular casts; tubular epithelial casts	Variable; may be normal
Urine WBC	Negative	2–4+	Variable
Urine RBC	Negative	2–4+	1+
Proteinuria	Negative	Positive	Negative

Other tests are also frequently required to assess for causes and complications of AKI. Blood urea nitrogen (BUN):creatinine ratio may also be useful to provide additional information on the underlying type of AKI (Bellomo et al., 2004a, 2012; Carrero et al., 2017; KDIGO, 2012; NICE, 2013). Patients electrolytes (sodium, potassium, magnesium, calcium, phosphorous, and bicarbonate) levels should be measured to identify complications (KDIGO, 2012; NICE, 2013). Other additional investigations may include venous or arterial blood gases for interpretation of acid–base disorders, complete blood count, liver function tests, muscle enzymes; imaging of the heart and lungs; and blood and body fluids cultures for infectious diseases (KDIGO, 2012; NICE, 2013). A summary of the characteristics of different types of AKI is presented in **Table 6**.

Prevention and Management

AKI can contribute significantly to the dysfunction of other organs, such as heart, lung, brain, and liver, and is associated with significant mortality. Hence primary prevention and early diagnosis of AKI are of central clinical importance. Once AKI is detected then secondary prevention to attenuate the effects of injury and treatment of consequences of injury are necessary (KDIGO, 2012; Bellomo et al., 2012).

Risk Assessment

The first step in preventing AKI is an adequate risk assessment. The initial care of patients at risk should be focused on identification, and if possible reversal of risk factors. **Table 2** summarizes the risk factors in different settings (KDIGO, 2012).

Ensure Adequate Hydration

Regardless of the nature of the insult, hemodynamic stabilization with optimization of cardiac output and blood pressure is a key factor in the prevention of AKI. The general aim is to optimize volume status based on physiological measurements, to maintain adequate hemodynamic status and cardiac output to ensure renal perfusion, and to avoid further insults such as hypotension or hypovolemia (KDIGO, 2012; NICE, 2013). Hence, fluid management is an important intervention for patients both in the initiation and extension phase of AKI. However, it is important to note that assessing the volume status is not without challenges, particularly in patients in the ICU or those with severe congestive heart failure where it can lead to worsening of symptoms (KDIGO, 2012; NICE, 2013). Therefore, the extent of fluid volume expansion needs to be balanced against the unwanted consequences of fluid accumulation and overload (KDIGO, 2012).

Prevention of Contrast Medium Nephropathy

Patients at risk of contrast induced AKI (CI-AKI) should receive intravenous hydration, the morning of the procedure or immediately before the intervention in case of emergency interventions (Trivedi et al., 2003). The prevention of CI-AKI consensus working panel recommends that preventative measures should be initiated in those with eGFR <60 mL/min/1.73 m^2 (KDIGO, 2012). The volume of the contrast administered should be lowered as much as possible as it has been shown to be a risk factor and independent predictor of CI-AKI. It is also important to avoid administration of contrast within 48–72 h of previous contrast administration (Taylor et al., 1998; Trivedi et al., 2003).

N-Acetylcysteine (NAC) is a tripeptide analogous to glutathione able to cross cellular membranes (Inda-Filho et al., 2014). NAC may reduce vasoconstriction and oxygen free radical generation after the administration of contrast material thereby reducing some of the cellular damage associated with post ischemic and nephrotoxic AKI (Inda-Filho et al., 2014). Several meta-analyses have concluded that NAC can lower the risk of CI nephropathy in high-risk patients and is recommended due to its low cost and excellent safety. In practice both hydration and NAC are combined in patients at high-risk for CI nephropathy (KDIGO, 2012; Mueller et al., 2002).

Glycemic Control

Glycemic control in critically ill patients is important as stress hyperglycemia and insulin resistance are common during critical illness and are associated with increased mortality (KDIGO, 2012; NICE, 2013). However, studies investigating aggressive blood glucose control have reported conflicting results with some studies showing no benefit, increased hypoglycemia and increased mortality whilst others are showing a reduction in the incidence of AKI. Whether there is any clear benefit in preventing or ameliorating AKI is still unclear and current KDIGO guidelines recommend maintaining appropriate control of blood glucose concentration in the range of 6.1–8.3 mmol/L (KDIGO, 2012; NICE, 2013).

Prevention of Nephrotoxin-Induced AKI

Amphotericin

Nephrotoxicity due to amphotericin occurs in one-third of the patients treated with amphotericin with the risk significantly higher in those treated with high doses. It is important to note that lipid formulation of amphotericin have less nephrotoxicity compared to conventional form (Australian Medicines Handbook, 2018). However, further studies are needed to clarify the nephrotoxicity across different formulations as available studies are not directly comparable with differences in definitions of nephrotoxicity, patient groups and study designs. Moreover, alternative antifungal agents such as caspofungin, voriconazole are recommended to be used in high risk patients rather than conventional amphotericin (Australian Medicines Handbook, 2018).

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, Non-Steroidal Anti-Inflammatory Drugs

NSAIDs should be avoided in patients with compromised renal function as they inhibit cyclooxygenase and block prostaglandin induced vasodilation of the afferent arteriole, thereby reducing GFR and renal blood flow.

Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs) despite their benefits can cause deterioration of kidney function through the efferent arteriolar vasodilation and reducing the intraglomerular pressure in renal impairment can result in reduced GFR. In patients with impaired renal function, SCr may increase after starting treatment or increasing the dose (usually stabilizes within the first 2 months). If increase is <30% or GFR reduction is <25%, there is no need to adjust dose. However, if increase is >30% (or GFR reduction >25%), in addition to investigating other causes a dose modification or discontinuation of the medication is recommended (Australian Medicines Handbook, 2018; Chronic Kidney Disease (CKD), 2012; Ludlow et al., 2017). It is also important to avoid combination of ACE/ARBs with NSAIDs as it contributes towards further deterioration of kidney function with along with diuretics (commonly known as "triple whammy"). It can result in pre-renal AKI in high risk patients (Australian Medicines Handbook, 2018; Chronic Kidney Disease (CKD), 2012).

Aminoglycosides

Aminoglycosides typically results in nonoliguric AKI with decreased urine concentration ability in AKI. Nephrotoxicity usually occurs 5–10 days after the initiation of the drug. Because of its toxicity KDIGO recommend avoiding the use of aminoglycosides in patients with AKI and those at risk of AKI unless no suitable alternative exists. In general, multiple daily administration of aminoglycosides correlates with nephrotoxicity, hence once daily administration of aminoglycosides should be considered in people with risk of AKI (Hughes et al., 2018; KDIGO, 2012).

Summary of Medications Used in the Prevention of AKI

A variety of drugs have been trialled in preventing AKI with most of them not showing any significant benefit in preventing AKI or improving health outcomes. A summary of some of the drugs used in the prevention of AKI is listed in **Table 7** (Bellomo et al., 2012; KDIGO, 2012; NICE, 2013).

Treatment of AKI

General Management

Appropriate management requires timely diagnosis of the clinical condition as there is no specific treatment that can reverse AKI or speed up the recovery. Another key question is whether AKI can be managed with non-dialytic therapies or if RRT is necessary. Initial management of established AKI includes careful assessment of the cause of renal dysfunction and the patient's volume status. The

Table 7 Summary of drugs used in the prevention of AKI

Drugs	*Rationale*	*Evidence*	*Results*
Dopamine	To increase renal blood flow to the kidney	RCTs	No effect on kidney function or mortality *Currently not recommended to prevent or treat AKI* (KDIGO, 2012)
Fenoldopam	Increase renal blood flow to the renal cortex and outer medulla	• Small RCTs • Meta-analysis	• No effect on Kidney function • Beneficial effect on kidney function Fenoldopam was shown to reduce the risk of AKI in postoperative or critically ill patients. However further studies are required. *Currently not recommended to prevent or treat AKI* (Aravindan et al., 2006; KDIGO, 2012)
Loop diuretics	Diuretic use is associated with worsening of kidney function and should be stopped if AKI is due to pre-renal causes.	• RCTs • Meta-analysis	Does not reduce in-hospital mortality associated with AKI, risk of requiring dialysis or the number of dialysis sessions required *Not recommended to prevent or treat AKI except to manage hypervolemia* (Ho and Sheridan, 2006; Karajala et al., 2009; KDIGO, 2012)
N-Acetyl cysteine	NAC may reduce vasoconstriction and oxygen free radical generation after the administration of contrast material thereby reducing some of the cellular damage associated with post-ischemic and nephrotoxic AKI	RCTs Meta-analysis	Variable beneficial effect in contrast induced nephropathy 600–1200 mg BID before and the day of contrast administration along with saline or IV bicarbonate (Inda-Filho et al., 2014; KDIGO, 2012; Mueller et al., 2002)
Natriuretics (Nesiritide)	Increase renal blood flow, urine production and reduce inflammation	RCT	AKI rates were lower in those undergoing cardiac surgery, however, no effect on RRT requirement or length of stay Further studies are required. *Currently not recommended to prevent or treat AKI* (Ejaz et al., 2009; KDIGO, 2012; NICE, 2013)

main goal is to maintain adequate hemodynamic status to ensure renal perfusion, avoidance of further kidney injury, reducing extrarenal complications, maintaining other organ functions and try to restore patient's renal function to pre-AKI baseline function (KDIGO, 2012; NICE, 2013).

Identification and management of AKI should be prompt. Pre-renal AKI should be managed by hemodynamic support and volume replacement. Post-renal AKI should be managed by removing the cause of obstruction. Loss of kidney function associated with other clinical conditions such as heart failure and liver failure include management of the comorbid precipitating event. In patients with acute or chronic renal impairment full recovery of kidney function to pre-AKI levels is unlikely (Bellomo et al., 2012; KDIGO, 2012; Kshatriya et al., 2012; NICE, 2013).

Hydration and Management of Volume Status

It is important to note that AKI may develop in the setting of volume depletion or overload and either condition may occur during the course of AKI. Oliguric AKI is more likely to result in volume overload and has been associated with poor outcomes (Godin et al., 2013). It is also important to avoid volume overload to prevent life threatening pulmonary edema, increased intra-abdominal pressure, renal venous congestion and decreased eGFR. On the other hand, volume depletion should be avoided because it can delay recovery from AKI (Godin et al., 2013; KDIGO, 2012). Hence, maintaining and managing the volume status is imperative and challenging at the same time particularly in those who are critically ill. Frequent monitoring of fluid intake and output, bodyweight, volume status, electrolytes with administration or restriction of fluid depending on the results are important (Godin et al., 2013; KDIGO, 2012).

The main goal of fluid therapy is to maintain or restore effective intravascular volume to ensure adequate tissues perfusion. First line therapies of volume resuscitation consist of crystalloids such as isotonic saline or balanced solutions. Colloids may be used for patients with burns or liver disease (Bellomo et al., 2004b; Finfer et al., 2004; Perel and Roberts, 2007; Young et al., 2015). Treatment of volume overload in patients with AKI can sometimes include using high doses of loop diuretics, these are given as multiple doses throughout the day or as infusion. In critically ill patients with vasomotor shock, vasopressors such as dopamine or norepinephrine may be used in conjunction with fluids in order to maintain adequate hemodynamics and renal perfusion (Bellomo et al., 2004b; Finfer et al., 2004; KDIGO, 2012; NICE, 2013; Perel and Roberts, 2007; Young et al., 2015).

Electrolyte Management

The initial management of electrolytes should start with medical management and proceed to RRT when medical management is no longer satisfactory.

Sodium Disorders

Hypernatremia and fluid retention are common complications of AKI. Total daily sodium intake should be monitored since excessive amounts may contribute to diuretic therapy failure (KDIGO, 2012; NICE, 2013). Several commonly administered medications especially antibiotics contain significant amount of sodium and can contribute to hypernatremia.

Hyponatremia is more common in AKI associated with heart failure, liver failure or diuretics. In these settings, water restriction to below output levels is important. Sodium restriction is usually necessary to treat fluid overload and edema. In patients with true volume depletion with associated pre-renal AKI, isotonic saline will need to be administered to correct both disorders (Bellomo et al., 2012; KDIGO, 2012; NICE, 2013).

Acid–Base Balance

Metabolic acidosis is the most common acid–base abnormality caused by reduced regeneration of sodium bicarbonate and failure to eliminate ammonium ions. In addition, accumulation of phosphate and anions such as sulphate, urate, hippurate, hydroxy propionate, furan propionate, and oxalate are contributory (KDIGO, 2012; NICE, 2013). However, despite the retention of anions in many patients' anion gap remains within normal limits. Sodium bicarbonate may be administered to treat metabolic acidosis as a complication of AKI if serum bicarbonate levels fall below 15–18 mmol/L. However, care should be taken to avoid volume overload (KDIGO, 2012; NICE, 2013).

Potassium Disorders

The most common electrolyte disorder encountered in patients with AKI is hyperkalemia, as more than 90% of potassium is renally excreted (Bellomo et al., 2012; KDIGO, 2012; NICE, 2013). Hyperkalemia can affect the cardiac conduction and can result in life threatening cardiac arrhythmias, so frequent monitoring of potassium is essential. It is important to identify and remove all other oral or IV sources of potassium including dietary restriction of potassium and drugs which retain potassium (e.g., ACEI/ARBs). Treatment of severe hyperkalemia (serum potassium >6.5 mmol/L or with electrocardiographic changes), IV administration of calcium gluconate to reduce the risk of arrhythmias is urgently needed followed by insulin plus dextrose/beta-adrenergic-agonists or sodium bicarbonate (if there is no concern of fluid overload) to shift extracellular potassium intracellularly (KDIGO, 2012; NICE, 2013). These effects are temporary and must be accompanied by measured to remove potassium from the body. The onset of action with insulin and dextrose is usually within 20–30 min and the effect last for about 2–6 h. Sodium bicarbonate-potassium lowering effects is most prominent in patients with metabolic acidosis (Hewitt et al., 2012). Beta-adrenergic agonists are less preferred for hyperkalemia as they have more side effects (KDIGO, 2012; NICE, 2013).

The potassium lowering must be sustained by administration of saline, loop diuretics and cation exchange resins such as sodium polystyrene sulphonate or calcium resins (KDIGO, 2012; NICE, 2013). For patients without oliguria, high dose of loop diuretics can be used to increase urine output and enhance potassium excretion. For patients with oliguria sodium polystyrene sulphonate or calcium resins can be used to induce osmotic diarrhea and fecal potassium loses (KDIGO, 2012; NICE, 2013). A summary of the drugs used in the management of hyperkalemia is presented in **Table 8** (Bellomo et al., 2012; KDIGO, 2012; NICE, 2013).

Calcium, Phosphorous and Magnesium Disorders

High phosphate and low calcium is common in patients with AKI. Hyperphosphatemia results due to reduced elimination of phosphate by the kidney, which in turn reduces the calcium levels resulting in hypocalcaemia. Other causes for low calcium could include low calcitriol production or increases resistance to parathyroid hormone (PTH). However, in most cases the levels of calcium reduction are mild to moderate and can be corrected easily (KDIGO, 2012; NICE, 2013; Workeneh and Batuman, 2018). The first step to correct calcium is to control phosphate by dietary phosphate restriction and oral phosphate binders (KDIGO, 2012; NICE, 2013). Calcium-based phosphate binders and other phosphate binders can be used in this setting.

Nutritional Considerations

AKI often results in protein energy malnutrition because of poor intake and high catabolic rate. Loss of the normal physiological and metabolic functions of the kidney and hypercatabolic response to stress and injury often has a significant impact on the metabolism of nutrients. Nutrition support should provide adequate calories with restricted potassium and phosphate, preventing protein-energy wasting with concomitant metabolic complications, promoting wound healing and tissue repair, supporting immune system function, and reducing mortality (Dellinger et al., 2008).

Table 8 Summary of the drugs used in the management of hyperkalemia

Treatment	*Onset of action*	*Reduction in potassium*	*Duration of action*	*Action*
Calcium gluconate	1–3 min	Nil	30–60 min	Stabilize the heart
Insulin (+dextrose)	15–30 min	0.65–1 mmol/L	4–6 h	Intracellular potassium uptake
Salbutamol (nebulized/IV)	30 min	0.6–1.0 mmol/L	2–4 h	Intracellular potassium uptake
Ion exchange resins	2–3 h	0.5–1.0 mmol/L	4–6 h	Potassium excretion
Hemodialysis	Immediate	≤1.5 mmol/L/h	While dialysis is ongoing	

Table 9 Indications for RRT (Bertsche et al., 2009; KDIGO, 2012; NICE, 2013)

Indications for RRT	*Clinical setting*
A: acid–base abnormalities	Metabolic acidosis
E: electrolyte disturbance	Hyperkalemia
I: Intoxication	Lithium, salicylates etc
O: Fluid overload	Pulmonary edema not responding to diuretics
U: Uremia	Symptoms of uremia or complications (e.g., encephalopathy, pericarditis)

KDIGO guidelines for patients with AKI recommend a total energy intake of 20–30 kcal/kg/day, preferably provided via the enteral route. Minimal nitrogenous waste production is desirable in AKI; however, protein restriction is no longer recommended in the management of AKI. KDIGO guidelines recommend protein goals of 0.8–1.0 g/kg/day in non-catabolic patients, 1.1–1.5 g/kg/day in patients receiving RRT, and a maximum of 1.7 g/kg/day in hypercatabolic patients or those who are receiving continuous RRT (KDIGO, 2012).

Renal Replacement Therapy

RRT is used to manage the complications of AKI. Common indications include life-threatening change in fluid, electrolyte, and acid-base balance that require urgent correction (**Table 9**) (Workeneh and Batuman, 2018). RRT should be discontinued as soon as it is no longer required, because the kidney function has recovered enough to meet the patient's needs or life sustaining therapy is no longer the goal (Bellomo et al., 2012; KDIGO, 2012; NICE, 2013; Workeneh and Batuman, 2018).

The four main modalities of acute RRTs are acute intermittent hemodialysis (iHD); continuous renal replacement therapy (CRRT); prolonged intermittent renal replacement therapy (PIRRT); sustained low-efficiency dialysis (SLED); and acute peritoneal dialysis (Levey and James, 2017).

CRRT is the most popular, however, practice patterns may vary depending upon cost, technology and reimbursement policies. It is a slow, continuous form of therapy delivered 24 h a day in the ICUs and is usually used for hemodynamically unstable patients (Levey and James, 2017). In patients who are hemodynamically stable, conventional intermittent HD may be used. However, more frequent sessions may be required to correct some of the fluid and electrolyte abnormalities. PIRRT provides prolonged dialysis using slower flow rates over longer sessions (>6 h/session). Studies comparing continuous versus intermittent HD in critically ill patients have found no significant differences in clinical outcomes such as length of hospitalization, and mortality (Palevsky, 2009; Pannu et al., 2008; Vinsonneau et al., 2006).

Drug Dosing in AKI

Optimizing drug dosing during AKI is often very challenging. SCr and eGFR are less accurate to guide dosing in the non-steady state than in the steady state (Levey and James, 2017). Other factors that could influence drug dosing include patients' residual drug clearance, fluid accumulation, and RRT. Expert consensus recommend close monitoring of drug response in patients with known nephrotoxicity or other toxicities and for renally eliminated drugs serum drug concentrations (Levey and James, 2017). It is also important to note that renal impairment can also independently impair non-renal drug elimination (Vilay et al., 2008). Further, the use of dosing guidelines based on the data derived from patients with stable CKD may not affect the clearance and volume of distribution in critically ill AKI patients. It is also important to note that in AKI adverse effects of many medications are increased. For example; bleeding risk of anticoagulants is increased in AKI due to the uremic platelet dysfunction; decreased clearance of low molecular weight heparins and direct oral anticoagulants. Pharmacists have a huge role to play in determining the drug dosing and determining the dosing interval in patients with AKI and those on dialysis (Levey and James, 2017).

Pharmacist's Role in AKI

Pharmacists being medication experts are in an ideal position to contribute to reduce the burden of AKI. Community pharmacists are often the first point of contact for most patients as they are easily accessible and are in an excellent position to identify patients who are at high risk of developing AKI (**Table 2**); engaging with them, supporting and developing their understanding of medication risks, and monitoring medicines that can cause kidney problems (CPPE, in press). Community pharmacists should be aware that drug-induced nephrotoxicity can often be predicted because it is more common in certain patients and in specific clinical situations. An example of such an intervention is with use of "triple whammy", that is, the use of ACEI/ARBs, diuretics and nonsteroidal antiinflammatory drugs (NSAIDs) in combination increases the risk of AKI in patients with risk factors for AKI (**Table 2**). Australian adverse drug reactions bulletins have highlighted "triple whammy" as a cause for community-acquired AKI (Thomas, 2000).

In the hospital setting, pharmacists play an essential part of the inter-professional team supporting prescribing decisions for patients with AKI, optimizing drug therapy, adjusting drug dosages related to kidney function, laboratory monitoring, patient and other health care professionals' education and medication reconciliation (Baum and Harder, 2010; Bourne and Choo, 2012; Gharekhani et al., 2014; St Peter et al., 2013; Such Díaz et al., 2013; Thomas, 2000). Pharmacists play an important role in

Table 10 Nephrotoxic agents leading to AKI

• Pre-renal azotaemia	Antihypertensives NSAIDs	
• Small vessel disease	NSAIDs ACEI/ARBs Radiocontrast agents Cyclosporine Tacrolimus Cocaine	Renal vasoconstriction
	Cyclosporine Tacrolimus Mitomycin C Quinine Clopidogrel	Thrombotic microangiopathy
• Glomerular disease	Penicillamine Hydralazine Propylthiouracil	Rapidly progressive GN
• Acute tubular necrosis	Amphotericin B Aminoglycosides Foscarnet Tenofovir, ciclofovir, adefovir Cisplatin Carboplatin Cyclosporine Tacrolimus zoledronate Ifosfamide Acetaminophen Herbal medications Radiocontrast agents Lithium	
• Acute interstitial nephritis	Antibiotics (Penicillins, cephalosporins, ciprofloxacin, sulphamethoxazole) NSAIDs Proton pump inhibitors Loop diuretics Cimetidine Allopurinol Phenytoin Mesalazine	
• Intratubular obstruction	Acyclovir Sulphonamides Indinavir Foscarnet Methotrexate Oral phosphate (high dose)	Crystal nephropathy
• Post-renal obstruction	NSAIDs, compound analgesics Anticholinergics, tricyclic antidepressants	Papillary necrosis Urinary retention

identifying drugs associated with nephrotoxicity and educating patients, health care professionals about drug-induced AKI and recommending alternatives to nephrotoxic medicines (Kane-Gill and Bauer, 2017).

Several diagnostic and therapeutic agents have been associated with drug-induced AKI and identification and avoidance of nephrotoxic agents in AKI is critical in the management of AKI. Nephrotoxicity is often reversible upon discontinuation of the individual drug, however in some cases it can lead to AKI or CKD. There are many mechanisms of nephrotoxicity and include alterations in the renal hemodynamics, direct tubular toxicity, generation of allergic reactions resulting in interstitial nephritis, and intratubular obstruction. Although the list is extensive the more common medications associated with AKI are listed in **Table 10** (Levey and James, 2017; Workeneh and Batuman, 2018).

In recent years, the use of herbal medicines and dietary supplements to promote health and treat chronic diseases has increased significantly. Many of these products are available as over the counter (OTC) in pharmacies and some may harm kidneys. Hospital pharmacists are also vital in liaising with community pharmacists and general practitioners (GPs) to ensure a continued supply of medication, monitoring or introduction of compliance aid as needed to ensure quality use of medicines in renal impairment patients (Saran et al., 2016).

Table 11 highlights some of the potential renal side effects of herbal medicines (Isnard Bagnis et al., 2004).

Table 11 Examples of kidney syndromes induced by herbal medicines (Isnard Bagnis et al., 2004)

Hypertension	*Glycyrrhiza* species (Chinese herbal teas, gancao, boui-ougi-tou)
	Ephedra species (ma huang)
Acute tubular necrosis	Traditional African medicine: toxic plants (*Securidaca longepedunculata*, *Euphoria matabelensis*, *Callilepis laureola*, Cape aloes), or adulteration by dichromate
	Chinese medicine: *Taxus celebica*
	Morocco: Takaout roumia (paraphenylenediamine)
Acute interstitial nephritis	Peruvian medicine *(Uno degatta)*
	Tung Shueh pills (adulterated by mefenamic acid)
Fanconi syndrome	Chinese herbs containing Aristolochic acids (AAs) (*Akebia* species, boui-ougi-tou, Mokutsu)
	Chinese herbs adulterated by cadmium
Papillary necrosis	Chinese herbs adulterated by phenylbutazone
Chronic interstitial renal fibrosis	Chinese herbs or Kampo containing AAs (*Aristolochia* species, *Akebia* species, Mu Tong, Boui, Mokutsu)
Urinary retention	*Datura* species, *Rhododendron molle* (atropine, scopolamine)
Kidney stones	Ma huang (ephedrine)
	Cranberry juice (oxalate)
Urinary tract carcinoma	Chinese herbs containing AAs

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Management of Renal Disorders and the Pharmacist's Role: Chronic Kidney Disease

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Learning Objectives

- Classify the stage or category of CKD based on patient history, physical examination, and laboratory values
- Identify risk factors for the progression of CKD and formulate management strategies to slow down the progression of CKD
- Assess for the presence of common complications of CKD
- Develop a plan to manage common complications of CKD
- Identify medications/medications classes that are associated with nephrotoxicity and required dosage adjustment in kidney disease

Key Concepts

- Chronic kidney disease (CKD) is defined by a decline in kidney function (i.e., an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2) and/or at least 3 months of structural or functional kidney damage (presence of albumin in urine).
- GFR is estimated through measuring serum creatinine (SCr) via GFR estimating equations, with chronic kidney disease epidemiology collaboration (CKD-EPI) equation the currently preferred equation. Albuminuria is measured by urine albumin/creatinine ratio: >30 mg/g indicating albuminuria.
- CKD is commonly associated with hypertension, diabetes, and cardiovascular disease (CVD).
- Early stages of CKD are often asymptomatic, causing CKD to be untreated, leading to further progression of kidney damage and worse prognosis.
- Although many patients with CKD progress to end-stage kidney disease (ESKD) and require renal replacement therapy (RRT), the majority die of nonrenal causes, particularly premature CVD.
- In patients with CKD it is important to monitor electrolyte levels, parathyroid hormone, and sodium bicarbonate levels to detect complications of CKD, including CVD, anemia, bone mineral disease, and acidosis.

- A growing body of evidence indicates that pharmacist services for CKD patients, including medication reconciliation and medication therapy management, positively affect clinical and cost outcomes, including lower rates of decline in glomerular filtration rates, reduced mortality, and fewer hospitalizations and hospital days, but more robust research is needed.

Introduction

Chronic kidney disease (CKD) is increasingly being recognized as a significant and growing public health problem, especially as our population ages (Radhakrishnan et al., 2014; Bruck et al., 2015; Khanal et al., 2015; Bruck et al., 2016). It is defined as a decline in kidney function (i.e., an eGFR of < 60 mL/min/1.73 m^2) and/or kidney damage (presence of albumin in the urine) lasting for 3 months or more (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). Currently, more than 322 million individuals are affected by CKD worldwide, and the number of patients with end-stage kidney disease (ESKD) treated with dialysis or transplantation globally exceeds 2.6 million people (Anand et al., 2013; Jha et al., 2013).

In Australia, around 1.7 million Australians (1 in 10) aged ≥18 years have clinical evidence of CKD (Chronic Kidney Disease, 2012; Australian Institute of Health and Welfare, 2017). However, CKD typically has no symptoms, with less than 10% of the people with CKD being aware that they have CKD. This means that over 1.5 million Australians are unaware that they have indicators of CKD. CKD is associated with an increased mortality rate, as well as an elevated risk of several comorbidities and adverse outcomes, including anemia, acute kidney injury, falls, and heart failure (Australian Institute of Health and Welfare, 2017). People with CKD also require extensive hospital services, particularly those with ESKD who need regular dialysis or a kidney transplant to survive (Chronic Kidney Disease, 2012; Australian Institute of Health and Welfare, 2017).

Definition and Staging of CKD

The definition of CKD has evolved over the past decade with advances in the knowledge of the prognosis (Chronic Kidney Disease Prognosis Consortium et al., 2010; Matsushita et al., 2010) According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines published in 2002, CKD is defined by structural and functional abnormality of the kidney (manifested by abnormalities in the composition of blood or urine or abnormalities in imaging tests), with or without decreased GFR (<60 mL/min/1.73 m^2) for 3 months (National Kidney Foundation, 2002). The staging system was modified by kidney disease improving global outcomes (KDIGO) in 2012 to reflect independent contributions of eGFR, albuminuria, and cause of CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). According to KDIGO, CKD is defined as abnormalities of kidney structure or function for more than 3 months. These abnormalities may be seen as persistent markers of kidney damage or GFR <60 mL/min/1.73 m^2 (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

Serum creatinine (SCr) is the most common filtration marker used to estimate GFR and carry out staging of CKD. The best available and currently most widely used equation to estimate GFR is the CKD epidemiology collaboration equation (CKD-EPI) (Johnson et al., 2012a,b). Urine albumin is recommended over urine protein assessment and is generally standardized to urine creatinine to normalize to 24-h excretion and account for any differences in concentration (albumin-to-creatinine ratio [ACR]) (Johnson et al., 2012a,b). The criteria for the definition of CKD is summarized in **Table 1**.

Epidemiology

Patients with CKD experience high morbidity and mortality rates, which result in a huge economic burden to the healthcare system due to hospitalization and the high costs of RRTs such as dialysis and transplantation (World Health Organization, 2013). The age-adjusted death rates attributable to CKD increased by 36.9% in 188 countries (1990–2013) and are now the 19th leading cause of life lost (World Health Organization, 2013). It is estimated that 8%–16% of the general population has CKD around the world and over 2.6 million people globally are undergoing RRT (dialysis or transplantation) (Anand et al., 2013; Jha et al., 2013; Australian Institute of Health and Welfare, 2017).

Table 1 Summary criteria for the definition of chronic kidney disease (CKD) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

CKD is defined as abnormalities in kidney function or structure, present for 3 months or more with implications for health. These may include:	
Decreased GFR	GFR < 60 mL/min/1.73 m^2
Markers of kidney damage	• Albuminuria (AER ≥30 mg/24 h; uACR ≥30 mg/g [≥3 mg/mmol]) • Urine sediment abnormalities • Electrolyte and other abnormalities caused by tubular disorders • Abnormalities detected through histology • Structural abnormalities detected through imaging • History of kidney transplantation

The prevalence of CKD increases disproportionately in older people because of the age-related decline in GFR of approximately 8 mL/min with each decade of life after the age of 40 years (Hanlon et al., 2011). People with CKD have the highest prevalence of CVD, diabetes, and hypertension, and is strong risk factor for future cardiovascular events including stroke and death (Chronic Kidney Disease, 2012; Tonelli et al., 2012; Australian Institute of Health and Welfare, 2017). It is reported that in people with CKD, the risk of dying from cardiovascular events is 20 times higher than the risk of requiring dialysis or transplantation (Keith et al., 2004; Mathew and Corso, 2009; Chronic Kidney Disease, 2012; Tonelli et al., 2012). Research suggests that people with CKD have 20% higher mortality than the general population (Chronic Kidney Disease, 2012). Hence, focusing on factors contributing to the decline in renal function, rather than on whether the decline is inevitable with age, helps in the prevention and treatment of the disease.

Evidence-based guidelines demonstrate that early recognition, proper management, and early referral have the greatest effect on slowing the progression of CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014). These strategies include better management of comorbidities such as hypertension, and diabetes and discontinuation of medications that are nephrotoxic or considered problematic in renal impairment (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014). It is reported that if CKD is detected early and managed appropriately, then the deterioration in kidney function can be reduced as much as 50%, and in some cases may be reversible (Johnson, 2004). Hence, many countries (e.g., the United States and Australia) have now implemented public health initiatives to reduce the proportion of people with CKD by increasing awareness; increase the proportion of the people with CKD who know they have impaired kidney function; reduce the rate of new cases of ESKD, and reduce mortality associated with CKD (World Health Organization, 2013).

Etiology and Risk Factors

Globally, diabetes mellitus (DM) is the most common cause for CKD responsible for 40%–50% of new cases of ESKD (Chronic Kidney Disease, 2012; National Kidney Foundation, 2012). Hypertension has shown to be responsible for about 25% of new cases of CKD, with glomerulonephritis accounting for 10% of the cases. Some of the other causes of CKD include urinary tract disease, polycystic kidney disease, and lupus (Chronic Kidney Disease, 2012; Phoon, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014). A summary of the risk factors for susceptibility and initiation of CKD is presented in **Table 2** (Inker et al., 2014).

Pathophysiology

Progression of CKD occurs gradually over several years and largely depends upon the main cause of the disease (Chronic Kidney Disease, 2012). Patients with diabetes often have glomerular mesangial expansion, while in patients with hypertension,

Table 2 Risk factors for susceptibility to, initiation, and progression of CKD (Inker et al., 2014)

Susceptibility/initiation risk factors	
Diabetes	Obesity
Hypertension	Systemic infections/inflammation
Cardiovascular disease	Urinary tract infections
Dyslipidemia	Urinary stones
Obesity	Urinary tract obstruction
Hyperuricemia	Neoplasia
Smoking	Family history
Low socioeconomic status	Acute kidney injury
Autoimmune diseases	Reduced kidney mass
Polycystic kidney disease	Exposure to drugs, e.g., analgesics
Nephrotoxins (NSAIDs, heavy metal exposure)	
Advanced age	
Racial or ethnic minority: Aboriginal and Torres Strait Islander people, African American	
Low income/education	
Low birth weight	
Exposure to chemical	
Progression risk factors	
Hyperglycemia	
Elevated blood pressure	
Proteinuria	
Smoking	

nephrosclerosis is often the problem (Tomino, 2014). However, the key elements to the progression of ESKD includes loss of nephron mass, glomerular capillary hypertension, and proteinuria. Exposure to the initiation risk factors can result in loss of nephron mass. However, a normal kidney consists of approximately 1 million nephrons, each of which contributes to the total GFR. In face of a renal injury, the kidney has an innate ability to maintain GFR. Despite progressive destruction of nephrons, the remaining nephrons compensate through the process of autoregulation. This nephron adaptability allows for continued normal clearance of plasma solutes. Plasma levels of substances such as urea and creatinine start to show measurable increases only after the total GFR has decreased to 50%.

After the initial loss of nephrons and the reduced perfusion pressure and GFR, renin release from the juxtaglomerular apparatus increases and converts angiotensinogen to angiotensin 1, which is then converted to angiotensin 2 (AT2). AT2, although a potent vasoconstrictor of both afferent and efferent arterioles, preferentially affects the efferent arterioles leading to increased pressure within the glomerular capillaries and resultant increased filtration. The higher intraglomerular capillary pressure impairs the size selective function of glomerular permeability barrier, resulting in increased urinary excretion of proteins. Furthermore, development of intraglomerular hypertension may also result in the development of systemic hypertension, which along with proteinuria is a risk factor for cardiovascular mortality and morbidity (Lopez-Novoa et al., 2010; Tomino, 2014; Gajjala et al., 2015).

Filtration of proteins (albumin, immunoglobulins, and cytokines) can further promote loss of nephrons through toxicity to the kidney tubular cells. Studies have shown that these proteins increase the production of inflammatory and vasoactive cytokines such as endothelin and monocyte chemoattractant protein (MCP1) and activate complement in the tubules. These events ultimately can result in scarring of the interstitial and progressive loss of nephrons and further reduced GFR (Lopez-Novoa et al., 2010; Tomino, 2014; Gajjala et al., 2015).

Clinical Presentation and Assessment

CKD is usually asymptomatic until later stages of stages 4–5 and is usually detected by routine blood testing (Chronic Kidney Disease, 2012; Phoon, 2012). Patients need to be asked about symptoms as they are often non-specific. Early identification and management have shown to reduce the progression of CKD as well as the risk of CVD (Chronic Kidney Disease, 2012; Phoon, 2012). A detailed medical history that includes medical conditions, family history of kidney disease, use of medications, and other risk factors listed in **Table 3** is warranted. Patients are often required to repeat blood tests (SCr, eGFR, and ACR) within 3 months to confirm the chronicity of kidney disease. Elevated blood urea nitrogen (BUN), creatinine, and low GFR are the best overall indicators of poor kidney function. eGFR is estimated by multivariable (SCr, age, sex, and race) prediction equations normalized to body surface area (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014).

The modification of diet in renal disease (MDRD) equation has been commonly used in clinical laboratories until recently but following KDIGO recommendations this has been replaced by the CKD-EPI which is the preferred reporting equation (Johnson et al., 2012a). Direct GFR clearance methods or Cystatin C measurement may confirm CKD in situation when SCr-based GFR is less accurate. Serum chemistries may also show hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, hyperglycemia, and decreased bicarbonate (Richards et al., 2008; Phoon, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014). Proteinuria is an important diagnostic and prognostic marker, and its presence indicates a higher risk of progression of CKD and CVD (Chronic Kidney Disease, 2012; Phoon, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). KDIGO recommends that the preferred method for assessing proteinuria is by the measurement of urine ACR using the early morning urine sample (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). Albuminuria is graded according to the A1 to A3 criteria highlighted in **Table 4**. Urinalysis may also reveal hematuria or formed elements such as casts.

Imaging of the kidneys may be required to identify the cause, taking into account the risk of administered contrast media. Structural abnormalities such as polycystic kidney disease, renal artery stenosis, and small kidney size can be detected by imaging studies such as ultrasound and magnetic resonance imaging (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014).

Table 3 KDOQI stages in CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

Stage of renal disease	*Damage*	*GFR (mL/min/1.73 m^2)*
Increased risk of developing kidney disease	Risk factors for CKD (diabetes, HTN, family history)	≥90
Stage 1	Kidney damage with normal GFR	≥90
Stage 2	Kidney damage with mild decrease in GFR	**60–89**
Stage 3	Moderate decrease in GFR	**30–59**
Stage 4	Severe decrease in GFR	**15–29**
Stage 5	Kidney failure	<**15**

Table 4 KDIGO categories of albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

Category	*Classification*	*ACR (mg/g)*	*Daily excretion (mg/24 h)*
A1	Normal to mildly increased	**<30**	**<30**
A2	Moderately increased	**30–300**	**30–300**
A3	Severely increased albuminuria	**>300**	**>300**
	Nephrotic-range proteinuria		**>3000**

Management of CKD

Patients with CKD should be frequently evaluated to assess the progression of CKD, identify complications, and manage the complications to reduce morbidity and mortality. Both pharmacological and non-pharmacological recommendations are applied as part of the general approach to the management of CKD and should include a multidisciplinary approach to address these. Multidisciplinary teams include renal physicians, general practitioners, social workers, dieticians, nurses, and pharmacists, and depend upon the severity of CKD (Chronic Kidney Disease, 2012).

Non-Pharmacological Therapy for CKD

Non-pharmacological management of CKD includes diet and lifestyle interventions aimed to reduce the risk factors for CKD progression or development of comorbidities such as CVD. These include smoking cessation, weight loss if appropriate, and physical activity of at least 30 min daily 5 times a week similar to other chronic disease states (Chronic Kidney Disease, 2012). People with CKD >30 mL/min should be encouraged to eat and adequate diet according to the energy requirements in line with dietary recommendations for other chronic disease states (Chronic Kidney Disease, 2012). However, depending upon the severity of CKD, dieticians should be involved to provide appropriate advice regarding nutrition for patients with eGFR <30 mL/min/1.73 m^2. The nutritional recommendations as per KDIGO are highlighted in **Table 5** (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

General Approach to the Management of CKD

Treatment of CKD is aimed at reducing the progression of CKD by treatment specific to the underlying disorders and alleviating the electrolyte and hormonal abnormalities that can lead to symptoms or complications.

Factors Causing Progression of CKD

It is well known that once CKD is developed kidney function decline usually occurs at a predictable rate in the absence of further insult to the kidney. Hence, management of factors causing progression of CKD is critical (Johnson, 2004).

Diabetes

The management of diabetes in patients with CKD includes reduction of proteinuria and achievement of desired blood pressure and HbA1c to slow down the progression of CKD (Chronic Kidney Disease, 2012; National Kidney Foundation, 2012; Phoon, 2012). All patients with Type 1 DM should begin annual monitoring for albuminuria 5 years after diagnosis while in Type 2 DM patients should have annual monitoring of albuminuria immediately after diagnosis (Chronic Kidney Disease, 2012; National Kidney Foundation, 2012; Phoon, 2012). Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)

Table 5 Nutritional recommendations in patients with CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

Daily intake	*Predialysis CKD*	*Hemodialysis*	*Peritoneal dialysis*	*Comments*
Protein (g/kg/IBW)	0.6-1.0 1.0 for patients with NS	1.1-1.2	1.0-1.3	Patients protein intake is often individualized depending upon the nutritional status, phosphate levels, dialysis adequacy
Energy (kcal/kg BW)	35 (<60 years) 30–35 (>60 years)	35 (<60 years) 30–35 (>60 years)	35 (<60 years) 30–35 (>60 years)	For PD patients including dialysis calories
Sodium (mmol)	<100 (more if salt wasting)	<100	<100	
Potassium	Reduce if hyperkalemic			
Calcium	In CKD stages 3–5 total intake of calcium should not exceed 2000 mg/day			Includes dietary calcium
Phosphorous	Reduce: level dependent on protein intake			

Table 6 BP target in patients with CKD and albuminuria

Severity of albuminuria	*Goal BP*	*Level of evidence*
Normal to mild albuminuria	140/90 mmHg	1B
Moderate to severe albuminuria	130/80 mmHg	2D

should be used with any degree of proteinuria, even if the patient is not hypertensive. ACEIs/ARBs are also the preferred agents for the management of blood pressure in patient's diabetic nephropathy (Chronic Kidney Disease, 2012; National Kidney Foundation, 2012; Phoon, 2012). The goal BP reading in patients with diabetic nephropathy as per KDIGO is highlighted in **Table 6** (National Kidney Foundation, 2012).

It is important to monitor patient's potassium levels and kidney function closely once an ACEI/ARBs are initiated as these agents can worsen kidney function or aggravate hyperkalemia in CKD. Providing the reduction in kidney function is < 25% within 2 months of starting therapy, the ACEI/ARB should be continued (Chronic Kidney Disease, 2012; Australian Medicines Handbook, 2018). If the reduction in GFR is more than 25% below the baseline value, the ACEI or ARB should be ceased and consideration given to referral to a nephrologist. Combined therapy with ACEI and ARB should be avoided except with specialist advice. Similarly, caution should be exercised if baseline K+ is ≥5.5 mmol/L, as rises in serum K+ of approximately 0.5 mmol/L are expected. Most patients will need diuretic in combination with an ACEI/ARB (thiazide with stages 1–3 and loop diuretics in stages 4–5). If BP is higher than 160/100 mmHg, consideration may be given to start with a two-drug regimen. However, combination therapy with ACEIs and ARB should be avoided (Chronic Kidney Disease, 2012; KDIGO Blood Pressure Work Group, 2012; National Institute for Health and Care Excellence, 2014; Australian Medicines Handbook, 2018).

The HbA1c target in patients with diabetic nephropathy should be about 7% (53 mmol/mol). However, higher targets may be considered in patients at a higher risk of hypoglycemia, limited life expectancy, or advanced CKD (National Kidney Foundation, 2012). It is important to note that HbA1c values may be falsely low in CKD patients as red blood cell life is decreased in patients with CKD. Metformin is the drug of choice for the management of Type 2 DM. However, it requires dosage adjustment in CKD and is contraindicated in unstable CKD or severe CKD (<15 mL/min) (Chronic Kidney Disease, 2012; Australian Medicines Handbook, 2018). Most of the oral antidiabetic agents such as gliptins (except linagliptin), sodium glucose cotransport inhibitors, and glucagon-like-peptide 1 (GLP-1) analogues do require dosage adjustment in CKD and contraindicated in CKD depending upon the severity of CKD. **Table 13** lists some of the drugs that need to be used with caution in CKD. Furthermore, the requirement of insulin in patients with CKD is generally less because of reduced metabolism of insulin by the kidney as GFR declines (Chronic Kidney Disease, 2012; Australian Medicines Handbook, 2018).

Blood Pressure Management

ACEIs/ARBs are an essential part of the best care approach for many patients in all stages of CKD with hypertension even in the absence of diabetes. Patients often need more than one drug and calcium channel blockers or diuretics are often used for that purpose. Beta-blockers may be useful in people with coronary heart disease, tachyarrhythmias, and heart failure, but are contra-indicated in asthma and heart block (Chronic Kidney Disease, 2012; KDIGO Blood Pressure Work Group, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; Australian Medicines Handbook, 2018). The BP goals as per KDIGO are listed in **Table 7** (KDIGO Blood Pressure Work Group, 2012).

Dyslipidemia

Patients with CKD often have abnormalities in lipoprotein metabolism. The KDIGO guidelines recommend assessing the fasting lipid profile in all adult patients with newly identified CKD (grade 1C recommendation). Follow-up lipid levels are generally not recommended unless the information is likely to alter the management (e.g., adherence to therapy). Only statin therapy has shown to reduce CV events in patients with CKD or a statin plus an ezetimibe combination. Treatment recommendations from KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Kidney Foundation, 2014) are in **Table 8**.

Cardiovascular Disease in CKD

CVD is an important risk factor for CKD as well as a consequence of CKD and the major reason for mortality in CKD patients (Saran et al., 2015; Australian Institute of Health and Welfare, 2017). Recent studies have shown that CKD is a more important

Table 7 Goals of BP management in patients with CKD

Target group	*Severity of albuminuria*	*Goal blood pressure (maximum)*	*Level of evidence*
Nondiabetic CKD	Normal to mild albuminuria	140/90 mmHg	1B
Nondiabetic CKD	Moderate to severe albuminuria	130/80 mmHg	2D moderate 2C severe

Table 8 Recommendations for dyslipidemia management in patients with CKD

Target group	*Treatment recommendations*	*Grade*
Age ≥50 years, stages 1–2	Statin	1B
Age ≥50 years, stages 3a–5	Statin or statin + ezetimibe	1A
Adults 18–49 years of age with CKD before dialysis or transplant with CAD, diabetes, stroke, or estimated CVD risk >10%	Statin	2A
Adults on therapy when dialysis initiated	Continue treatment	2C
Adults with dialysis-dependent CKD	Do not start therapy[a]	2A
Adult kidney transplant recipients	Statin	2A

[a]Studies have failed to show any great benefit in terms of CV outcomes in patients on dialysis when initiated with statins. Some studies have shown worse outcomes (Wanner et al., 2005; Palmer et al., 2013; Palmer et al., 2012).

risk factor for CKD than diabetes (Go et al., 2004; Vanholder et al., 2005; Ardhanari et al., 2014). For people with CKD, the risk of dying from cardiovascular events is up to 20 times higher than the risk of requiring dialysis or transplantation. The prevalence of any form of CVD is double in CKD patients compared to patients without CKD (70% vs. 35%) (Australian Institute of Health and Welfare, 2010). Risk factors for CVD in CKD patients include both traditional risk factors such as diabetes, dyslipidemia, hypertension, left ventricular hypertrophy, smoking, and obesity, and nontraditional risk factors such as anemia, proteinuria, inflammation, and abnormal calcium and phosphate metabolism resulting in vascular calcification (Ardhanari et al., 2014).

However, there is a shortage of RCTs concerning the efficacy and safety of interventions to reduce risk of CVD in patients with CKD (Choi et al., 2014). Available evidence supports recommendations that patients with CKD should stop smoking, achieve excellent blood pressure control (but avoid an SBP less than 120 mmHg), and receive statin therapy for dyslipidemia (Chronic Kidney Disease, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013; National Institute for Health and Care Excellence, 2014). Further, RCTs are required to determine the relative safety and efficacy of aspirin and other platelet inhibitors.

Treatment OF CKD Complications

Anemia

Anemia is a common complication of CKD (stages 3a–5) caused by a relative deficiency of erythropoietin, although several other factors such as reduced availability of iron, chronic inflammation, bone marrow suppression by uremic toxins, and reduced nutrition may also play a role (Jelkmann, 2011; Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Anemia may have multiple adverse effects including worsening cardiac dysfunction by increasing cardiac output and exacerbating left ventricular hypertrophy, exacerbating the decline in kidney function, and reducing cognition and concentration (Chronic Kidney Disease, 2012). The desired outcomes of anemia management are to increase oxygen-carrying capacity, decrease signs and symptoms of anemia, and decrease the need for blood transfusions (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012).

Hemoglobin (Hb) is the preferred marker for monitoring red blood cell production and as per KDIGO guidelines should be monitored annually in patients with stage 3a CKD, twice a year in patients with stage 4, and every 3 months in patients with stage 5 CKD (**Table 9**) (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Patients should also have an assessment of their iron stores, vitamin B-12 and folate levels to rule out other causes of anemia (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Anemia is diagnosed when Hb is <130 g/L in men and <120 g/L in women. Patients are often commenced with treatment for anemia when Hb levels fall below 100 g/L. The main goals of anemia treatment are to decrease morbidity and mortality, reduce left ventricular hypertrophy, increase exercise tolerance, and increase quality of life (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012).

Table 9 KDIGO guidelines for frequency of laboratory monitoring in CKD stages 3–5 (KDIGO, 2009)

	Stage 3 CKD	*Stage 4 CKD*	*Stage 5 CKD*
Calcium	Every 6–12 months	Every 3–6 months	Every 1–3 months
Phosphorus	Every 6–12 months	Every 3–6 months	Every 1–3 months
PTH	Baseline	Every 6–12 months	Every 3–6 months
Alkaline phosphatase	Baseline	Every 12 months	Every 12 months
25-hydroxyvitamin D	Baseline	Baseline	Baseline

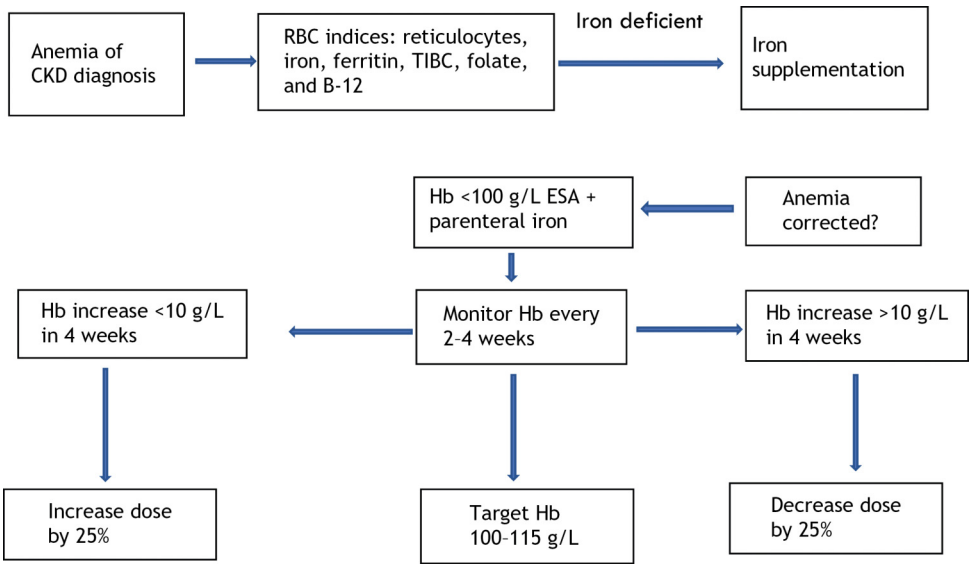

Figure 1 Algorithm for the management of anemia of CKD (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012).

Erythropoiesis stimulating agents (ESAs) (e.g., epoetin alfa and beta, and darbepoetin alfa) are administered to reduce transfusions in anemic CKD patients. A target Hb of 100–115 g/L is reasonable to avoid premature and excessive ESA use (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Higher Hb concentrations are associated with adverse CVD events and it is recommended that Hb concentrations should not exceed 130 g/L (Phrommintikul et al., 2007; Pfeffer et al., 2009; Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). It is also important not to correct Hb rapidly, with current recommendations targeting to correct Hb no >10 g/L every 2–4 weeks (Phrommintikul et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Additionally, iron sufficiency should be present, defined as transferrin saturation > 20% and ferritin >100 ng/mL, before ESA therapy is initiated (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Maintenance of ESAs includes individualized dosing and using the lowest dose of ESA enough to reduce the need for red blood cell transfusions and adjusting dose as appropriate.

It is important that ESA dosing should be monitored with Hb monitoring every 2–4 weeks during the initiation phase and monthly during the maintenance phase in dialysis patients and every 3 months in non-dialysis patients (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). Patients BP and iron studies should also be monitored. Dosing adjustments should be made in increments of 25% upward or downward according to the current dose. In practice practitioners often consider spacing out the ESAs to counter the rapid rise in Hb (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012). For example, darbepoetin may be administered every 3 weeks at the same dose instead of every 2 weeks if the rise in Hb is rapid or approaching 115 g/L rather than withholding treatment (**Fig. 1**).

ESAs: Four ESAs are available in Australia—Epoetin alfa, beta, darbepoetin, and methoxy PEG epoetin beta (Australian Medicines Handbook, 2018). All ESAs are clinically equivalent and different only in their frequency of administration (Australian Medicines Handbook, 2018). Iron deficiency is the most common cause of erythropoietin resistance; however, the increased use of intravenous iron products has reduced this problem. Infection and inflammation, chronic blood loss, hyperparathyroidism, aluminum toxicity, folate or vitamin B-12 deficiency, malignancies, malnutrition, hemolysis, and vitamin C deficiency may also be some of the factors associated with ESA resistance (Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012).

Bone and Mineral Disorders

Disturbances in bone and mineral metabolism is common in CKD patients and include abnormalities in the parathyroid hormone, calcium, phosphorous, vitamin D, fibroblast growth factor-23 (FGF-23), bone turnover, as well as soft tissue calcification (KDIGO, 2009). These abnormalities historically were known as renal osteodystrophy (ROD). However, the clinical, biochemical, and imaging abnormalities identified as correlates of ROD are defined more broadly these days by the syndrome CKD-mineral and bone disorder (CKD-MBD) (KDIGO, 2009). The spectrum of skeletal abnormalities seen in ROD includes the following: the bone abnormalities include osteitis fibrosa cystica (high bone turnover disease), osteomalacia (low bone turnover disease), adynamic bone disease, osteopenia/osteoporosis, combination of these abnormalities termed as mixed ROD, and other abnormalities with skeletal manifestations (chronic acidosis, β2-mircoglobulin amyloidosis). CKD-MBD is the main cause of morbidity and mortality in patients undergoing dialysis (KDIGO, 2009).

Table 10 KDIGO categories in CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013)

GFR category	*Terms*	*GFR (mL/min/1.73 m^2)*
G1	Kidney damage with normal or high GFR	≥90
G2	Kidney damage with mildly decreased GFR	**60–89**
G3a	Mildly to moderately decreased GFR	**45–59**
G3b	Moderately to severely decreased GFR	30–44
G4	Severely decreased GFR	15–29
G5	Kidney failure	<15

The pathophysiology of CKD-MBD is complex and is typically apparent in categories G3 to G5 (KDIGO, 2009) (**Table 10**). Calcium and phosphorous homeostasis is mediated through calcitriol, FGF-23 on the bone, GI tract, kidney, and parathyroid gland (Gutierrez, 2010). CKD results in reduced phosphate elimination, which results in hyperphosphatemia and in turn reduces serum calcium concentration. Hypocalcemia stimulates the secretion of PTH by the parathyroid glands, while hyperphosphatemia increases PTH synthesis and release through its direct effects on the parathyroid gland. PTH increases calcium reabsorption by the distal tubules, reduces phosphate reabsorption in the proximal tubules of the kidney, and increases calcium mobilization from bone (Roberts and Singer, 2010). FGF-23 production in bone also increases in response to high phosphate levels and promotes phosphate excretion by the kidney. The result is a relative normalization of calcium and phosphorus, in the early stages of CKD. The increase in PTH, although notable when GFR is <60 mL/min/1.73 m^2 (0.58 mL/s/m^2), worsens as kidney function further declines. As kidney function declines further, the initial adaptive increments in FGF-23 and PTH become maladaptive and abnormalities in calcium and phosphorus worsen. Over time the negative effects of sustained hyperparathyroidism on bone results in a spectrum of bone and other mineral disorders together known as CKD-MBD (Gutierrez et al., 2008; Gutierrez, 2010; Roberts and Singer, 2010).

It is also important to note the role of calcitriol (1-α, 25-dihyroxycholecalicferol) in CKD-MBD. As kidney disease progresses the concentration of calcitriol, which is the active form of vitamin D, also reduces due to the loss of 1-α-hydroxylase activity in the kidney (Roberts and Singer, 2010). Calcitriol promotes intestinal absorption of calcium and also has a direct suppressive action on PTH production.

The resultant vitamin D deficiency leads to reduced intestinal calcium and phosphorus absorption and worsening hyperparathyroidism (Roberts and Singer, 2010). Calcitriol deficiency can also occur due to increase in FGF-23. Deficiency in 25(OH) vitamin D is also common in patients with CKD due to decreased dermal synthesis of vitamin D, decreased exposure to sunlight, and reduced dietary intake of vitamin D (Gutierrez et al., 2008; Gutierrez, 2010; Roberts and Singer, 2010). These abnormalities of CKD-MBD lead to alterations in the structural integrity of bone and other associated consequences. Disturbances in phosphate metabolism have been linked to adverse clinical outcomes, including CVD and death among patients undergoing dialysis (KDIGO, 2009). Several studies have reported an increase in calciphylaxis or rapid calcification of subcutaneous tissues, in patients with CKD-MBD, elevated phosphate, and warfarin use (Nigwekar et al., 2015). Medications used as phosphate binders, in particular calcium-based binders, have been associated with coronary artery calcification. Hence, it is important to consider all consequences of elevated PTH, calcium, and phosphorus, not just their effects on bone (KDIGO, 2009; Roberts and Singer, 2010; Nigwekar et al., 2015).

Clinical management of CKD-MBD is based on repeated measurement of circulating laboratory values, specifically PTH, calcium, and phosphorus concentrations, and therapeutic interventions using combinations of phosphate binders, cholecalciferol and calcitriol, and calcimimetic agents that are dose adjusted to keep these biochemical parameters within specific target ranges, while minimizing potential side effects of the various therapies (KDIGO, 2009). Treatment considerations also depend on the stage of CKD, the mechanism of action.

CKD-MBD-related symptoms are insidious in onset where patients may experience fatigue and musculoskeletal and GI pain, calcification may be visible on radiography, and bone pain and fractures can occur if progression is left untreated (KDIGO, 2009; Roberts and Singer, 2010). Treatment goals are summarized in **Table 11** (KDIGO, 2009).

Nondrug therapies for CKD-MBD include dietary phosphate restriction of 800–1000 mg/day in stage 3 or higher (KDIGO, 2009). Parathyroidectomy is generally reserved for patients with unresponsive hyperthyroidism. Patients generally require phosphate-binding agents despite being on dialysis (depending upon the modalities) as it would be insufficient to maintain phosphate balance (KDIGO, 2009). Common phosphate binders used include calcium-based phosphate binders such as caltrate

Table 11 CKD-MBD treatment goals

	CKD stage 3	*CKD stage 4*	*CKD stage 5*	*CKD stage 5 on dialysis*
Corrected calcium	Normal	Normal	Normal	Normal
Phosphorus	Normal	Normal	Normal	Near normal
Intact PTH	Normal	Normal	Normal	2–9 times upper normal

or cal-sup, and sevelamer (Renagel), while lanthanum (Forenol), sucroferric oxyhydroxide, and aluminum hydroxide may also be used (Australian Medicines Handbook, 2018). Occasionally, phosphate-binding agents may be combined for their additive effect and achieve the desired target levels (KDIGO, 2009).

Calcium-based phosphate-binding agents are widely used as phosphate binders especially in the pre-dialysis patients as they are cheaper. They act by binding to phosphorus in the gut. Hence, they are to be taken with meals to be effective (Australian Medicines Handbook, 2018). Occasionally, calcium may also be used as a supplement as hypocalcemia occurs sometimes in patients with CKD which typically is prescribed away from meals. However, it has to be used with caution to avoid hypercalcemia.

Sevelamer, a nonabsorbable phosphate binder, is one of the most commonly prescribed drugs in patients with CKD. It binds to dietary phosphate and is consider primary therapy in patients on dialysis. It is generally well tolerated and can also lower LDL-cholesterol and increase HDL-cholesterol while in some patients may worsen metabolic acidosis (Australian Medicines Handbook, 2018). Lanthanum, a flavorless chewable tablet, is another phosphate-binding agent that has similar indications to sevelamer but is not widely used as sevelamer. It can be considered if the patient has hypercalcemia. Sucroferric oxyhydroxide is made up of iron-oxyhydroxide complex, sucrose, and starches. The iron complex is insoluble and binds to phosphate. It is a newer drug with no long-term safety data (Australian Medicines Handbook, 2018). Aluminum hydroxide is best avoided because of the risk of aluminum toxicity (encephalopathy, adynamic bone disease, and erythropoietin resistance). However, it may be used as a short-term (4-week) course when serum phosphate is not adequately controlled by other measures. Currently, there is no data indicating that one phosphate binder is superior over the other in terms of reducing mortality or hospitalizations. However, sevelamer and lanthanum have shown to cause less hypercalcemia and reduce calcium burden (KDIGO, 2009).

Vitamin D and vitamin D analogues are often used in the management of CKD-MBD mainly to suppress PTH synthesis and concentrations. However, they have to be used with caution as they can increase hypercalcemia (KDIGO, 2009; Roberts and Singer, 2010). Calcitriol, which is the pharmacologically active form of vitamin D (1,25-dihydroxy cholecalciferol), is used in the management of CKD-MBD mainly to treat hypocalcemia and to prevent and treat secondary hyperparathyroidism. Studies have shown that calcitriol is effective in reducing hypocalcemia; however, it does not significantly reduce PTH concentration. The major limitation of using calcitriol is hypercalcemia that will have to be monitored closely (Australian Medicines Handbook, 2018). Paracalcitriol, which is a Vitamin D analogue, is indicated for the prevention and treatment of secondary hyperparathyroidism has a lower incidence of causing hypercalcemia compared to calcitriol but is used less often (Australian Medicines Handbook, 2018).

Calcimimetics such as cinacalcet that attach to the calcium receptor on the parathyroid gland with resultant increase in sensitivity of the receptors to serum calcium concentrations thereby reducing PTH concentrations is indicated for secondary hyperparathyroidism in dialysis patients with high calcium, phosphate, and PTH. Studies in dialysis patients have shown that cinacalcet is effective in significantly reducing PTH, calcium, and phosphate. However, a recent trial (EVOLVE) has shown that cinacalcet did not significantly reduce all-cause mortality or CV events in patients with stage 5 CKD (Chertow et al., 2012). Hence, the drug has been delisted from the pharmaceutical benefits scheme (PBS) in Australia. Cinacalcet is partially metabolized by cytochrome P450 CYP3A4, and there is potential for drug–drug interactions. It also can cause hypocalcemia, hence close monitoring of serum calcium levels are indicated (Australian Medicines Handbook, 2018).

Electrolyte Imbalance in CKD

The ability to concentrate or dilute the urine is usually retained until GFR falls to less than 30%. However, both hyponatremia and hypernatremia can occur in patients with CKD depending upon whether they are fluid overloaded or dehydrated as in the case of elderly patients (Chronic Kidney Disease, 2012; National Institute for Health and Care Excellence, 2014).

The kidneys play a huge role in potassium balance and hyperkalemia is a common problem in patients with CKD. Potassium levels need to be monitored closely and managed appropriately. The management of hyperkalemia is summarized in the previous chapter.

Patients with CKD have a fall in the serum bicarbonate concentration in association with a reduced pH (metabolic acidosis), when GFR falls typically below 20%–25%. The metabolic acidosis results from reduced acid excretion, leading to positive proton balance (Chronic Kidney Disease, 2012; National Institute for Health and Care Excellence, 2014). The electrolyte pattern seen with metabolic acidosis of CKD is often of the high anion gap variety, but frequently a hyperchloremic (nonanion gap) or combined high anion gap and nonanion gap pattern can be observed. The degree of acidosis is usually mild to moderate but in most cases serum bicarbonate concentration remains stable unless there is a significant decline in kidney function. It is important to note that acidosis can worsen hyperkalemia and depending upon the severity of CKD sodium bicarbonate may be supplemented to correct acidosis (Chronic Kidney Disease, 2012; National Institute for Health and Care Excellence, 2014).

Treatment Options for ESKD

The progression of CKD to ESKD would necessitate either dialysis or transplant to survive. Indications for commencing RRT include (Chronic Kidney Disease, 2012; Chen et al., 2018):

- A: Acidosis (not responsive to bicarbonate)
- E: Electrolyte abnormality (hyperkalemia, hyperphosphatemia)
- I: Intoxication (e.g., lithium, salicylate)

Table 12 Different treatment options for patients at Stage 5 CKD

Treatment	*Types*	*Involves*	*Lifestyle impact/outcomes*
Transplant	Living donor	Surgery	Freedom to work and travel once stabilized
	Deceased donor	Lifetime immunosuppressants	Less dietary restriction
		May involve long waiting times	High infection rates and cancer
Peritoneal dialysis (PD)	Continuous ambulatory peritoneal dialysis (CAPD)	Four exchanges daily, performed manually	Need PD catheter Freedom to work and travel Good quality of life Risk of peritonitis
	Automated peritoneal dialysis (APD)	Overnight exchange by machine	Not suitable for everyone
Hemodialysis (HD)	Home HD	Need to create permanent access (arteriovenous fistula)	Long training Good flexibility with work Slightly better outcomes
		Can be performed daytime (4–6 h each) or nighttime (8 h each) 3–5 treatments weekly	
	Center-based HD	Need to create permanent access (arteriovenous fistula)	Strict routine Dietary restriction
		Hospital/satellite-based treatment	Transport to hospital/satellite center
		3 times a week (4–6 h each)	Less flexibility with work and travel
Supportive care	No dialysis or transplant Palliative care team Managed in the community	Medication and diet control	In older people with comorbidities no greater benefit with dialysis compared to supportive care

- O: Fluid overload (pulmonary edema)
- U: Uremia (pericarditis and weight loss)

Patients and their families/carers should receive sufficient information and education regarding the nature of stage 5 CKD, and the options for the treatment to allow them to make an informed decision about the management of their condition. Dialysis initiation and its timing should be a shared decision between physician, patients, and family members, and should be tailored to the individual patient's needs. Patients need to be referred to a nephrologist in a timely fashion to allow adequate pre-dialysis care and planning. Planning is required for dialysis initiation when a patient's kidney function declines to CKD stage 4 (eGFR < 30 mL/min/1.73 m^2). While the intent of this chapter is not to exhaustively compare and contrast the different options, a brief overview of the different options available is presented in **Table 12** (Chronic Kidney Disease, 2012).

Role of Pharmacist

Drug therapy problems (DTPs) are very common in patients with stages 1–5 CKD and patients undergoing dialysis. On average patients with end-stage renal diseases undergoing hemodialysis are prescribed 12 medications and present with around six comorbidities (Manley et al., 2003; Manley et al., 2004). Additionally, the rates of nonadherence to prescribed oral medication are as high as 67% (Schmid et al., 2009).

Pharmacists being medication experts are in an ideal position to contribute in this area of management for CKD patients. Pharmacists' activities that have strong association with improved patient outcomes include participating in ward rounds, interviewing patients, performing medication reconciliation (prescription, nonprescription, herbal, and nutritional supplements), discharge patient counseling, and post-discharge follow-ups (Kaboli et al., 2006). Calculation of creatinine clearance and adjusting the dose of renally cleared medications (**Table 13** [Chronic Kidney Disease, 2012]) based on the degree of kidney function is a routine activity clinical pharmacists' carryout on a day-to-day basis in hospitals. Appropriate measures should also be taken for patients with CKD to decrease the risk of nephrotoxicity from radiocontrast agents, antibiotics such as aminoglycosides, as well as nonsteroidal anti-inflammatory drugs and ACEIs. Specialist renal pharmacists are also involved in providing education to other healthcare professionals on management of some of the complications of CKD (Stemer and Lemmens-Gruber, 2011a,b; Qudah et al., 2016). A systematic review of eight controlled trials involving CKD patients demonstrated that clinical pharmacist interventions improved the management of anemia, blood pressure, and lipids, as well as calcium and phosphate parameters (Salgado et al., 2012). These studies showed that clinical pharmacists' interventions in CKD patients were able to reduce hospital admissions and length of hospital stay (Stemer and Lemmens-Gruber, 2011a,b; Salgado et al., 2012; Qudah et al., 2016).

Although not mandated to be part of the care team, renal pharmacists are active members of the care team in some CKD and especially dialysis settings in the United States, Australia, and the UK inclusion of renal pharmacists have resulted in reduction in DTPs. Pharmacists involvement in the management of patients with CKD is very well defined and standardized in Canada as listed in **Tables 14 and 15**.

Table 13 Some examples of medications/medication classes that require dosage adjustment or are to be avoided in renal impairment (Chronic Kidney Disease, 2012)

Drugs/drugs class	*Agents requiring dosage adjustment*
Antibiotics	Almost all parenteral antibiotics require dosage adjustment (exceptions: ceftriaxone, clindamycin, linezolid, metronidazole, macrolides, nafcillin)
Anticoagulants	Enoxaparin, fondaparinux, apixaban, rivaroxaban, dabigatran
Cardiac medications	Atenolol, ACEI, ARBs, digoxin, Spironolactone[a], fibrates, rosuvastatin
Pain medications	Codeine, tramadol, pethidine, morphine, hydromorphone, and other agents may also require adjustment
Neurological agents	Gabapentin, pregabalin, lithium, topiramate, vigabatrin, levetiracetam
Antidiabetic drugs	Gliptins (except linagliptin), exenatide, insulins, metformin, gliflozins, glibenclamide+, glimepiride+
Others	Allopurinol, H_2 receptor antagonists, NSAIDs[a]

[a]Avoid if <30 mL/min; + does not require dosage adjustment but shorter acting ones are preferred.

Table 14 Standard of clinical practice for renal pharmacists (Raymond et al., 2013)

The pharmacist *must* perform these core clinical activities on fully staffed weekdays[a] (in order of priority):

1. Attend all MRP clinics (includes PD, home and rural HD, and CKD stages 1–5 clinics, total of 24 half-day clinics per week):
   a. Review laboratory test result and medication for all patients
   b. Document in health record any recommendations, suggestion, or further patient information required for patients not seen by a pharmacist
   c. For patients seen by a pharmacist, generate best possible medication history and perform medication reconciliation (National Kidney Foundation, 2002) by a pharmacist
2. Attend multidisciplinary patient care rounds (twice weekly for HD and PD patients):
   a. Contribute to interprofessional discussion about patients.
   b. Identify admitted patients for discharge medication reconciliation.
   c. Identify patients for medication review by a pharmacist.
3. Perform discharge (and transfer) medication reconciliation for admitted patients receiving dialysis before discharge or at first subsequent dialysis session (HD patients only) (National Kidney Foundation, 2002):
   a. Reconcile inpatient medication with home and in-center HD medications.
   b. Perform detailed medication review and document recommendation in the patient's medical record.
   c. Write discharge prescription for medication, including appropriate medications for in-center HD and new medications started in hospital contact prescribing nephrologist to make recommendations and confirm prescription
   d. Provide patient with medication card and counseling.
4. Review monthly laboratory test results for HD patients.
5. Perform detailed medication review for new starts to HD or PD within 2 weeks.
6. Perform detailed medication review for other patients.

The pharmacist will perform the following "must do activities" (prioritized according to pharmacist's professional judgment):

- Ensure follow-up laboratory tests are ordered, according to pharmacist's recommendation.
- Ensure patient have adequate prescriptions and refills.
- Liaise with community pharmacy as appropriate (e.g., to facilitate prescription delivery, compliance aid, and drug coverage)
- Liaise with patient, caregivers, family members, and other healthcare professionals as appropriate to provide medication-related information to or for patients.
- Provide drug information for immediate patient care that day.
- Provide education to pharmacy students and residents.
- Provide monitoring and follow-up for recommendation.[b]
- Provide communication between MRP and other pharmacists within the facility.[b]

The pharmacist shall perform the following desirable activities as appropriate and as pharmacist is available:

- Participate in MRP and pharmacy program initiatives (e.g., development of drug protocols review of preprinted orders, participation on committees, development of policy and procedures, and responses to drug shortages).
- Provide education-related activities to healthcare professionals.
- Provide communication between MRP and other pharmacists at other facilities.
- Provide drug-use management activities, including prospective audits.
- Participate in projects or research.
- Investigate medication incidents or errors.
- Review or triage medication orders to identify drug therapy problems related to appropriateness, duration, and dosing of each medication, as well as drug interaction (as an activity separate from medication review, medication reconciliation, or MRP clinic visit).

CKD = chronic kidney disease, HD = hemodialysis, PD = peritoneal dialysis.

[a]Evening HD patients are reviewed and seen by pharmacists who work later shifts periodically, in order that all patients are seen by a pharmacist. Weekend pharmacist coverage consists of centralized dispensary pharmacist coverage at each site.

[b]When the pharmacy is short-staffed, these are considered "should do" (rather than "must do") activities.

Table 15 Steps in review of patients with chronic kidney disease for drug therapy problems (Raymond et al., 2013)

General medication review:
- For new dialysis patients, before nephrologist review or clinic visit (every 6 months to 1 years) or at the request of another healthcare professional
- Interview patient, caregivers, family members, and other healthcare professionals
- Generate best possible medication history and perform medication (National Kidney Foundation, 2002)
- Review laboratory test results, investigations, physical findings, and medications to identify DTPs
- Documents medication review, DTP, and recommendation in the medical record
- Identify and resolve actual/potential DTPs during discharges, medication reviews, clinic visits, between clinics visits (after review of laboratory test results), on medication order review, or detailed medication review

Assess patient for general DTP (Mathew and Corso, 2009; Hanlon et al., 2011; Johnson et al., 2012a,b; Tonelli et al., 2012; World Health Organization, 2013; Keith et al., 2004)
- Allergies and intolerances
- Drug–drug interaction
- Adverse drug reactions
- Medication causing or exacerbating a symptom
- Duplication of pharmacological or therapeutically similar medications
- Appropriate dosage form and route of administration
- Medication therapy not indicated
- Medication indicated but not utilized
- Medication adherence
- Problems related to IV administration
- Medication that require renal dose adjustments
- Medications that are contraindicated in CKD or that should be minimized
- Medication that are no longer required in dialysis

Assess patient for DTPs specific to CKD by assessing the following:
- *Anemia*: assess hemoglobin, transferring saturation, ferritin, use of erythropoietic-stimulating agent, iron, and renal multivitamin consider erythropoietin hyporesponsiveness (Johnson, 2004; National Kidney Foundation, 2012; Phoon, 2012; Inker et al., 2014; National Institute for Health and Care Excellence, 2014; Tomino, 2014).
- *Mineral and bone disease*: Assess corrected calcium, serum phosphate, parathyroid hormone, alkaline phosphatase, albumin, calcium bath concentration, phosphate and calcium additives to the dialysate, surgical history (for parathyroidectomy), use of phosphate binders, vitamin D analogue, or cinacalcet. Liaise with dietitian about diet (Lopez-Novoa et al., 2010; Gajjala et al., 2015).
- *Cardiovascular risk*: Assess for presence of cardiovascular disease and risk factors, and therapies to reduce this risk (antiplatelets, proteinuria, antihypertensives, statins, antianginal therapies, and antiarrhythmics) (Richards et al., 2008; Gajjala et al., 2015; Australian Medicines Handbook, 2018).
- *Hypertension and proteinuria*: Assess blood pressure before, during, and after dialysis, in clinic and at home, assess dry weight, proteinuria, antihypertensives, and antiproteinuric therapies (KDIGO Blood Pressure Work Group, 2012; Richards et al., 2008; Gajjala et al., 2015; Australian Medicines Handbook, 2018).
- *Diabetes mellitus*: Assess glucose monitoring before and after dialysis, in clinic and at home, as well as glycated hemoglobin and use of hypoglycemic agents (Wanner et al., 2005; Palmer et al., 2012; National Kidney Foundation, 2014; Gajjala et al., 2015).
- *Pain*: Assess source of pain, its quantity and quality, and use of opioids, NSAIDs, and adjunctive therapies (Palmer et al., 2013; Saran et al., 2015).
- *Peripheral neuropathy*: Assess source of pain, its quantity and quality, and use of antidepressants, anticonvulsants, and opioids (Ardhanari et al., 2014).
- *Restless leg syndrome*: Assess symptom severity and frequency, sleep disturbance, daytime fatigue, and use of dopamine agonists, gabapentin, levodopa, benzodiazepines, and opioids (Go et al., 2004; Vanholder et al., 2005).
- *Smoking status*: Assess readiness to quit and use of nicotine replacement therapy, bupropion, or varenicline provide education (Australian Institute of Health and Welfare, 2010).
- *Cramps*: Assess symptom severity and frequency, as well as use of quinine or vitamin E (Choi et al., 2014).
- *Pruritus*: Assess symptom severity and use of topical or systemic agents.
- *Gastrointestinal issues (e.g., reflux, history of bleeding, ulcer, dyspepsia, constipation, diarrhea)*: Assess signs and symptoms, as well as use of antacids, laxatives, stool softeners, agents to treat diarrhea, NSAIDsor corticosteroids.
- *Infectious diseases (e.g., IV catheter-related infection, skin infection, peritonitis) requiring treatment or prophylaxis, including antibiotic locks and intraperitoneal antibiotics*: Assess signs and symptoms, as well as culture and sensitivity results (Phrommintikul et al., 2007; Jelkmann, 2011; Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, 2012).
- *Hyperkalemia (for stages 1–5 CKD patients)*: Assess serum potassium, presence of hemolyzed sample, and use of potassium supplements, ACE inhibitors, ARBs, potassium-sparing diuretics, and other agent known to increase serum potassium. Assess use of potassium-binding resins and diuretics. Liaise with dietitian regarding diet (Pfeffer et al., 2009)
- *Metabolic acidosis (for stages 1–5 CKD patients)*: Assess serum bicarbonate concentrations and use of supplementation (Gajjala et al., 2015).
- *Depression, anxiety, and insomnia*: Assess consultations with other healthcare professionals and use of antidepressants, antipsychotics, benzodiazepines, and sedatives (KDIGO, 2009).
- *Gout (for patients with stages 1–5 CKD)*: Assess serum uric acid level, frequency and severity of gout attacks, and use of xolchicine, NSAIDs or corticosteroids, allopurinol, and febuxostat (Gutierrez, 2010).
- *Review patient for the use of the following high-alert medication*: Digoxin, lithium, phenytoin, and immunosuppressive therapy.
- Assess serology and vaccination status for hepatitis B, pneumonia, and influenza (Roberts and Singer, 2010; Gajjala et al., 2015).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug.

Currently, although there are some studies that demonstrate the evidence of pharmacist' interventions in CKD patients, the literature is sparse, of variable quality and with heterogeneous outcomes. With the best available evidence, pharmacists' intervention may have a positive impact on CKD patient outcomes (Salgado et al., 2012). Therefore, future pharmacists' intervention in CKD patients should be well documented and conducted in robust study designs to demonstrate the actual benefit on clinical outcomes.

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Management of Endocrine Disorders and the Pharmacist's Role: Adrenal Insufficiency

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Learning Objectives

- Understand the critical role of the adrenal gland in regulating energy, salt, and fluid homeostasis via the production of the glucocorticoid cortisol and the mineralocorticoid aldosterone.
- Understand the need for lifelong glucocorticoid and mineralocorticoid replacement therapy in adrenal insufficiency and the clinical signs and symptoms suggestive of under-replacement or over-replacement of therapy.
- Understand the necessity of increasing the glucocorticoid dose in times of medical and surgical stress to prevent adrenal crisis.
- Understand that acute adrenal crisis is a life-threatening medical emergency requiring immediate treatment.
- Understand the importance of patient, family, medical and other health care providers education on sick day management planning and glucocorticoid stress dosing to prevent acute adrenal crisis and optimize quality of life.

Take Home Messages

- Adrenal insufficiency is defined as primary, secondary, or tertiary depending on whether the problem arises at the level of the adrenal gland, pituitary gland, or hypothalamus, respectively.
- Primary adrenal insufficiency is defined by loss of cortisol, aldosterone, and androgen production.
- Secondary or tertiary adrenal insufficiency is defined by loss of cortisol production only.
- Treatment involves adequate replacement of deficient hormones to prevent acute adrenal crisis, associated complications, and improve quality of life.
- Acute adrenal crisis is a life-threatening medical emergency requiring immediate treatment and glucocorticoid replacement is the most important aspect of initial resuscitation.
- Ongoing education of the patient, their family and clinical practitioners on glucocorticoid replacement, appropriate sick day management, including instructions on glucocorticoid dose increases during intercurrent illness, stress or surgery, use of emergency hydrocortisone injector kits in an emergency, when to present to the Emergency Department, and the importance of wearing a Medic-Alert or equivalent identification at all times, forms the cornerstone of management of adrenal insufficiency.

Introduction

Adrenal insufficiency is an important endocrine disorder, characterized by deficient glucocorticoid (cortisol) production by the adrenal cortex. Deficient mineralocorticoid (aldosterone) and adrenal androgen production is also a feature of primary adrenal insufficiency (PAI or Addison's disease). Adrenal insufficiency can be either primary (PAI), secondary (SAI), or tertiary (TAI), depending on whether the cause arises at the level of the adrenal gland, pituitary gland, or hypothalamus. Regardless of the etiology, untreated adrenal insufficiency is lethal given the central role of cortisol and aldosterone in energy, salt, and fluid homeostasis. Consequently, acute adrenal crisis is a life-threatening medical emergency. Despite the seriousness of this condition, the diagnosis of adrenal insufficiency is often missed or delayed due to its generally subacute, nonspecific clinical features. Importantly, once diagnosed, adrenal insufficiency can be treated with lifelong replacement pharmacotherapy. The central role of pharmacotherapy in the management of adrenal insufficiency includes the appropriate dose of oral glucocorticoid and mineralocorticoid maintenance therapy and ongoing patient, family, medical, and other health care provider education on sick day management planning and glucocorticoid stress dosing to prevent acute adrenal crisis and optimize quality of life.

Epidemiology and Etiology

Primary Adrenal Insufficiency

PAI has a reported incidence of approximately 4 per 1 000 000 per year (Bornstein et al., 2016). Up to 90% of PAI in developed countries is due to autoimmune adrenalitis (Bornstein et al., 2016). Autoimmune adrenalitis is characterized by autoimmune destruction of the adrenal cortex, with sparing of the adrenal medulla. Steroid 21-hydroxylase antibodies are detected in most patients with PAI (Betterle et al., 2002).

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders generally caused by mutations in *CYP21A2*, the gene that encodes adrenal steroid 21-hydroxylase. As this enzyme is needed for the conversion of the precursors for cortisol and aldosterone production, mutation results in impaired cortisol synthesis and adrenal insufficiency (Speiser et al., 2018).

X-linked adrenoleukodystrophy (X-ALD) is another rare genetic disorder caused by mutations in the *ABCD1* gene that result in accumulation of very long chain fatty acids in various tissues, including the central nervous system, testes and adrenal cortex (Suryawanshi et al., 2015). Involvement of the adrenal cortex results in impaired steroidogenesis, leading to PAI.

Infectious adrenalitis is the most common cause of PAI in developing countries (Melmed et al., 2016). Tuberculosis, cytomegalovirus, acquired immunodeficiency syndrome (AIDS) and fungal infections are all associated with PAI.

Hemorrhage or adrenal vein thrombosis leading to bilateral adrenal infarction is another important cause of PAI (Rao et al., 1989). This is most commonly iatrogenic in the context of critical illness, for example, due to coagulopathies including the heparin-induced thrombocytopenia syndrome, and in those with underlying sepsis or trauma. The antiphospholipid syndrome and meningococcal sepsis are also strongly associated with adrenal hemorrhage (Caron et al., 1998).

Metastases to the adrenal gland, most commonly from primary lung and breast neoplasms or lymphoma, may lead to PAI if there is sufficient destruction of the adrenal gland, although this is uncommon. Infiltrative diseases such as sarcoidosis, amyloidosis, and hemochromatosis have also been associated with PAI.

Pharmacotherapies including the anticonvulsant aminoglutethimide, the anesthetic etomidate, the antifungal ketoconazole, in addition to metyrapone and mitotane, may also cause PAI by inhibiting glucocorticoid synthesis (Jabre et al., 2009; Schoneshofer and Claus, 1985; Sonino, 1987; Wagner et al., 1984). In addition, pharmacotherapy that activates or accelerates glucocorticoid metabolism by inducing hepatic cytochrome P450 enzymes, such as the anticonvulsant phenytoin and carbamazepine, the barbiturate phenobarbital, the antibiotic rifampicin, and St John's wort can also cause adrenal insufficiency in the setting of impaired or borderline hypothalamic-pituitary-adrenal (HPA) axis function, for example concomitant exogeneous glucocorticoid therapy (Bornstein, 2009).

Secondary and Tertiary Adrenal Insufficiency

Conditions that disturb the HPA axis (**Fig. 1**) at the level of the pituitary gland or hypothalamus can lead to SAI or TAI by disrupting adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) secretion, respectively. The HPA axis deficiency may be isolated or occur in association with other pituitary hormone deficits.

Pituitary adenomas arising within the sella are the most common cause of hypopituitarism and are generally benign (Regal et al., 2001). Most adenomas are either nonfunctioning or prolactin-secreting (prolactinomas). Hypopituitarism may be apparent at presentation due to mass effect of the adenoma or be iatrogenic following pituitary surgery. Craniopharyngiomas are the most common suprasellar tumors and are associated with panhypopituitarism and diabetes insipidus. Other space occupying lesions such as gliomas, metastases, and primary hematological malignancies such as leukemia and lymphoma can also lead to hypopituitarism—either via direct infiltration and destruction or secondarily due to treatment.

Infiltrative disease, for example sarcoidosis and hemochromatosis, are also associated with hypopituitarism. Lymphocytic infiltration causing autoimmune (lymphocytic) hypophysitis is an increasingly important cause of SAI. This is associated with isolated destruction of the ACTH producing cells of the pituitary gland. The advent of immunomodulatory therapy such as the human anticytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) antibody ipilimumab and the antiprogrammed cell death 1

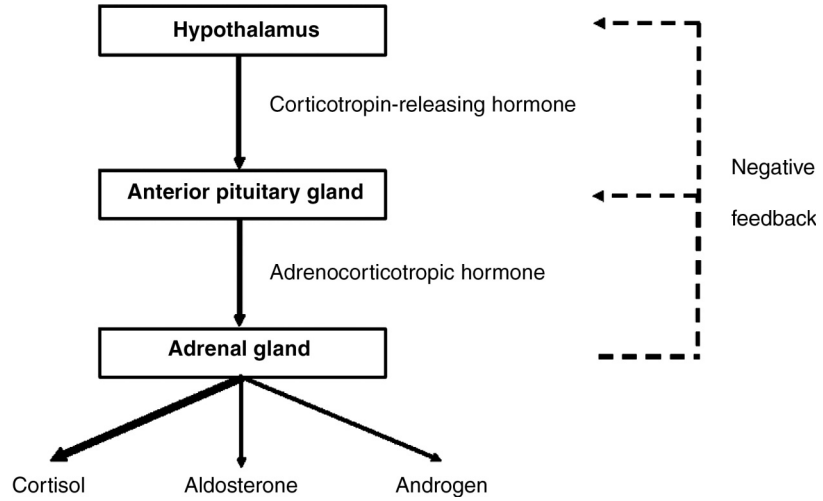

Figure 1 The hypothalamic-pituitary-adrenal axis.

(anti-PD-1) antibody pembrolizumab for metastatic melanoma and other solid organ malignancies has been associated with a significantly increased incidence of autoimmune hypophysitis (Faje et al., 2014; Faje, 2016; Lam et al., 2015; Sweeting and Chua, 2015).

Sheehan's syndrome is classically associated with pregnancy and postpartum hemorrhage causing severe hypotension and resultant pituitary ischemia and hypopituitarism. Pituitary apoplexy similarly results from hemorrhage or infarction, generally arising from a preexisting pituitary adenoma. Most cases occur spontaneously; however, reported precipitating factors include closed head trauma, hypo- or hyper-tension, previous cranial irradiation, anticoagulant therapy, and dopamine agonists (Nawar et al., 2008).

Traumatic brain injury and cranial irradiation for tumors or hematological malignancy distant to the hypothalamic-pituitary axis is associated with significant rates of irreversible and progressive hypopituitarism, with a reported prevalence of any degree of hypopituitarism of 66% (Appelman-Dijkstra et al., 2011).

Pharmacotherapy is another important cause of SAI and TAI. The most common cause is long-term administration of exogenous glucocorticoid therapy, which can include oral, inhaled and even long-term dermal routes (Lee et al., 2015; Woods et al., 2015). Opioids have multiple acute and chronic effects on several endocrine axes, primarily mediated via κ-receptors in the hypothalamus and pituitary. Opioids are associated with both isolated reversible ACTH deficiency and gonadal hormone deficiency, with time to recovery dependent on duration of opioid exposure (Vuong et al., 2010). The causes of adrenal insufficiency are summarized in Table 1.

Table 1 Causes of adrenal insufficiency

Primary adrenal insufficiency
Autoimmune adrenalitis
Infection
• Tuberculosis, AIDS, fungal—cryptococcosis, histoplasmosis
Hemorrhage
• Meningococcal sepsis, antiphospholipid syndrome
Infiltrative disease
• Lymphoma, amyloidosis, and hemochromatosis
Bilateral adrenalectomy
Genetic
• Adrenoleukodystrophy, congenital adrenal hyperplasia, and adrenal hypoplasia congenita
Drug-induced
• Anticoagulants (heparin, warfarin)
• Tyrosine kinase inhibitors (sunitinib)
• Aminoglutethimide
• Ketoconazole, fluconazole, and etomidate
• Phenobarbital
• Anticonvulsants (phenytoin, carbamazepine)
• Rifampicin

(*Continued*)

Table 1 Causes of adrenal insufficiency (*cont.*)

Secondary adrenal insufficiency
Space occupying lesions or trauma • Pituitary tumors, sella or suprasellar tumors—adenomas, Rathke's cleft cyst, craniopharyngiomas, and gliomas • Malignant infiltration/Neoplasm—brain tumors, hematological malignancy (leukemia, lymphoma), and lung/breast metastases • Trauma (pituitary stalk lesions)
Pituitary surgery for pituitary tumors or other neurological tumors
Irradiation • Cranial, pituitary, nasopharyngeal carcinoma
Autoimmune • Immunomodulatory therapy (Ipilimumab, Pembrolizumab, and Nivolumab), classic lymphocytic hypophysitis
Infection • Tuberculosis, meningitis
Infiltration • Granulomatous diseases (Sarcoid, Wegener's granulocytosis), Langerhan's cell histiocytosis, hemochromatosis
Infarction • Apoplexy, Sheehan's syndrome
Traumatic brain injury • Acute insult, subarachnoid hemorrhage, and cerebrovascular event
Congenital • Pituitary hypoplasia/aplasia, genetic mutations (Prader-Willi Syndrome)
Drug-induced • Abrupt withdrawal of glucocorticoid therapy (systemic or topical), opioids
Tertiary adrenal insufficiency
Space occupying lesions or trauma • Craniopharyngiomas or metastases • Surgery or irradiation for central nervous system or nasopharyngeal tumors
Infection • Tuberculosis, meningitis
Infiltration • Lymphocytic hypophysitis, hemochromatosis, sarcoidosis, and histiocytosis X
Trauma, injury (fracture of skull base)
Drug-induced • Abrupt withdrawal of glucocorticoid therapy (systemic or topical) • Mifepristone • Chlorpromazine • Imipramine

Clinical Presentation of Adrenal Insufficiency

The clinical presentation of adrenal insufficiency may be either acute or chronic depending on its severity, rate of onset, and underlying cause. In general, the development of adrenal insufficiency is gradual, and its clinical features are nonspecific. Thus, the diagnosis is often delayed until an intercurrent illness precipitates an acute adrenal crisis.

The signs of chronic adrenal insufficiency predominantly arise from glucocorticoid and mineralocorticoid deficiency—the latter a feature of PAI only, as mineralocorticoid production by the zona glomerulosa of the adrenal gland is preserved in SAI. Signs include orthostatic hypotension due to dehydration, and electrolyte abnormalities such as hyponatremia, hyperkalemia, metabolic acidosis, and increased urea concentration. Abnormalities in the full blood count including anemia, lymphocytosis and eosinophilia may occur, in addition to hypoglycemia and increased liver transaminases.

As the mineralocorticoid activity of the adrenal gland is intact in SAI and TAI, hypotension is generally less severe, and hyperkalemia does not occur. Hypoglycemia is however common, due to the ACTH deficiency and associated growth hormone deficiency. Other pituitary hormone deficiencies may also be present. Mass effect signs and symptoms such as headaches or visual field deficits arising from a space occupying lesion, hemorrhage or infiltrative disease may also be present.

Table 2 Clinical presentation of adrenal insufficiency

- Lethargy
- Dizziness
- Postural hypotension
- Nausea and vomiting
- Weight loss
- Hypoglycemia

Symptoms of adrenal insufficiency include salt craving, anorexia, weakness, malaise, fatigue, muscle cramps, arthralgia, nausea, vomiting, abdominal pain, and diarrhea or constipation. Adrenal insufficiency may also be associated with psychiatric symptoms including depression, anxiety, memory impairment and psychosis. Hyperpigmentation of the skin, particularly in sun exposed areas and mucous membranes, is a characteristic feature of PAI, reflecting the stimulation of the melanocortin-1 receptor resulting from the increased secretion of ACTH and other pro-opiomelanocortin peptides. Deficiency of adrenal androgen secretion in PAI is clinically more apparent in women, and results in loss of axillary and pubic hair, loss of libido, amenorrhea, dry skin, and pruritus. The clinical symptoms and signs of adrenal insufficiency are summarized in Table 2.

Acute adrenal insufficiency, or an adrenal or Addisonian crisis, is a medical emergency. Acute adrenal crisis is defined primarily by hypotension and shock, altered level of consciousness, marked biochemical derangement, and often low-grade fever. Other symptoms of chronic adrenal insufficiency including anorexia, nausea and vomiting, abdominal pain and malaise may also occur. Epidemiological studies suggest an incidence of between 5 and 10 adrenal crises per 100 patient years, which is lethal in 1 in every 200 patients (Allolio, 2015). It most commonly occurs in PAI. In patients with undiagnosed PAI, acute adrenal crisis may occur when they are subjected to serious infection or acute, major stress. In patients with known PAI, acute adrenal crisis may occur in those who do not take additional glucocorticoid during infection, major illness or surgery; due to persistent vomiting caused by gastroenteritis or other gastrointestinal disorders; in patients who are abruptly withdrawn from both oral and inhaled doses of glucocorticoid; or following bilateral adrenal hemorrhage or infarction. Acute adrenal crisis is an increasingly common presentation of immunomodulatory therapy-related autoimmune lymphocytic hypophysitis. Acute adrenal crisis may also complicate SAI during acute stress or surgery.

Diagnosis of Adrenal Insufficiency

The diagnosis and type of adrenal insufficiency is established by the presence of low serum cortisol in combination with plasma ACTH, which may be either elevated in PAI or inappropriately normal or low in SAI and TAI. Subsequent investigations should confirm the diagnosis and determine the underlying cause.

It is important to note that the approach to the diagnosis of adrenal insufficiency is guided by the clinical presentation. In acute adrenal crisis, treatment should be initiated immediately even before the results of plasma ACTH and cortisol measurement are available, as delayed treatment is a significant contributor to the excess mortality in acute adrenal insufficiency complicating PAI (Bornstein et al., 2016; Cooper, 2017).

Evidence suggests that adrenal insufficiency can be excluded at early morning cortisol concentrations >450 nmol/L and is likely at levels <100 nmol/L (Grossman, 2010). PAI is defined by raised plasma ACTH and low serum cortisol. Specifically, this should be assessed by simultaneous measurement of morning (0600–0800) serum cortisol and plasma ACTH, as cortisol concentrations are greatest in the early morning and are lowest in the afternoon. A morning cortisol concentration <140 nmol/L and ACTH concentration greater than two-fold above the upper limit of the reference range is consistent with PAI (Bornstein et al., 2016).

The recommended gold standard diagnostic test for PAI is the standard-dose ACTH stimulation test or short synacthen test (Bornstein et al., 2016). This involves the administration of 250 mcg of intravenous (IV) or intramuscular (IM) synthetic ACTH (1–24) with simultaneous measurement of serum cortisol and plasma ACTH at baseline (0 min), followed by serum cortisol measurement at 30 min and at 60 min to assess the response of the adrenal glands poststimulation. Although assay dependent, peak cortisol concentration <500 nmol/L at 30 or 60 min is suggestive of PAI.

In addition, simultaneous measurement of plasma renin and aldosterone can be performed, with increased plasma renin concentration or activity and normal or low aldosterone concentration confirming the presence of mineralocorticoid deficiency in PAI.

Imaging, specifically with a computed tomography (CT) scan of the adrenal glands, should be performed in the absence of adrenal (steroid 21-hydroxylase) antibodies. X-ALD should be considered in males who present with adrenal insufficiency with negative adrenal antibodies.

The diagnosis of SAI is suggested by an inappropriately normal or low plasma ACTH in combination with a low serum cortisol. The presence of other pituitary hormone deficiencies or panhypopituitarism is also supportive of SAI, although isolated ACTH deficiency is a feature of autoimmune hypophysitis. If early morning cortisol concentrations are within the equivocal range (i.e. cortisol concentration greater than 100 nmol/L but less than 450 nmol/L), referral to an Endocrine Centre for a stimulation test such as an Insulin Tolerance Test is recommended to determine if there is an appropriate cortisol rise to stress, in the absence of

contraindications (i.e., seizures or ischemic heart disease) (Grossman, 2010; Sweeting and Chua, 2015). Adequate response is defined as a peak cortisol concentration >550 nmol/L which has doubled from baseline in response to hypoglycemia (blood glucose level <2.2 mmol/L) (Dons, 1998). A short synacthen test may also be undertaken with the caveat that it may fail to detect SAI and TAI of recent onset as the adrenal glands have not yet atrophied. The underlying cause of SAI should be further assessed with a pituitary MRI.

Management of Adrenal Insufficiency

Pharmacotherapy replacement of glucocorticoid deficiency (and mineralocorticoid deficiency in PAI) is the mainstay of treatment for adrenal insufficiency. PAI can be lethal if left untreated - prior to the widespread availability of glucocorticoid therapy, most patients with PAI died within 2 years of diagnosis (Esposito et al., 2017). There are several important considerations regarding the appropriate formulation of pharmacotherapy, dosing regimen, education and monitoring of treatment efficacy.

Acute Adrenal Insufficiency

Acute adrenal insufficiency (adrenal crisis) is a life-threatening complication of adrenal insufficiency and accounts for a significant proportion of mortality associated with this condition (Rushworth et al., 2017). Acute adrenal insufficiency is therefore an emergency requiring immediate treatment. The aim of initial management is to treat the hypotension and electrolyte abnormalities (i.e., hyponatremia and hyperkalemia), and to reverse the glucocorticoid deficiency (Gargya et al., 2016). Immediate administration of parenteral preferably IV hydrocortisone, or IM if no IV access is immediately available, is required. Fifty to 100 mg of IV hydrocortisone 6–8 h is generally recommended (Melmed et al., 2016). Rapid infusion of normal saline is also required, given the associated significant deficit in both sodium and water. Five percent dextrose saline should be added if hypoglycemia is present. Specific mineralocorticoid replacement is not necessary with a total daily hydrocortisone dose ≥50 mg, as this provides adequate mineralocorticoid cover (Charmandari et al., 2010). The presence of an intercurrent illness which may have precipitated the acute adrenal insufficiency (frequently gastroenteritis and flu-like illness) should also be investigated and treated.

Hydrocortisone therapy should be weaned over 3–4 days once the clinical condition has stabilized. A typical regimen would be 50 mg IV 6 h, then 8 h, then 12 h, followed by oral hydrocortisone 40 mg in the morning and 20 mg at 1500–1600. This can then be rapidly weaned to an oral maintenance dose in PAI such as 20 mg in the morning and 10 mg at 1500–1600. In PAI, fludrocortisone 50–100 mcg should be commenced once the total daily dose of hydrocortisone is less than 50 mg.

Chronic Adrenal Insufficiency

Lifelong glucocorticoid and mineralocorticoid replacement therapy is required in PAI, while only glucocorticoid replacement therapy is required in SAI (and TAI). In addition, replacement of other pituitary hormone deficiencies may also be needed in SAI.

Glucocorticoid Replacement

Chronic oral glucocorticoid maintenance therapy should preferably be administered at a dose and timing that mimics the normal cortisol production rate and pattern. A range of possible glucocorticoid preparations and dosages may be used. Either the natural glucocorticoid hydrocortisone or cortisone acetate, which is converted to hydrocortisone in the liver, is preferred. Glucocorticoid formulations such as prednis(ol)one or dexamethasone are not recommended because their longer duration of action has been associated with complications associated with chronic glucocorticoid excess, including reduced bone mineral density, and increased adiposity (Bleicken et al., 2008). The exception is in situations where higher glucocorticoid doses are needed to treat co-existing medical conditions (e.g., rheumatoid arthritis); with prednisone the recommended maintenance therapy. The prednisone dose can be increased during a flare in the underlying medical condition (Electronic Therapeutic Guidelines, 2018). The relative potency and half-life of these various glucocorticoid formulations is summarized in **Table 3**.

Hydrocortisone is generally administered in two to three divided doses with one half to two thirds of the total daily dose taken in the morning, mirroring the physiological diurnal cortisol secretion pattern (Bornstein et al., 2016). Given SAI is associated with some endogenous glucocorticoid production, a low dose twice daily regimen is generally appropriate.

Table 3 Relative potency and half-life of glucocorticoid formulations

Glucocorticoid	*Relative glucocorticoid potency*	*Relative mineralocorticoid potency*	*Equivalent dose for glucocorticoid effect*	*Estimated biological half-life (hours)*
Hydrocortisone	1	1	20 mg	8–12
Cortisone acetate	0.8	0.8	25 mg	8–12
Prednisone	4	0.8	5 mg	18–36
Methylprednisone	5	0.5	4 mg	12–36
Dexamethasone	25–50	0	400–800 mcg	36–54

In a twice daily dosing regimen, two-thirds of the daily dose should be administered in the morning, immediately upon waking, and one-third of the dose should be administered between 1400 and 1500 (Electronic Therapeutic Guidelines, 2018). In a three-daily dosing regimen, 40%–60% of the dose should be administered in the morning, immediately upon waking, 25%–35% of the dose should be taken at midday, and 15%–25% of the dose should be taken in the late afternoon, prior to 1700 (Electronic Therapeutic Guidelines, 2018). It is not necessary to take hydrocortisone with food, and it should not be taken after 1700 as this may cause insomnia and physiological glucocorticoid levels are lower in the evening.

There is no strictly objective clinical or biochemical measure to ascertain the optimal dose of oral maintenance hydrocortisone therapy, and thus this is associated with significant controversy (Torpy, 2017). The standard hydrocortisone tablets available in Australia are 20 mg and 4 mg. The equivalent strengths of cortisone acetate tablets are 25 mg and 5 mg. The traditional fixed hydrocortisone dose of 30 mg daily or cortisone acetate dose of 37.5 mg daily is now considered to be excessive for most adults with PAI and may be associated with reduced bone mineral density (Bornstein et al., 2016).

As patients with SAI may still have some endogenous glucocorticoid production, the replacement dose is generally lower than in PAI. Hydrocortisone doses of 10 mg in the morning and 10 mg in the afternoon, or even lower (e.g., 8 mg in the morning and 4 mg in the afternoon), are frequently used (Sweeting and Chua, 2015).

Studies have shown mean endogenous cortisol production rates of between 5 and 8 mg/m^2 daily, depending on age and body composition, equivalent to oral hydrocortisone replacement of 15–25 mg daily or cortisone acetate 20–35 mg daily (Purnell et al., 2004). Accordingly, weight-based dosing for hydrocortisone and cortisone acetate is increasingly recommended in both PAI and SAI (Mah et al., 2004). Specifically, hydrocortisone maintenance doses of approximately 0.24 mg/kg daily or an equivalent cortisone acetate dose of 0.3 mg/kg daily for PAI, with less required in SAI, is advised (Electronic Therapeutic Guidelines, 2018).

There is no laboratory test to assess the adequacy of glucocorticoid replacement and thus clinical assessment is key. However, serum cortisol day curves may aid glucocorticoid dose adjustment for hydrocortisone or cortisone acetate, although they are not useful for prednisone therapy. Peak cortisol concentration can be measured 2 h postdose. A peak cortisol concentration greater than 700 nmol/L may suggest that the dosage should be reduced (Electronic Therapeutic Guidelines, 2018).

Clinical assessment includes weight and body composition, blood pressure, skin pigmentation, evidence of Cushing's syndrome, and overall well-being (Bornstein et al., 2016). Inadequate replacement may be associated with reduced energy levels, postural hypotension, nausea, abdominal pain, and progressive pigmentation in PAI, whilst over-replacement will lead to weight gain, insomnia, peripheral edema, Cushingoid features and osteoporosis. Bone mineral density should be monitored for osteoporosis.

Mineralocorticoid Replacement Pharmacotherapy

Mineralocorticoid replacement therapy is essential in PAI to maintain intravascular euvolemia and prevent hyponatremia and hyperkalemia. In addition, adequate mineralocorticoid replacement facilitates a lower glucocorticoid replacement dose, thus attenuating the long-term adverse effects of glucocorticoid excess (Esposito et al., 2017).

Fludrocortisone (9-alpha-fluorohydrocortisone) therapy is the treatment of choice, usually at a dose of 100 mcg daily (range 50–200 mcg daily) (Bornstein et al., 2016). Fludrocortisone should be administered as a single dose in the morning, mimicking the peak daily physiological serum aldosterone concentration (Williams et al., 1972).

The dose titration of fludrocortisone is based on more specific clinical signs and biochemical findings than that of glucocorticoid therapy, and includes assessment of body weight, postural blood pressure, serum electrolytes and plasma renin activity. Specifically, blood pressure, serum sodium, and potassium concentrations should be maintained in the normal range, and plasma renin at the upper end of the normal range. For example, postural hypotension, salt craving, elevated plasma renin activity and electrolyte abnormalities indicate inadequate dosing of fludrocortisone therapy; conversely, hypertension, peripheral edema and decreased plasma renin activity suggests that the dose of fludrocortisone should be reduced. Acute adjustments of mineralocorticoid dose are not required for stress or intercurrent illness.

The appropriate dose of fludrocortisone therapy is also dependent upon the concomitant glucocorticoid therapy being used. Specifically, higher doses of fludrocortisone may be needed with prednisone or dexamethasone, due to their lack of mineralocorticoid activity. In contrast, a lower dose of fludrocortisone would be expected when combined with hydrocortisone therapy, given hydrocortisone has some mineralocorticoid activity (**Table 3**).

The dose of fludrocortisone may need to be temporarily increased by 50%–100% in warmer weather or in situations associated with excessive sweating, such as intensive exercise, and increased salt intake should also be recommended (Bornstein et al., 2016). Moreover, in the setting of persisting hypertension where the fludrocortisone dose has already been reduced and/or seems appropriate, antihypertensive pharmacotherapy should be commenced in combination with fludrocortisone (Inder et al., 2015).

Dehydroepiandrosterone

The need for dehydroepiandrosterone (DHEA) or adrenal androgen replacement is not routine in PAI. Nevertheless, it may be considered in premenopausal women with PAI, given the adrenal cortex is the primary source of the androgen precursors DHEA, DHEA sulfate (DHEAS) and androstenedione. A trial of morning oral DHEA replacement dose of 25–50 mg is recommended, titrated by measuring serum DHEAS concentrations in the morning pre-DHEA dose (Bornstein et al., 2016). Some studies report beneficial effects on mood, sexual function, and general well-being in women with PAI treated with DHEA, given androgen deficiency in women may be associated with decreased libido, mood disorders and fatigue (Binder et al., 2009). However, in a meta-analysis and systematic review, DHEA treatment was not associated with any substantial clinical benefit (Alkatib et al., 2009).

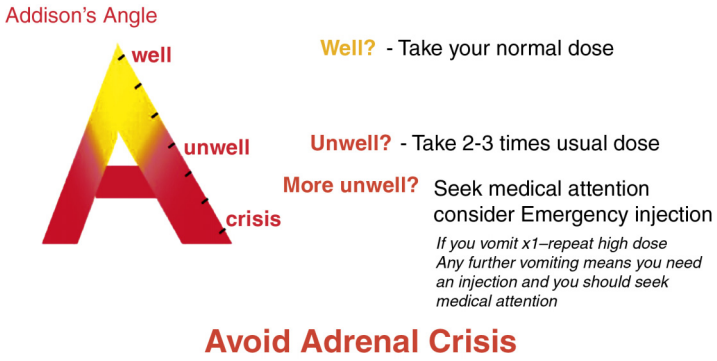

Figure 2 Addison's Angle. This image is copyright of Sydney Local Health District, 2018. Apart from any use permitted under the Copyright Act 1968 (Cth), no part may be reproduced by any process, nor may any other exclusive right be exercised, without the permission of Sydney Local Health District. *Source: Hetherington, J., Chua, E., Gargya, A. (2018). Addison's Angle: A 10-min teaching tool to avoid adrenal crisis. 18th International Congress on Endocrinology, Cape Town, South Africa.*

Education, Sick Day Management and Stress Dosing

Patient and family education is a critical aspect of the management of adrenal insufficiency, with the primary aim being the prevention of acute adrenal crisis. Even with treatment, the health-related quality of life in those with adrenal insufficiency is often reduced (Løvås et al., 2002), underscoring the importance of appropriate management and education.

Education should be regularly revised and should focus on the need for life-long replacement therapy and the importance of increasing the dose of glucocorticoid therapy during illness and stress. Patients must wear a medical alert (Medic Alert) bracelet or necklace. Patients should also be provided with parenteral glucocorticoid injector kits (i.e., "Acto-O-Vial" 100 mg hydrocortisone IMI) for use in emergencies, such as nausea and vomiting in which oral therapy is unable to be tolerated. The patient and their family should also be taught how to administer these glucocorticoid injector kits, and when to present to the Emergency Department, and this should be discussed at each visit. Useful resources include:

http://slhd-intranet.sswahs.nsw.gov.au/SLHDintranet/videos.html?l=1;
http://www.addisoncrisis.info/emergency-injection/emergency-injection-cortico-steroids-solu-cortef-act-o-vial-two-chamber-ampul/;
https://www.addisons.org.uk/;
https://addisons.org.au/.

A sick day management plan is a useful resource in this regard, detailing the recommended dose increases of glucocorticoid therapy in specific situations and advising when parenteral hydrocortisone should be administered, and when to present to casualty for urgent medical assessment. The "Addison's Angle" is a simple tool which illustrates these important concepts and is shown in Fig. 2.

In general, appropriate glucocorticoid stress dosing for mild illness or surgery, for example febrile illness, mental stress, or dental extraction, is considered two to three times the usual oral maintenance dose. The three by three rule is a useful guide, advising tripling the usual maintenance dose for 3 days or for the duration of mild illness, after which the patient resumes their usual replacement therapy dose (Nieman, 2013). An example of a sick day management plan is shown in **Table 4**.

In addition, 50–100 mg IV hydrocortisone administered immediately prior to minor surgery may also be appropriate. In contrast, regular high dose IV hydrocortisone is required during major illness or surgery, generally at doses of 50–100 mg every 6–8 h (Arlt, 2009), although others advocate lower dosing regimens (Nenke and Torpy, 2014). This dosing regimen can be weaned to the usual maintenance regimen based on the clinical course as detailed in the management of acute adrenal crisis.

Finally, in women with adrenal insufficiency during pregnancy, hydrocortisone should be increased in the later stages of pregnancy, for example by 20%–40% from 24 weeks' gestation, mimicking the physiological increase in serum cortisol during pregnancy due to both increased free cortisol and cortisol binding globulin levels (Bornstein et al., 2016). Fludrocortisone may also need to be increased due to the progressive rise in maternal progesterone concentration during pregnancy, which acts as a mineralocorticoid antagonist, although the increase in hydrocortisone replacement may be sufficient (Lebbe and Arlt, 2013). Intrapartum, women require IV saline and a similar IV hydrocortisone regimen as for major illness and surgery. Hydrocortisone can, however, be rapidly weaned to maintenance doses immediately postpartum.

Current and Future Trends

Given that adrenal insufficiency remains associated with increased morbidity and mortality even with treatment, the potential of glucocorticoid formulations that may better reflect physiological diurnal cortisol patterns have recently been evaluated. A novel once-daily oral hydrocortisone dual-release tablet, compared with the standard formulation and dosing regimen for oral

Table 4 An example of a sick day management plan for patients with adrenal insufficiency

Issue	*Symptoms*	*Temperature*	*Dose adjustment*	*Duration of oral dose adjustment*
Trivial illness	e.g. mild cold	No temperature (less than 37.4°C)	No change	N/A
Mildly unwell	e.g. mild infection (such as cystitis) with low grade temperature	37.5–38.5°C	2× normal oral dose	Until recovery plus 1–2 days
More unwell	e.g. high fevers	>38.5°C	3× normal oral doset	Until recovery plus 2 days
	e.g. gastroenteritis with vomiting ± diarrhoea or pneumonia etc	Could be normal or raised	Early parenteral hydrocortisone (50–100 mg IV bolus followed by 25–50 mg IV every 8 h till the condition stabilizes) then 2–3× normal oral dose	Until recovery plus 2 days
Minor dental procedure (>I h under local anesthetic), significant injury or major emotional stress			2× normal oral dose	24 h
Major surgery or procedure with general anesthetic			Parenteral hydrocortisone (50–100 mg IV bolus at induction followed by 25–50 mg IV every 8 h till stable) then 2× normal oral dose	Continue for 48 h post procedure

From (Gargya et al., 2016)

hydrocortisone, provided a sustained serum cortisol profile 0–4 h-post dose, with decreased late afternoon and evening and 24-h cortisol exposure (Johannsson et al., 2012; Nilsson et al., 2017). Furthermore, the novel formulation was associated with a small but significant reduction in mean weight, blood pressure, and improved glucose and lipid metabolism in patients both with and without preexisting diabetes. Based on these findings, the modified release oral hydrocortisone formulation (Plenadren) is now available in Europe as both 5 and 20 mg modified release tablets.

However, it is important to note that the modified release formulation does not mimic the gradual cortisol increase before wakening, associated prandial increases or frequent pulses of cortisol, and thus only partly mimics the physiological profile of cortisol. Further, the improvements in glucose and lipid metabolism were generally not maintained during 6 months' follow-up (Johannsson et al., 2012). There is also not enough evidence that the novel modified release formulation reduces the excess morbidity or mortality associated with adrenal insufficiency. Thus, further research is needed to determine the optimal glucocorticoid replacement therapy.

Role of Pharmacist

Given the critical role of pharmacotherapy in the treatment of adrenal insufficiency, the pharmacist has an important role in the management of this condition. In particular, the pharmacist should play an active role in patient education, emphasizing the importance of adherence, including the appropriate timing of glucocorticoid replacement. In the setting of concomitant pharmacotherapy that may inhibit steroidogenesis or accelerate glucocorticoid metabolism, or when the patient with adrenal insufficiency is unwell, the pharmacist should advise the patient of the need to increase their glucocorticoid dose. It is also important to educate the patient regarding the fact that their glucocorticoid therapy is in fact replacement therapy, rather than being used as anti-inflammatory therapy, ensuring that can be taken on an empty stomach, and thereby alleviating concern over possible adverse effects associated with chronic glucocorticoid use. The pharmacist should ensure that the patient has an emergency hydrocortisone injector kit, is confident in its administration, and that it is not expired. Furthermore, it is important to understand the difference between hydrocortisone vials for general parenteral use as compared with an emergency hydrocortisone injector kit, which is specifically designed for the treatment of acute adrenal crisis.

Conclusions

Adrenal insufficiency is an important endocrine disorder in which lifelong pharmacological glucocorticoid and (in PAI) mineralocorticoid replacement therapy is required to avoid associated morbidity and mortality. The aims of treatment in adrenal insufficiency are to provide physiological glucocorticoid replacement, minimize over- or under-replacement of glucocorticoid therapy and associated adverse sequelae; improve patient quality of life, and most importantly, prevent life-threatening acute adrenal crisis. Accordingly, education of the patient, family, medical and other health care providers, including the pharmacist, on the importance of compliance with replacement therapy, sick day management and stress dosing of glucocorticoid therapy is essential to achieving these treatment goals. Nevertheless, even with treatment, patients with adrenal insufficiency have increased morbidity and mortality, underscoring the importance of ongoing education in managing this condition and the need to further optimize glucocorticoid replacement formulations, dosing and administration regimens to greater replicate physiological diurnal cortisol patterns.

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Management of Endocrine Disorders and the Pharmacist's Role: Diabetes

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Introduction

Diabetes has been described as an escalating global epidemic, which imposes a huge cost burden on families, communities, and health-care systems. The most recent estimates suggest that worldwide approximately 425 million adults have diabetes and that this will increase to 642 million by 2040 (International Diabetes Federation, 2017). The prevalence is rising rapidly in both developed and developing countries with one in 11 adults diagnosed with type 2 diabetes (T2DM), and over 1 million children and adolescents affected by type 1 diabetes (T1DM) (International Diabetes Federation, 2017). However, the most dramatic increases in diabetes have occurred in Pacific island nations and in the Middle East and North Africa region, which now have the highest prevalence rates in the world. In Polynesia and Micronesia, where prevalence is highest, more than one in five adults have diabetes. In 2014, the annual global health-care costs associated with diabetes were estimated to be 825 billion dollars, disproportionately experienced in middle- and lower-income countries where, between 1980 and 2014, prevalence of diabetes increased by 35% (NCD Risk Factor Collaboration (NCD-RisC), 2016). Much of this burden is driven by the costs of managing the long-term complications such as cardiovascular disease (CVD), kidney and eye disease, and amputations.

The first section of this chapter will present a brief overview of current understandings of the pathophysiology and complications of the various forms of diabetes, the rationale and role of early screening for T2DM and the role of the pharmacist, contemporary evidence-based approaches for the management of diabetes including lifestyle modification, pharmacotherapy, diabetes education, and self-management support. This is followed by an overview of pharmacist roles in the care of people with diabetes, focusing on the elements of pharmaceutical care and disease management support that may be delivered in community pharmacies and other health-care settings and how these may be incorporated into routine practice. The final part of the chapter will examine the evidence of efficacy, effectiveness, and cost-effectiveness of pharmacists' interventions for people with diabetes.

What Is Diabetes?

Disease Definitions

Diabetes is a complex metabolic disorder with varying clinical presentations. The clinical and diagnostic feature common to all is hyperglycemia resulting from damaged or dysfunctional β pancreatic cells.

The current classification of diabetes distinguishes four categories (American Diabetes Association, 2018a).

1. *T1DM is due to autoimmune destruction of β cells leading to absolute deficiency in insulin;*
2. *T2DM; the most common form of diabetes mellitus, characterized by insulin resistance and progressive loss of insulin secretion.*
3. *GDM—carbohydrate intolerance resulting in hyperglycemia of variable severity, with onset, or first recognition, during pregnancy.*
4. *Diabetes due to other causes, for example, MODY; other endocrine diseases, pancreatic diseases (e.g., cystic fibrosis), or iatrogenic causes, for example, corticosteroid therapy.*

Pathophysiology of T1DM and T2DM

T1DM: In a predisposed individual, environmental triggers encountered early in life such as infections, chemicals, and nutrients, are able to activate an autoimmune cascade against pancreatic islet β cells, involving production of both cellular (T lymphocytes) and humoral autoantibodies. The presence of antibodies alone, however, is not diagnostic or prognostic of T1DM since some individuals who are antibody positive will not develop T1DM. In those who will progress to T1DM, early destruction of β cells may be initially compensated through pancreatic reserve. Over time, the progressive destruction of β cells heralds the development of hyperglycemia. Only once the majority of β cells have been destroyed will T1DM develop (Zaccardi et al., 2016).

T2DM: The hallmarks of T2DM are insulin resistance and β cell dysfunction. It has long been believed that insulin resistance predates β cell dysfunction such that early in T2DM, insulin resistance leads to β cell hypersecretion of insulin to compensate ("hyperinsulinemia") and thus maintain glucose homeostasis. Over time, as insulin resistance worsens, the pancreatic cells are unable to compensate leading to frank hyperglycemia, that is, T2DM (Kahn et al., 2014). More recently, it has been understood that because of the operation of a feedback loop between β cells and insulin sensitive tissues, β cell dysfunction is already present at the preclinical stages of T2DM (Kahn et al., 2014). It is the magnitude of reduction of β cell function that determines the degree of hyperglycemia. In T2DM, there are also other types of dysfunction in organs such as the liver, which produces too much glucose, the pancreas where α cells increase glucagon secretion and the gut with reduction in GLP-1 levels and increased intestinal transit time for food and the kidney with increased glucose reabsorption. In adipose tissue (visceral fat), dysregulation of hormones such as adiponectin and the production of inflammatory cytokines contribute to insulin resistance (Cornell, 2012).

Long-Term Complications

Chronic uncontrolled hyperglycemia causes damage to blood vessels and nerves, which leads to long-term complications among people with any form of diabetes. The complications are classified as "microvascular" (due to damage to small blood vessels) and "macrovascular" (due to damage to the arteries). Microvascular complications include eye disease or "retinopathy," kidney disease termed "nephropathy," and neural damage or "neuropathy". In diabetic retinopathy, vascular leakage and ischemia in the retina can lead to blindness and is a leading cause of the condition in adults aged 20–74 years. Diabetic nephropathy is the most common cause of end-stage renal disease in developed countries and also an independent risk factor for cardiovascular morbidity and mortality. Neuropathy is a highly variable complication initially affecting the peripheral nerves. Its associated complications cause significant morbidity and include foot ulceration, amputations, gangrene, sexual dysfunction, and even cardiac arrhythmia leading to sudden death.

The major macrovascular complications include myocardial infarction and stroke. An individual with diabetes has a threefold greater risk of myocardial infarction compared to someone without diabetes (Forbes and Cooper, 2013). The atheroma and myocardial damage are likely to occur at least in part as consequences of hypertension, altered vascular permeability, and ischemia. However, long-term glycemic control remains the best predictor of CVD risk in people with both T1DM and T2DM. Other complications include depression and dementia (Forbes and Cooper, 2013).

Diagnosis

Diabetes may be diagnosed using either a fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) after a 75 g oral blood glucose tolerance test (OGTT) or HbA1c. Criteria for diagnosis are as follows: FPG≥126 mg/dL (7.0 mmol/L); or 2-h PG≥200 mg/dL (11.1 mmol/L) or HbA1C ≥6.5% (48 mmol/mol); or random plasma glucose (RPG) ≥200 mg/dL (11.1 mmol/L) in patient with symptoms of hyperglycemia). Unless there is a clear clinical diagnosis, a second test is required for confirmation (American Diabetes Association, 2018a) HbA1c testing should not be used as the basis for diagnostic testing if any condition is present that leads to a short red blood cell survival time (e.g., anaemia, chronic renal failure, and hemolysis), as this increases the risk of a false negative result.

Diabetes Screening and Prevention

This section will focus on screening for T2DM. For a variety of reasons including the absence of appropriate screening tests for other forms of diabetes, the mainstay of pharmacist screening is with T2DM.

Risk Factors for Diabetes

T2DM develops over time as a result of multiple biomedical, lifestyle, and social risk factors. Nonmodifiable risk factors such as increasing age, ethnicity, genetic variation, and male gender play an important role. A range of modifiable risk factors also act as key risk factors for diabetes onset. Key established risk factors at a population level include obesity, inadequate physical inactivity, suboptimal diet, and gestational diabetes (Bellamy et al., 2009; Wilmot and Idris, 2014). Effective interventions to prevent diabetes typically emphasise lifestyle modification within a structured program (Diabetes Prevention Program Research, 2002; Kosaka et al., 2005; Li et al., 2008; Tuomilehto et al., 2001). Adoption of key goals for modifiable risk behaviors by participants, such as the following evidence-based goals from the benchmark Finnish Diabetes Prevention Study (Tuomilehto et al., 2001), supports improved outcomes:

- losing body weight (typically 5% or more)
- achieving moderate physical activity on a daily basis (30 min or more)
- increasing fiber intake (e.g., 15 g/1000 calories)
- reducing total calories from fat (30% or less energy derived from dietary fat, 10% or less from saturated fats)

A recent meta-analysis suggests that lifestyle interventions lasting 6–24 months can reduce the average risk of diabetes onset long-term by 31% (Barry et al., 2017), with further gains possible from longer interventions (3–6 years' duration). Metformin also appears to also have a significant protective effect against diabetes during short and longer term (Barry et al., 2017), but there are fewer trials compared with lifestyle interventions and it is unclear if a beneficial effect persists after withdrawal of metformin.

The role of certain drugs in stimulating cardiometabolic disturbances and potentially causing increased rates of new-onset diabetes is well known. This is classified as secondary diabetes. Key drug groups implicated include corticosteroids, thiazide diuretics, beta-blockers, atypical antipsychotics (esp. olanzapine, clozapine), and antiretroviral therapies (Anyanwagu et al., 2016). The last two groups have come increasingly under the spotlight—as the life expectancy of patients taking these therapies has increased in recent years, a greater need to consider long-term risks and conduct cardiometabolic monitoring has evolved. Statins have also been implicated, with the level of risk possibly dependent on the dose and individual statin's potency (Anyanwagu et al., 2016). Currently, it is felt that the relative risk of diabetes onset is low, and the clinical benefit of statin use usually warrants continued treatment.

Evidence suggests that a range of other highly prevalent clinical and other factors, for which associations with diabetes incidence are established, may actually have causal relationships with diabetes. Such factors include poor sleep quality and obstructive sleep apnoea, shift work, smoking, socioeconomic status, and low birth weight (Anothaisintawee et al., 2016; Wannamethee et al., 2001; Whincup et al., 2008). The role of social determinants of health such as lack of availability of fresh food and physical activity opportunities at a neighborhood level are increasingly acknowledged as having adverse consequences for risk factor prevalence. More recent research is actively exploring the potential additional role of factors such as environmental pollutants (particularly persistent organic pollutants from pesticides) (Henríquez-Hernández et al., 2017) and the gut microbiome (Moreno-Indias et al., 2014) in diabetes onset.

Screening Tools

Several options now exist to screen for diabetes risk and for undiagnosed diabetes. A number of countries have validated noninvasive diabetes risk scores—either bespoke or adapted—for use in their population to determine likelihood of future diabetes onset, including China, Finland, France, Mauritius, Mexico, the United States, Germany, United Kingdom, India, and Australia (Kengne et al., 2014). These risk scores are largely based on patient self-reported attributes and anthropometric measures of obesity (e.g., BMI, waist circumference). They identify people at elevated risk of diabetes with reasonable accuracy and are highly cost-effective by not requiring use of laboratory or point of care testing. However, it is only appropriate to use such a score if it has been validated for the population of interest. Such scores are widely used as the initial basis for referral to diabetes prevention programs, but clinical judgment needs to be exercised. For example, some who exceed the threshold score largely as a result of points stemming from increased age and gender may already have quite a healthy lifestyle and little to gain from a lifestyle intervention. Attributes of some key international risk assessment tools are outlined in **Table 1** as examples of the similarities and variation that many occur.

It is important to understand the specific attributes of the particular risk assessment tool in use for several reasons. A key consideration is that tools are typically designed or validated for use in particular settings, which may affect feasibility in a pharmacy setting (Noble et al., 2011). Some have been developed for self-administration by patients, others to be administered by health professionals, and some will be designed for population-level use that draws on database information. The score development should be scrutinized to determine what exactly the score is measuring—for example, is it undiagnosed diabetes, high-risk of diabetes, or a combined outcome? Levels of sensitivity (percent with diabetes who receive a positive test result) and specificity

Table 1 Core attributes of several common diabetes risk assessment tools used internationally (adapted from Krass and Armour, 2011; Noble et al., 2011 and individual validation studies). (Bang et al., 2009; Gray et al., 2010; Lindström and Tuomilehto, 2003)

Risk scale	*Country*	*Validation age range*	*Factors included*	*Sensitivity (Se) Specificity (Sp) Receiver operating curve (ROC)*
ADA Diabetes screening score (Bang et al., 2009) Cut point ≥4 (undiagnosed diabetes or prediabetes) Cut point ≥5 (undiagnosed diabetes) Score range −1 to −9	USA	≥20 years	Age, sex, family history of diabetes, history of hypertension, obesity, and physical activity	73% (Se) 57% (Sp) 0.72 (ROC) (using values cut-point ≥4 as the more comparable with diabetes risk scores)
Leicester Diabetes Risk Score (Gray et al., 2010) Cut point ≥12 Score range 0–47	United Kingdom	40–75 years	Age, ethnicity [white European vs. other (predominantly South Asian)], sex, first-degree family history of diabetes, antihypertensive therapy or history of hypertension, waist circumference and body mass index	81% (Se) 45% (Sp)_ 0.72 (ROC)
Finnish Diabetes Risk Score (FINDRISC) (Lindström and Tuomilehto, 2003) Score cut-point >11 Score range 0–26	Finland	35–64 years	Age, BMI, waist circumference, physical activity, daily consumption of fruits, berries and vegetables, history of anti-hypertensive drug treatment, history of blood glucose, and family history of diabetes	66% (Se) 69% (Sp) 0.73 (ROC) (females) 70%(Se) 61% (Sp) 0.72 (ROC) (males)
The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) (Noble et al., 2011) Score cut point >12 Score range 0–36	Australia	≥25 years	Age, gender, ethnicity, and family history of diabetes, hypertension, smoking, fruit and vegetable consumption, history of blood glucose, waist circumference, physical activity	78%(Se) 58% (Sp) 0.75 (ROC)

(percent without diabetes who are correctly identified as such) vary widely and should be understood so that a result can be correctly interpreted for the screening participant (Noble et al., 2011). It is also important to realize that such tools are typically not validated for ongoing monitoring, for example, to determine the effect of an intervention on an individual's risk. If nonmodifiable factors such as demographics are heavily weighted in calculating a risk score, diabetes risk scores may not improve substantially for many making health gains. Similarly, the items included in the final tools may or may not have a direct causal relationship with the diabetes outcome; they are included on the basis of their predictive value alone. Conversely, some items are added to self-administration tools even if they do not add to the discrimination power of the tool—for example, questions about physical activity and vegetable consumption are only added to the Finnish FINDRISC tool to emphasise their importance in diabetes prevention (Lindström and Tuomilehto, 2003).

Tests to screen for undiagnosed diabetes involve measurement of glucose abnormalities using HbA1c, 2-h plasma glucose levels following oral glucose tolerance testing, or fasting plasma glucose (see Section 2.4, diagnostic criteria) (Siu, 2015; The Royal Australian College of General Practitioners, 2016). Where impaired fasting glucose, impaired glucose tolerance, or T2DM is detected, a repeat test should be used to confirm the diagnosis. While increasingly accepted, there remains some concerns about the validity of HbA1c as a population screening tool and so country-specific guidelines should be followed (Incani et al., 2015). Laboratory-standard screening tests are not accessible by pharmacists in most countries, but the availability of point of care HbA1c and capillary blood glucose testing as a preliminary screening tool is increasingly common, particularly in developed countries.

Guidelines for Screening

The most appropriate mechanism for screening will depend upon the national or local health system. In a pharmacy context, best practice for screening typically involves a two-stage process. The first step is to establish if a patient falls into a high-risk group, using one of the risk scores described above where validated for the patient population. Where a risk stratification tool does not exist, local guidelines may recommend other approaches to identifying high-risk groups within the population (e.g., previous history of CVD, aged 45 years or over and obese) (American Diabetes Association, 2018b; The Royal Australian College of General Practitioners, 2016). Step two involves a point of care test for those identified as belonging to a high-risk group. Krass et al. (2007) demonstrated the superiority of two-step sequential screening in pharmacy compared with risk stratification only, with respect to detection of undiagnosed diabetes.

Use of capillary, nonfasting tests in pharmacies often uses random rather than fasting glucose concentrations. If testing regimens are likely to produce less reliable results than their laboratory equivalents, a more conservative referral threshold is probably necessary. Few head-to-head comparisons of different screening models in community pharmacy exist to confirm the key attributes of effective screening, however the Pharmacy Diabetes Screening Trial underway in Australia may provide insights in key areas such as the type of capillary screening test performed (Krass et al., 2017) and performance of certain referral thresholds for diagnostic testing.

Pharmacists' Role in Screening

Globally, it is estimated that over 45% of people with diabetes remain undiagnosed—a large majority (83%) of such individuals are in low- and middle-income countries, but it also remains a challenge in developed countries (Beagley et al., 2014). Given the frequency with which undiagnosed and at-risk individuals visit pharmacies, including those who are otherwise healthy, pharmacists can play an important role in increasing access to screening (Mc Namara et al., 2012).

In general terms, screening intervals for diabetes should adhere to guidelines for the health system. Typically, key international guidelines recommend annual screening for those with prediabetes (American Diabetes Association, 2018c; The Royal Australian College of General Practitioners, 2016), while other individuals without prediabetes should be screened every 3 year from about 40–45 years of age. Country-specific variation regarding screening frequency and when to commence screening often exists for a range of at-risk social and clinical subgroups (e.g., ethnic minorities, history of cardiovascular disease or gestational diabetes, obese individuals, elevated diabetes risk score, or using antipsychotic medication). Pharmacists have a responsibility to provide a professional level of service in terms of ensuring patient privacy and handling of blood products. They should also take the time to interpret the result for patients, indicating the level of risk implied by the results and the reliability of the test. At a minimum, pharmacists should provide brief advice regarding health behaviors to prevent diabetes, and factors that might be implicated in any positive screening or elevated risk score. Because most pharmacists do not have direct access to medical advice or diagnostic testing, assuring continuity of care is especially important if offering screening services. This may extend to direct communication of results in writing to a nominated doctor if the patient consents, especially for positive screenings (Krass et al., 2017)—a large proportion of referred patients fail to attend medical services for further investigation if referral support is not provided. Pharmacists should consider effective referral as an integral part of the screening process. Further training may be required for pharmacists seeking to deliver lifestyle interventions.

Psychosocial Issues

Clear communication including a discussion of the benefits and risk of screening is valued by patients and supports an informed decision to participate. Potential harms from screening include associated time and costs, incorrect diagnosis, and distress associated with a positive screening or diagnosis (Thoolen et al., 2006). Stigma associated with diabetes may also need to be addressed for some individuals—this may be more prevalent in culturally and linguistically diverse groups, or other vulnerable communities. In such communities, challenges with screening may stem from factors such as misunderstanding of the disease, treatment options and prognosis, or where a culture of prevention is not commonplace (Alzubaidi et al., 2015). Poor patient–provider relationships can often delay diagnosis further, even when symptomatic (Alzubaidi et al., 2015). Effective health awareness messages and counseling to complement screening programs may be necessary in such situations.

Guidelines for Diabetes Management

Current Goals of Therapy

Goals of therapy in patients with diabetes are customized and dictated by patients' individual factors such as age, lifestyle, comorbid conditions, lifestyle, and well-being (Endocrinology Expert Group, 2017). This has followed growing awareness of the high prevalence of mental health/well-being issues such as depression, feelings of stigma, and diabetes-related distress. These have adverse consequences in their own right but can negatively impact an individual's capacity to undertake vital self-care activities and need to be adequately managed. However, regardless of these factors, the key goals of therapeutic management for patients with diabetes are to relieve symptoms such as polyuria and polydipsia, control blood glucose levels, prevent acute diabetes complications such as hyperosmolar hyperglycemia and diabetic ketoacidosis, and also prevent and treat chronic complications such as neuropathy, nephropathy and retinopathy, and ischaemic cardiovascular disease (American Diabetes Association, 2018c; Endocrinology Expert Group, 2017). Current best practice recommends that all HCPs involved in caring for people with diabetes adopt a patient-centred approach. Furthermore, choice of therapy is also dependent on drug characteristics and patient preferences. This orients the goal of diabetes pharmacological management toward minimizing medication side effects while ensuring adequate glycemic control (American Diabetes Association, 2018c; Endocrinology Expert Group, 2017; Rossi, 2017). Avoiding hypoglycemia is a priority when designing and reviewing diabetes therapy and its goals. The potential effect of therapy on patients' weight and cost considerations are also important factors that drive the individualization of diabetes therapy and the development and implementation of a diabetes management plan.

Table 2 Treatment targets for patients with diabetes (Endocrinology Expert Group, 2017; The Royal Australian College of General Practitioners, 2016)

T1DM	
HbA1c	≤53 mmol/mol ≤7%
Blood glucose concentration	4–7 mmol/L (fasting and preprandial) 5–10 mmol/L (postprandial)
T2DM	
HbA1c	<53 mmol/mol (7%)[a]
Blood glucose concentration	4–8 mmol/L (fasting and preprandial)[b] <10 mmol/L (postprandial)
LDL-C	<2 mmol/L (primary prevention) <1.8 mmol/L (secondary prevention)
HDL-C	≥1 mmol/L
TC	<4 mmol/L
TG	<2 mmol/L
BP (adults)[c]	≤140/90 mmHg

[a]In patients at high risk of hypoglycemia levels of 64 mmol/mol [8.0%] is appropriate.
[b]In patients at high risk of hypoglycemia levels of 6–8 mmol/L is appropriate.
[c]The target for patients with diabetes and albuminuria/proteinuria is <130/80 mmHg.

Goals of therapy in diabetes should consider individualization of treatment targets and take account of key contributors to diabetes complications. Addressing CVD risk and also improving cardiovascular outcomes are important factors influencing drug choice and goals in patients with diabetes. This is particularly relevant since CVD is the leading cause of death in patients with diabetes (The Royal Australian College of General Practitioners, 2016). Because the majority of patients with diabetes actually die from cardiovascular complications, early and effective management of CVD risk factors, as described in Chapter XX, are also a core focus of management. CVD risk factors are typically already present upon diagnosis of diabetes (Herman et al., 2015).

In both T1DM and T2DM, glycemic targets should be individualized to patients, while ensuring that hypoglycemia is avoided. Treatment targets are summarized in **Table 2**.

Lifestyle Modification

Lifestyle modifications are important in the overall management of all patients with diabetes. In T1DM the dietary principles focus on adequate caloric intake for normal growth and ideal body weight and maintenance of near normal blood glucose levels by balancing food intake with insulin and physical activity. In T2DM lifestyle modification also centres on nutrition and physical activity, but for many people with T2DM weight loss is required to address insulin resistance. As previously discussed, smoking cessation and psychological care are also recommended as part of lifestyle modification interventions where applicable (American Diabetes Association, 2018b).

Following diagnosis of T2DM diabetes, the initial management usually commences with lifestyle modification focusing on both carbohydrate and energy restriction and increase in physical activity for a period of three months, since lifestyle changes alone may result in glycemic control. However, it should be emphasized that for patients with underlying symptoms, those unlikely to achieve goals with lifestyle modifications alone or in patients with consistently high glucose levels, it may be appropriate to commence pharmacotherapy earlier than 3 months. Lifestyle modifications continue to play a significant role in the management of diabetes patients throughout course of disease management, especially in relation to glycemic control and management of CVD risk (The Royal Australian College of General Practitioners, 2016).

Various studies indicate that nutritional interventions based around calories restriction result in HbA1c reductions between 0.3% and 2.0%. Modest persistent weight loss, defined as sustained reduction of 5% of initial body weight, can delay the need for initiation of pharmacotherapy. However, to achieve optimal outcomes in control of glycemia, blood pressure, and lipids, a sustained weight loss of 7% is recommended. This weight loss can be achieved with various programs that result in energy deficit of 500–760 kcal/day (or programs tailored at 1200–1500 kcal/day for women and 1500–1800 kcal/day for men adjusted based on individual baseline body weight) (American Diabetes Association, 2018c).

In relation to physical activity, current recommendations suggest that patients with T2DM benefit from a total of 30 min of physical activity in most days per week (if not all days) (The Royal Australian College of General Practitioners, 2016). In children and adolescents, 60 min/day over 3 days/week of moderate to vigorous intensity activity is recommended. Aerobic exercise has been associated with similar reduction of HbA1c levels (0.73%) compared to single medication use alone (0.9%). Resistance-based exercises are associated with smaller reductions (The Royal Australian College of General Practitioners, 2016). Other major lifestyle modifications are based around reduced sodium intake (especially in patients with comorbidities such as hypertension) and limited

alcohol consumption (≤2 drinks for men and ≤1 drink for women per day). The above lifestyle modifications should be considered in all treatment plans designed for diabetes patients. It should be emphasized that a patient-centred approach toward lifestyle modifications in patients with diabetes should be tailored to achieve realistic goals (American Diabetes Association, 2018c; The Royal Australian College of General Practitioners, 2016).

Pharmacotherapy and Treatment Algorithms

All people with T1DM require insulin replacement therapy either with multiple daily injections (MDI) including basal and bolus inulin or insulin delivered by an insulin pump. In this section, the focus is on T2DM since this is the most common form of diabetes that pharmacists encounter in practice. Pharmacotherapy in T2DM is usually initiated when patients fail to achieve glycemic control approximately 3 months after introduction of lifestyle modification. Short-term insulin to stabilize blood glucose levels may be needed in patients with particularly high levels of blood glucose concentrations and/or in patients displaying significant symptoms (Endocrinology Expert Group, 2017). It is important to note that the risk of irreversible microvascular complications such as glomerular damage and retinopathy can be prevented with a timely initiation of pharmacotherapy in patients with T2DM. To achieve this, it is pivotal not to delay pharmacotherapy, and this can be facilitated by patient motivation to start treatment (Bailey, 2015).

Pharmacotherapy initiation does not replace lifestyle modifications and they should be complementary to each other.

The emergence of new classes of diabetes drugs has resulted in the availability of a wider range of glucose-lowering medicines. The mechanism of action of currently available antihyperglycemic agents is based around eight underlying pathophysiological mechanisms (i.e., "ominous octet"). These are reduction of insulin secretion from pancreatic β cells, increased liver production of glucose, increased secretion of glucagon from α cells in the pancreas, increased reabsorption of renal glucose, impaired glucose uptake by peripheral tissues, insulin resistance in the brain and neurotransmitter dysfunction, heightened lipolysis, and diminished small intestinal incretin effect (Chaudhury et al., 2017). Currently used types of antihyperglycemic agents in T2DM are summarized in **Table 3** including their mode of action, risk of hypoglycemia, weight gain, and considerations in relation to key side effects.

Initiating Pharmacotherapy in T2DM

Provided there are no contraindications, metformin is the drug of choice as monotherapy in patients who have failed to achieve glycemic control after initial introduction of lifestyle modifications. As a drug choice, metformin is safe and can be very useful in

Table 3 Antidiabetic drug classes: their mode of action and key effects (American Diabetes Association, 2018c; Chaudhury et al., 2017; Cornell, 2012)

Class	*Mode of action*	*Hypoglycemia risk*	*HbA1C reduction (%)*	*Weight*	*Adverse effects and considerations*
Biguanides *Metformin*	insulin sensitiser; effects on inhibition of glucose production	No	1–2	Neutral	GI effects common: nausea, diarrhea vitamin B12 deficiency
Sulphonylureas (SU) *glyburide, glipizidem, gliclazide, glimepiride*	increases pancreatic insulin secretion	Yes	1–2	Gain	Nausea, diarrhea, metallic taste, headache, rash
Acarbose	Delay of intestinal absorption of carbohydrates in the small intestine	No	0.5–0.8		Flatulence, diarrhea, abdominal pain
Thiazolidinediones *pioglitazone, rosiglitazone*	Insulin sensitizer; decrease free fatty acid accumulation, reduce inflammatory cytokines, increase adiponectin levels, and preserve β-cell integrity and function	No	0.5–1.4	Gain	Peripheral oedema, headache, dizziness, arthralgia, congestive heart failure, bone fracture, increased LDL (rosiglitazone), bladder cancer (pioglitazone)
GLP-1 analogs *exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide*	Promote glucose-mediated insulin secretion; reduces glucagon secretion and slows gastric motility	No (only in combination with SU)	0.5–1.5	Loss	Thyroid C-cell tumors, nausea, vomiting diarrhoea (common), pancreatitis risk (?)
DPP-IV inhibitors *sitagliptin, saxagliptin, linagliptin, alogliptin*	Reduces degradation of endogenous GLP-1 and GIP	Low (when used with insulin or a SU)	0.5–0.9	No effect	Joint pain, acute pancreatitis runny nose, sore throat, headache, musculoskeletal pain
SGLT-2 inhibitors *canagliflozin, dapagliflozin, empagliflozin*	Inhibits sodium-glucose co-transporter 2, reducing glucose reabsorption in the kidney	Low (when used with a sulfonylurea or insulin)	0.5–0.7	Loss	Genitourinary infections, increased LDL, amputation canagliflozin), bone fracture risk (canagliflozin)

patients who are overweight. It is not expensive and reduces the risk of cardiovascular events. Additionally, compared to the usual next antihyperglycemic choice (i.e., sulfonylureas), metformin also has a better outlook on cardiovascular mortality and impact on patients HbA1c levels and weight (Maruthur et al., 2016). Because it is renally excreted, patients with diabetes who experience decline in renal function while taking metformin need close monitoring. Declining renal function is often present in ageing patients who have had diabetes for a number of years. Leading international guidelines recommend withdrawal of metformin when eGFR declines below 30 ml/min per 1.73 m^2, to avoid the risk of lactic acidosis resulting from a build-up of metformin.

Intensifying Pharmacotherapy in T2DM

There is a chronological decline in the efficacy of oral antihyperglycemic monotherapy, which parallels a decline β cell function. Following failure to achieve glycemic control with metformin monotherapy at optimized doses, a second antihyperglycemic agent is added. Current ADA guidelines suggest that, if metformin is contraindicated or not tolerated, a dual combination therapy may be initiated in newly diagnosed patients with HbA1c levels ≥9% (American Diabetes Association, 2018c). When patients have markedly high blood glucose levels (e.g., in patients with HbA1c levels of ≥10% or 86 mmol/mol or with hyperglycemic symptoms), insulin should be considered as part of any of the combination regimen leaving open the possibility that as the clinical outlook improves, the regimen may be simplified accordingly (American Diabetes Association, 2018c). A meta-analysis comparing the effects of four antihyperglycemic drug-classes introduced as initial therapy (sulfonylurea, basal insulin, GLP-1 analog, and DPP-4 inhibitor) indicated that HbA1c levels are reduced by 0.9%–1.1%, with the second addition (Nathan et al., 2013). If glycemic control is not achieved within 3 months of dual therapy, a third agent is added and if this escalation fails to achieve HbA1c target with another 3 months, then combination injectable therapies are considered (**Fig. 1**). It should be noted that, regardless of addition of other antihyperglycemic agents, metformin therapy should be continued (if tolerated and not contraindicated) due to further glycemic benefits of this continuation.

To guide the initiation and escalation of pharmacotherapy in patients with T2DM, a number of algorithms have been proposed by various professional organizations. In all cases, it is important to note that principles of a patient-centred approach underpin the application of these algorithms. Patient preferences, drug-related adverse effects, comorbidities, body weight, risk of hypoglycemia, and medication cost must all be factored into designing the treatment plan. The continuing emergence of new pharmacological agents and a lack of high-quality studies investigating combination therapies represent important challenges in the development and application of algorithms. **Fig. 1** represents an algorithm that is based around algorithms from the American Diabetes Association (ADA) algorithm for the management of T2DM and the Australian algorithm for blood glucose treatment (American Diabetes Association, 2018c; The Royal Australian College of General Practitioners, 2016).

Self-Management Support

Self-management education and support are essential components of diabetes care. The extent to which an individual is active and able to self-manage their condition positively contributes to the achievement of glycemic targets. The ADA recommends all patients with diabetes should participate in self-management-based activities aimed at facilitating knowledge and skills required in diabetes self-care (American Diabetes Association, 2018c).

Generally, self-management support facilitates patient's self-care behaviors and informed decision-making process through programs which empower patients to engage in their health management and takes into account their preferences (Marrero et al., 2013). These programs should also take into account patients' health literacy level. Providing active patient support is focused on four key stages of transition for patients with diabetes: at point of disease diagnosis, at regular assessments, when patients experience factors with detrimental effects on diabetes (e.g., other health conditions, physical limitations), and also during the transition of care.

Evidence suggests that self-management education and support programs in patients with diabetes result in better HbA1c control, lower weight, and reduced mortality, better coping, improved quality of life, disease knowledge and self-care behaviors, as well as cost savings (American Diabetes Association, 2018c; Chrvala et al., 2002; Cooke et al., 2013; Frosch et al., 2011; Haas et al., 2014; Malanda et al., 2012; Norris et al., 2002; Steinsbekk et al., 2012).

There are various programs aimed at facilitating patients' self-management and education. These programs are usually focused around optimal nutrition, physical activity, hypoglycemia management and avoidance, smoking cessation if applicable, alcohol, blood pressure, lipid management, foot care, sick day management, as well as medication management (American Diabetes Association, 2018c).

An important component of diabetes self-management is self-monitoring of blood glucose (SMBG). SMBG allows patients to review response to therapy and can also guide them in relation to nutrition and physical activity programs. At the time of diagnosis, it serves to enhance an individual's understanding of how their diet, lifestyle, and medication influence their blood glucose levels. Ongoing SMBG is not generally recommended in low-risk patients on oral antihyperglycemics. A Cochrane review concluded that there are limited clinical benefits to continuing SMBG in patients with T2DM (Malanda et al., 2012). SMBG is recommended in patients on insulin and oral antidiabetic drugs causing hypoglycemia (e.g., sulphonylureas), during pregnancy and prepregnancy planning, when major pharmacotherapy and lifestyle modifications occur and when actively monitoring hyperglycemia due to a condition and in situations where HbA1c results are not reliable (The Royal Australian College of General Practitioners, 2016). SMBG monitoring regimens may be intensive involving preprandial and 2-h post prandial measurements with each meal and a

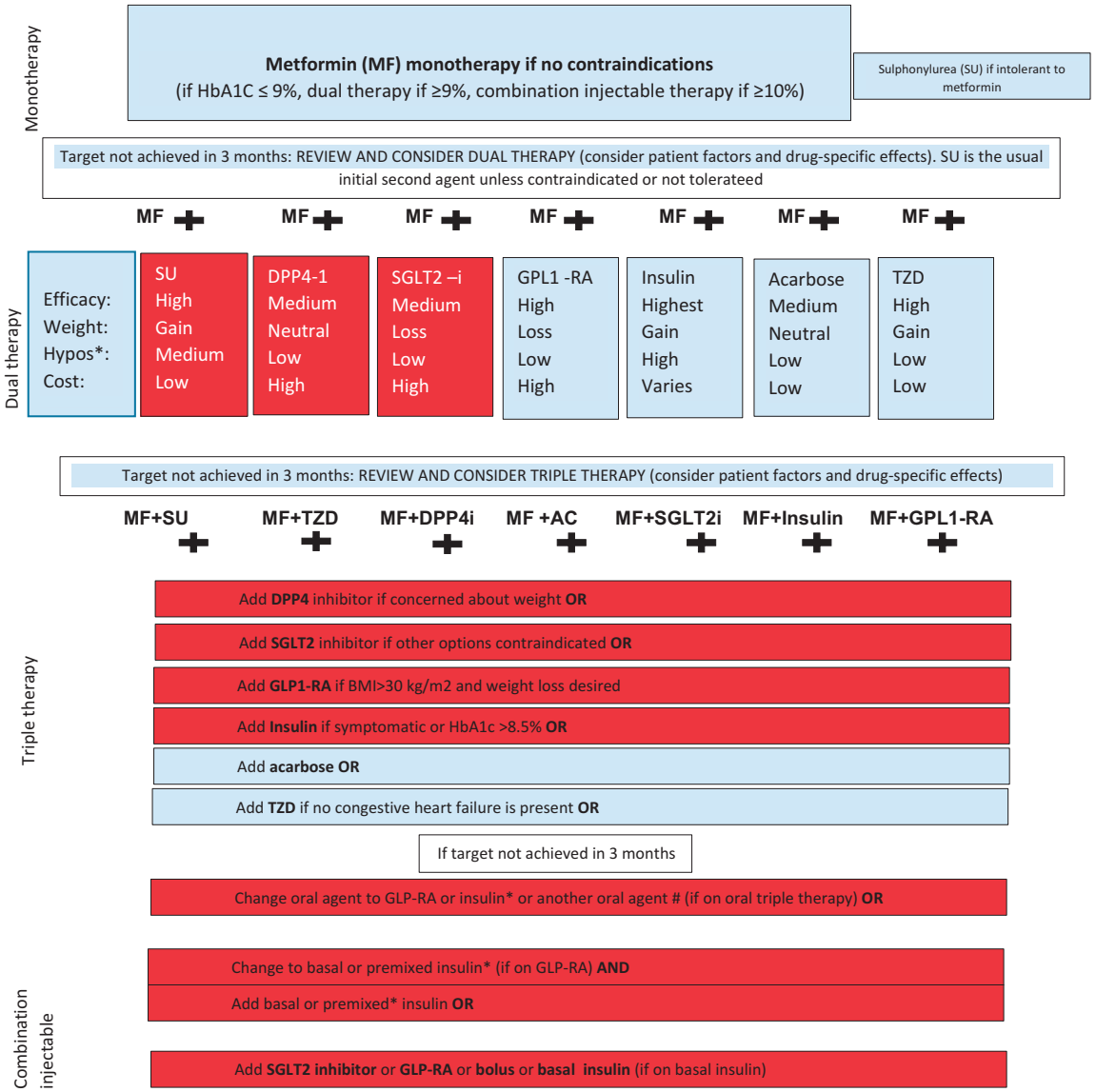

Figure 1 Treatment algorithm for patients with T2DM (American Diabetes Association, 2018c; Hoti, 2016; The Royal Australian College of General Practitioners, 2016). *Note: Red boxes indicate usual therapeutic strategy. MF*, metformin; *SU*, sulfonylurea; *TZD*, thiazolidinedione; *DPP4-i*, DPP-4 inhibitor; *AC*, Acarbose; *SGLT2-i*, SGLT2 inhibitor; *GLP1-A*, GLP-1 analogs (receptor agonists). #smallest effect; *Metformin is usually continued in combination with insulin.

night-time level. Another approach is to vary the time of measurement to different times of the day and repeat measurements on subsequent days at times when BGL is not controlled (pattern management) to determine if this is a pattern and to identify the cause (International Diabetes Federation, 2009).

Pharmacists Role in Diabetes Disease Management Support Through Pharmaceutical Care

Pharmacist Interventions in Diabetes

As a chronic condition, diabetes provides a suitable context through which pharmacists can actively engage in the care of people with diabetes. Pharmacists' medication expertise coupled with easy accessibility of pharmacies places them in an ideal position to assist diabetes patients through active monitoring and provision of pharmaceutical care.

Pharmacist interventions within a pharmaceutical care plan should be systematic because this allows achievement of optimal patient outcomes and fulfillment of treatment goals (Hughes et al., 2017). This approach starts with activities focused around patient assessment (i.e., medical history, physical, laboratory results status, allergies and contraindications, health literacy, and diabetes risk factors), followed by patient treatment plan (i.e., drug-related problem (DRP) screening, individualization,

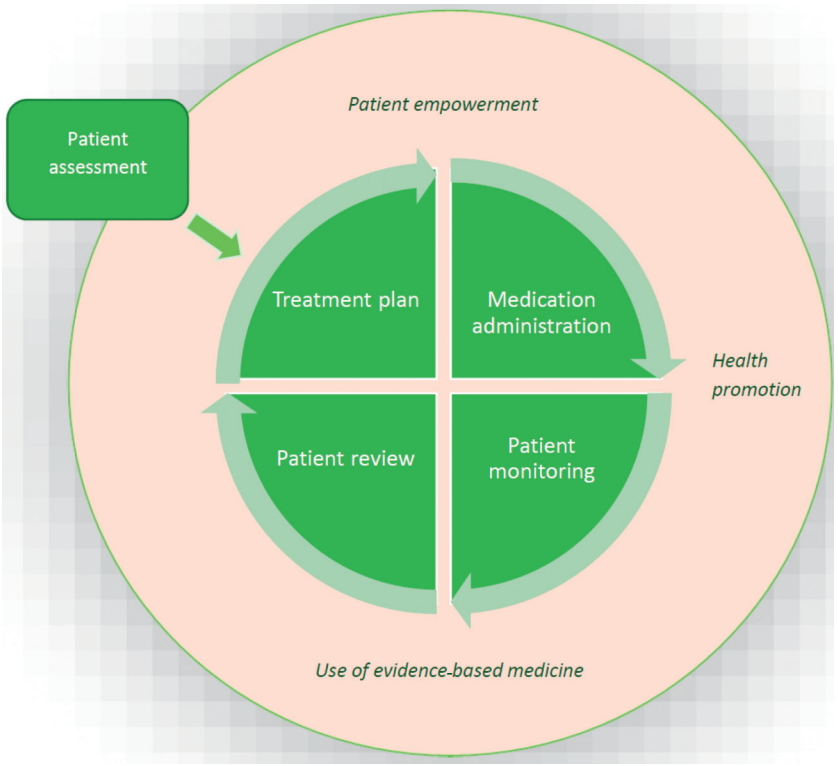

Figure 2 Key steps in delivering systemic pharmaceutical care in patients with diabetes (adapted from Hughes et al., 2017)

and development of treatment plan, patient education), medication administration (including preparation, accurate dispensing and counselling), monitoring (focus on adherence, adverse effects, treatment outcomes, and diabetes complications) and regular review (i.e., results, need for treatment adjustment and referral). These steps are illustrated in **Fig. 2** (Hughes et al., 2017).

Throughout the delivery of pharmaceutical care, pharmacists must ensure that their activities support patient empowerment, incorporate health promotion, and evidence-based medicine. The use of motivational interviewing and collaborative goal setting by pharmacists as complementary strategies to facilitate self-management support have been shown to be effective in improving health outcomes in T2DM (Mitchell et al., 2011). Pharmacists should also endeavour to pursue a multidisciplinary collaborative approach as part of the patient's diabetes care team. A further requirement for delivering diabetes interventions is to provide appropriate conditions and resources to patients with diabetes, including (but not limited to): counseling areas, patient privacy, and necessary accurate equipment such as glucometers, blood pressure meters, and BMI readers.

A number of pharmacist interventions have been documented to improve the overall management of T2DM. Overall, the evidence suggests that pharmacist interventions result in improved patient support and better management and improved glycemic control (Deters et al., 2018; Hughes et al., 2017). More details about the evidence regarding the impact of pharmacists' interventions have been provided in the next section.

Evidence for Impact of Pharmacy Diabetes Interventions Applying the ECHO Model

Any comprehensive evaluation of a pharmacy diabetes intervention requires the ECHO (economic, clinical, and humanistic outcomes) approach, which determines its value as a combination of traditional clinical-based outcomes with more contemporary measures of economic efficiency and quality (Kozma et al., 1993). Evidence for the efficacy and effectiveness of pharmacy diabetes interventions is therefore considered in terms of the ECHO model (Kozma et al., 1993). Clinical outcomes refer to a range of intermediate measures such as HbA1c, FPG, SBP and DBP, BMI, lipids including TC, LDL-C, HDL-C, TG and 10 year absolute CVD risk. Other clinically related impact measures include changes in medication adherence, screening for complications, and/or resolution of drug-related problems (Hughes et al., 2017). Evidence of impacts on more meaningful long-term clinical outcomes such as such as hospitalizations, micro and macrovascular complications is lacking due to the short times frames of pharmacy diabetes intervention studies. Humanistic/social outcomes comprise patient-centred impacts such as health-related quality of life (HRQoL) and diabetes-specific related quality of life, well-being, patient satisfaction, and self-management activities. Economic evaluations typically consider incremental cost-effectiveness of pharmacy diabetes care intervention relative to "usual care" from a third part payer perspective (i.e., government, health insurer).

Clinical Outcomes

Glycemic control

The accumulated evidence for the benefit of pharmacist diabetes interventions on glycemic control comes from several systematic reviews published in the last decade (Hughes et al., 2017). The most comprehensive review, published in 2016, included 36 RCTs conducted across a range of both developed and developing countries and diverse health-care settings including community pharmacy, outpatient clinics, and hospitals. In the 26 studies, which reported an impact on $HbA1_C$, the difference between intervention and "usual care" groups ranged from −1.8% to −2.1% (Pousinho et al., 2016). In this review, 23 studies reported significant reductions in blood glucose (random, fasting, or post prandial) in intervention groups from baseline to follow-up and 20 reported greater improvements in this outcome in intervention compared to control groups (Pousinho et al., 2016). More recently, a meta-analysis of six RCTs of pharmacist diabetes interventions implemented in community pharmacies, which included 670 patients, showed a mean difference in $HbA1_C$ of −0.66% (95% CI −0.86%–0.45%) between intervention and "usual care" groups (Deters, 2018). The differences in effect size between studies may reflect variations in the scope of interventions themselves. The systematic review of community pharmacist diabetes interventions by Deters et al., conducted an analysis of the effectiveness of the different components of pharmacist diabetes interventions. Based on data from 11 RCTs, the most successful components were found to be sending feedback to physicians, individual goal setting, review of medications, and assessing and addressing patient health beliefs and medication knowledge (Deters, 2017). However, the successful components were incorporated to varying extents in each of the studies included in the systematic review. Differences in effect size may also reflect differences in the trial subject characteristics. For example, the higher the baseline glycemic levels and the younger the patient cohort, the greater the impact of the intervention on glycemic control (Hughes et al., 2017).

Cardiovascular—BP, lipids, BMI, absolute CVD risk

On the whole, there is some evidence of positive impacts of pharmacist diabetes interventions on CVD risk factors (Pousinho et al., 2016; Santhschi et al., 2012). In the systematic review by Pousinho et al., there were mixed findings of benefit with statistically significant differences between intervention and "usual care" groups in reductions of SBP and DBP found in only 9/18 studies which measured SBP, 5/15 which measured DBP and 4/15 studies measuring LDL-C and 2/12 studies which included triglycerides. However, a meta-analysis that provides a more robust measure of impact through pooling of data, found that compared with "usual care," pharmacist diabetes interventions were associated with statistically significant reductions in SBP (12 studies with 1894 patients; −6.2 mmHg [95% CI −7.8 to −4.6]); DBP (9 studies with 1496 patients; −4.5 mmHg [−6.2 to −2.8]); TC (8 studies with 1280 patients; −15.2 mg/dL [−24.7 to −5.7]); LDL-C (9 studies with 8084 patients; −11.7 mg/dL [−15.8 to −7.6]); and BMI (5 studies with 751 patients; −0.9 kg/m(2) [−1.7 to −0.1]). No significant change was found in HDL cholesterol. The included studies involved solo delivery of the intervention by pharmacists in 8 studies and in collaboration with physicians, nurses, dietitians, or physical therapists in 7 studies.

Impact on absolute CVD risk was reported in only 6 studies included in the review by Pousinho et al. (2016). The studies used different methods of estimation including UKPDS risk engine, Framingham prediction methods and other prediction charts, which estimate the risk of a cardiovascular event over a 10 year period. An overall decrease in CVD risk was reported in all 6 studies for the pharmacist intervention group between baseline and follow-up and greater improvements compared to the control groups. However, the difference in changes between groups was only statistically significant in 2 studies. Because of different methods of estimation a range of impact cannot be defined (Pousinho et al., 2016).

Medication adherence

Medication adherence has also been shown to improve as a result of pharmacist diabetes interventions; however, a corresponding impact on health outcomes is inconclusive (Omran et al., 2012). A systematic review of RCTs of pharmacist interventions to improve adherence to antidiabetic medication found that while compared to "usual care," 5 of the 8 included studies reported significant improvements in adherence rates with the pharmacist intervention, improvements in glycemic control were found in only 2/8 studies (Omran et al., 2012).

Humanistic/social outcomes

The key humanistic outcome is health-related quality of life (HRQoL). Overall there is conspicuous lack of RCTs of pharmacist diabetes interventions which have included measurement of HRQoL and when included there has been a notable variation in the HRQoL instruments used.

A systematic review evaluating interventions delivered by a pharmacist either alone or as part of a team care arrangement for patients with T2DM found that of the 17 included studies, 12 used generic nonvalidated instruments; and the remainder used a validated generic HRQoL instrument such as the SF-36 or the EQ-5D (Krass and Dhippayom, 2013). Only 6 studies used diabetes-specific HRQoL scales; and one study used both a generic and diabetes specific measure. Thirteen of the 17 studies reported significant improvements in overall or subscale scores post intervention. The effect size varied as did the detail in reporting of overall vs. subscale scores. This variation in effect may be due to the different instruments used, lack of sensitivity of the instruments to subtle effects of the intervention, and/or differences in the nature of the pharmacist diabetes intervention. Because of the different scales used and the level of detail, it is also difficult to compare between studies. Overall, the findings of this (Krass and Dhippayom, 2013) and a subsequent review (Pousinho et al., 2016) suggest some preliminary evidence that pharmacist diabetes

interventions can improve HRQoL with the evidence pointing to a greater effect on mental rather than physical health. Pharmacist diabetes interventions have also been shown to increase patients' knowledge of their condition and its complications and self-management of diabetes (Wubben and Vivian, 2008).

Economic outcomes

Even fewer studies of pharmacist diabetes interventions have examined the economic benefits of this type of pharmacist activity. A recent systematic review identified 25 studies that had conducted some form of economic evaluation in the period between 2006 and 2014. Only 11 were full economic evaluations, which were of moderate quality and most adopted a third-party payer or provider perspective. The studies used a variety of settings, but most were either in community pharmacy or clinic-/hospital-based outpatient facilities. The most common pharmacist diabetes interventions comprised targeted education and general pharmacotherapeutic monitoring. However, variation in the type, mix, and intensity of pharmacist's interventions delivered would necessarily influence the costs (such as labor costs associated with the pharmacist time, costs of medication, which typically increases as a result of medication review, etc.), and thereby affect cost savings or cost-effectiveness. In general, these increased costs are offset by reductions in medical care costs from fewer emergency room visits and hospitalizations. According to the findings of this review, pharmacist-managed services resulted in cost savings ranging from $7 to $65,000 ($8 to $85,000 in 2014 US dollars) per person per year, and generated higher quality-adjusted life years with lower costs, compared with usual care (Wang et al., 2016).

A summary of pharmacists' ley interventions in relation to clinical outcomes and the effect of individual intervention component on HbA1c level have been provided in **Table 4**.

Table 4 A summary of key pharmacists' interventions (Deters et al., 2018; Hughes et al., 2017)

Pharmacist intervention (54)	*Clinical outcome*
Clinical review based around goal setting, HbA1c monitoring, education sessions, adherence sessions	60% vs. 40% controlled HbA1C, −0.3% improvement in HbA1c
Lifestyle education, self-care, and therapy review	HbA1c: +0.2% to −2.1% (vs Control); SBP: −0.5 to −18.6 mmHg; DBP: −0 to −17.4 mmHg; TC: 0 to −39 mg/dL [0 to −1.0 mmol/L]; LDL: −6 to −15.6 mg/dL [−0.16 to −0.40 mmol/L]; HDL: +1.95 to −4.3 mg/dL; TG: −13.0 to −53.4 mg/dL [−0.15 to −0.60 mmol/L]
Education on diabetes, diet and exercise, medication counseling, adherence assessment, and pharmacotherapy adjustment	HbA1c: −0.76% (vs control); FBG: −29.32 mg/dL [−1.62 mmol/L];
Education, communication, regular follow-up, feedback on BG; improved pharmacist–physician communication strategies	Significant improvements in adherence
Medication management, educational interventions to patients, feedback to health-care professional (e.g., DRP identification, recommendation and discussion)	SBP: WMD −6.2 mmHg ([−7.8 to −4.6], studies conducted in community pharmacy greater reduction in SBP (–10.0 mmHg vs –5.5 mmHg); DBP: WMD −4.5 mmHg (−6.2 to −2.8); TC: WMD −15.2 mg/dL (−24.7 to −5.7) [−0.39 mmol/L (−0.64 to −0.15)], LDL: WMD −11.7 mg/dL (−15.8 to −7.6), [−0.30 mmol/L (−0.41 to −0.20)]
Medication management and adherence based interventions, measurement of CVD risk factors	HDL: WMD +0.2 mg/dL (−1.9 to 2.36) [−0.005 mmol/L (−0.049 to 0.061)], BMI: WMD −0.9 kg/m^2 [−1.7 to −0.1]
Counseling and education on diabetes, medication, lifestyle modification, and self-monitoring, medication adherence strategies, screening, DRPs, pharmacotherapy adjustments	HbA1c: −0.18% to −2.1% (vs control); SBP: −3.3 to −23.05 mmHg; DBP: −0.21 to −9.1 mmHg; TC: +18.95 to −32.48 mg/dL [0.49 to −0.84 mmol/L]; LDL: +7.35 to −30 mg/dL [+0.19 to −0.78 mmol/L]; HDL: −5.8 to +11 mg/dL [−0.15 to +0.28 mmol/L]; TG: +12 to −62 mg/dL [0.14 to 0.70 mmol/L]; BMI: Reduced; Adherence: Improved; 10-Year CVD risk: improved

Individual intervention component (55)	*Mean HbA1c (%) reduction*
Medication review and DRP identification	−0.79
Diabetes-related complications (DM)	−0.60
Health beliefs and medication knowledge (DM)	−0.74
Nutrition, exercise, and smoking recommendations (DM)	−0.66
Goal setting (individual)	−0.81
Diabetes knowledge	−0.54
Review of diabetes record books (DM)	−0.74
Blood glucose measurements	−0.70
Medication adherence	−0.60
Patients' satisfaction with pharmacists' interventions	−0.67
Health status	−0.74
Feedback and recommendations to the physician	−0.81

DRP, Drug-related problem; *BG*, blood glucose; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *TC*, total cholesterol; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *TG*, triglyceride; *FBG*, fasting blood glucose; *BGM*, blood glucose monitoring; *CVD*, cardiovascular disease; *WMD*, weighted mean difference; *BMI*, body mass index; *DM*, disease management.

Documentation of Interventions

When delivering pharmaceutical interventions, it is recommended that pharmacists engage in documentation of patient care. This is crucial to ensure not only continuity of care and patient safety but also to achieve good quality of interventions delivered. Given that diabetes is a progressive condition and also due to the fact that oral diabetes therapy diminishes in efficacy over time, documentation of interventions by pharmacists, in a timely manner, is essential to support the decision making processes during these key stages of diabetes care. Furthermore, documenting these interventions also assists pharmacists in communicating and disseminating patient results to other health-care professionals (HCPs) involved in the patient's diabetes care.

Documentation of pharmacist's care can be achieved through preparation of patient treatment plans, monitoring forms and drug and clinical problem identifications. In general, these documents should enable accurate recording and easy legibility of interventions provided by pharmacists through all stages of intervention and should allow for documentation of all components involved in the documentation, for example, education, patient assessment information, details of treatment plan, medication assessments, medication counseling and administration, DRP identification and other clinical issues identified, action taken and resolution steps, monitoring and regular follow-up details, health promotion activities, screening and risk assessments, and other disease state management details. Various pharmacy professional organizations provide templates or guidelines for pharmacists documenting the above activities aimed at improving patient' diabetes care (Australian Government Department of Health, 2015; Pharmaceutical Care Network Europe, 2017). These are important considerations for inclusion into all forms of design of pharmacists care plans when delivering interventions for diabetes patients.

Conclusion

Pharmacists have a valuable contribution to make to improving health outcomes for people at risk of diabetes, with undiagnosed diabetes and/or those with established disease. Opportunistic screening of "at-risk" people visiting the pharmacy is key to enabling early intervention to prevent the onset of subsequent diabetes and its complications. For people with established diabetes, optimizing the benefits of pharmacotherapy therapy through medication counseling and monitoring for DRPs is a core pharmacist activity. There is, however, a much wider scope for pharmacists' interventions, including self-management education, supporting SMBG, and providing continuity of care and support over time. At each visit to the pharmacy, there is an opportunity to review patient progress, troubleshoot problems, and thereby assist the patient to achieve better control and prevent downstream complications. There is also an opportunity for pharmacists to seek to become a part of the diabetes care team in a model of multidisciplinary health care.

Glossary

Prediabetes The presence of either IFG or IGT
Receiver Operating Curve It is a plot of the true positive rate against the false positive rate for the different possible cut points of a diagnostic test
Sensitivity The ability of a screening test to correctly identify individuals with the condition
Specificity The ability of a screening test to correctly identify individuals who do not have the condition

Abbreviations

ADA	American Diabetes Association
BMI	Body Mass Index
BP	Blood pressure
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DRP	Drug-related problem
ECHO	Economic, clinical, and humanistic outcomes
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin
HCP	Health-care professional
HDL-C	High-density lipoprotein cholesterol
HRQoL	Health-related quality of life
IFG	Impaired fasting glucose

IGT	Impaired glucose tolerance
LDL-C	Low-density lipoprotein cholesterol
MDI	Multiple daily injections
MODY	Mature-onset diabetes of the young
NCD	Noncommunicable disease
OGTT	Oral blood glucose tolerance test
RPG	Random plasma glucose
ROC	Receiver operating curve
Se	Sensitivity
Sp	Specificity
SBP	Systolic blood pressure
SMBG	Self-monitoring of blood glucose
TC	Total cholesterol
TG	Triglycerides
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

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Management of Endocrine Disorders and the Pharmacists' Role: Thyroid Disorders

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Learning Objectives

After reading this chapter, the reader should be able to:

- Understand the importance of the hypothalamic–thyroid–pituitary axis and the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4).
- Define the thyroid disorders hypothyroidism and hyperthyroidism and list the common causes of these conditions.
- Discuss the management of hypothyroidism and hyperthyroidism, including the place of medications available for their treatment and side effects, including any pharmaceutical formulation considerations.
- Discuss the current role and the future roles of the pharmacist in the management of thyroid disorders.

Key Concepts

- The thyroid gland and the hormones T_3 and T_4 have an integral role in the functioning of many important systems and processes within the human body, working alongside the nervous system to regulate metabolic processes and heart rate.
- Thyroid function tests (TFTs) are often undertaken if symptoms and signs of thyroid disorder are present.
- As pharmacist roles in independent prescribing become more common, their involvement in management of thyroid disorders is becoming more common.
- In both the community and hospital setting, pharmacists should work with patients to the management of the condition. Pharmacists can support medication taking and encourage patient medicine adherence.
- Advice regarding the management of side effects is also a role of the pharmacist. Advising patients on what to do if a patient experiences side effects will allow medication-related problems to be addressed promptly.

- If the patient wishes, the pharmacist can advise and liaise with the patient's doctor or endocrinologist if further support is needed.
- Pharmacists have a strong role to play in the future of thyroid disorder management. Pharmacists are playing an important role in thyroid clinics and as part of a multidisciplinary team. The role in this area has mainly been around the initiation, maintenance, and modification of medicines for specific individuals who have been diagnosed with thyroid disorders. This role has been conducted under the guidance of written protocols by the chief endocrinologist of the hospital or within an established team.
- The advanced role of the pharmacist in this field is yet to be well-defined; further research needs to be undertaken to evaluate the scope, protocols, and effectiveness of pharmacists in this role.

Introduction to the Thyroid and Thyroid Disorders

The thyroid is the largest endocrine gland in the body; it is a butterfly-shaped gland located at the front of the neck inferior to the Adam's apple (American Association of Clinical Endocrinologists, 2015). It is responsible for a number of functions, including the regulation of metabolism, growth, and homeostasis (American Association of Clinical Endocrinologists, 2015; Jonklaas and Talbert, 2011). The gland consists of two lobes, connected by bridge called an isthmus (Hulisz, 2018). The gland secretes the hormone thyroxine (T_4) and triiodothyronine (T_3) (Jonklaas and Talbert, 2011; Hulisz, 2018; Rousset et al., 2015) and calcitonin (Hulisz, 2018). Reservoirs of these hormones in the gland and in the blood ensure that there is constant availability (Jonklaas and Talbert, 2011). Under- or over-activity of the thyroid gland may negatively affect a number of integral systems and processes within the body, including the cardiovascular, skeletal, and metabolic systems (DeEugenio and Smith, 2004; Freeman, 2009; Jonklaas and Talbert, 2011). Calcitonin has a number of roles including the regulation of calcium homeostasis (Felsenfeld and Levine, 2015; Hulisz, 2018).

Thyroid disorders can range from those that are subclinical and require no intervention, to those that are life-threatening and so requiring immediate intervention. According to the World Health Organization's International Statistical Classification of Diseases and Related Health Conditions 10th revision (ICD-10), *Thyroid gland and Thyroid hormone disorders* sits within the *Endocrine, nutritional and metabolic diseases classification (E00-E07)* (World Health Organisation, 2016). Within this classification, the ICD-10 further differentiates eight thyroid conditions (World Health Organisation, 2016):

- Congenital iodine-deficiency syndrome
- Iodine deficiency-related thyroid disorders
- Subclinical iodine-deficiency hypothyroidism
- Other hypothyroidism
- Other nontoxic goiter
- Thyrotoxicosis (hyperthyroidism)
- Thyroiditis
- Other disorders of the thyroid

The most common of the thyroid disorders and those that the pharmacist is most likely to encounter in daily practice are hypothyroidism and hyperthyroidism. Ultimately the goal of treatment of both hypothyroidism and hyperthyroidism is to achieve a euthyroid state (The Royal College of Physicians, 2011); the background, management, and the role of the pharmacist within hypo- and hyperthyroidism will be discussed in this chapter.

To understand these conditions more fully, it is firstly important to understand the importance of the hypothalamic–thyroid—pituitary axis and the thyroid hormones T_3 and T_4.

The hypothalamic–pituitary–thyroid axis is responsible for the production and the release of thyroid hormones and is sensitive to small changes in circulating levels, which subsequently drive alterations in secretion to ensure that circulating levels are maintained within a narrow range (DeEugenio and Smith, 2004; Freeman et al., 2009; Jonklaas and Talbert, 2011). The hypothalamus produces thyrotropin-releasing hormone (TRH), which subsequently promotes the synthesis and release of thyroid-stimulating hormone (TSH) from the anterior pituitary (Freeman et al., 2009; Jonklaas and Talbert, 2011). The synthesis and release of the main thyroid hormones (T_3 and T_4) occurs when TSH acts on the thyroid gland (Best Practice NZ, 2010; DeEugenio and Smith, 2004). While the thyroid gland produces all of the body's T_4, the majority of T_3 is produced in the liver and the kidney by removing an iodide from the T_4 structure. T_3 is two to three times more potent than T_4, and, therefore, there is less T_3 in circulation (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011). The axis is controlled and maintained by negative feedback from thyroid hormones at both the hypothalamic and the pituitary levels (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011). In a person who has a normally functioning system, as T_4 and T_3 concentrations increase, the pituitary and the hypothalamus decrease production of TSH and TRH. This ensures the regulation of thyroid hormone production (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011).

Thyroid Disorders—An Overview

Prevalence and Etiology

Thyroid disorders have been estimated to represent 30%–40% of presentations in endocrine practice (Garmendia Madariaga et al., 2014). However, the prevalence of abnormal thyroid function is still debated (Canaris et al., 2000), this is mainly due to

differences in the definitions of these disease states and the sample populations that have been evaluated in studies (Canaris et al., 2000). A recent meta-analysis of nine studies in Europe found that there was a 3.82% mean prevalence (when both diagnosed and undiagnosed was taken into consideration) (Garmendia Madariaga et al., 2014). While a US-based study reported the incidence to be 4.78% (Garber et al., 2012). In NZ, it is estimated that 5% of women and 1% of men are affected by thyroid disorders (Best Practice NZ, 2010). Despite this variation, what *is clear* from research is that prevalence is higher in women than in men and the prevalence increases with age (American Association of Clinical Endocrinologists, 2015; Eggertsen et al., 1988; Okamura et al., 1989; Sawin et al., 1979; Vanderpump, 2011).

Hypothyroidism has been strongly associated with dietary iodine (Vaidya and Pearce, 2008); goiter (swelling of the thyroid) and congenital hypothyroidism are prevalent in areas where daily intake of iodine is less than 50 μg and per 25 μg, respectively (Vanderpump, 2011). Remote and mountainous areas of South-East Asia, Latin-America, and Central Africa are areas that are deemed high risk for thyroid disorders (Vanderpump, 2011). Iodization programs have proven beneficial (Rousset et al., 2015); for example, the use of iodized salt in bread became mandatory in Australia and New Zealand in 2009, which rendered the countries iodine sufficient (Walsh, 2016), although there have been reports of iodine deficiency reemerging (Foundation TAT, 2018).

In areas where dietary iodine is sufficient, a common cause of thyroid disorders is thought to be autoimmune (Walsh, 2016). Antithyroid antibodies have been identified and appear to vary across sex, age, and ethnicity. The prevalence of antibodies is greater in females, increases with age, and is greater in whites and Mexican Americans than in African Americans (Canaris et al., 2000; Hollowell et al., 2002). While the presence of antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) does not determine whether a patient needs to be treated, it does increase the risk of thyroid dysfunction (Åsvold et al., 2012; Walsh et al., 2010).

Additionally, patients who are at higher risk of thyroid disease include those with other autoimmune diseases, dyslipidemia, past history of neck surgery or irradiation, suspicious thyroid symptoms postpartum or a previous episode of postpartum thyroiditis, chronic cardiac failure, coronary heart disease, arrhythmias, hypertension, elevated pulse of >90 bpm, menstrual disturbance or unexplained infertility, some genetic conditions, and patients who are taking certain medications, for example, lithium, amiodarone (NZ BP, 2005).

In the case of amiodarone, this medication can induce both hypo- and hyperthyroidism, due to its high iodine content and also its ability to have a toxic effect on the thyroid gland. Guidelines vary withregard to the type of monitoring that should be conducted (Best Practice NZ, 2010); however, most do suggest monitoring of TSH while on this medication. An initial rise in TSH may occur in the first 6 months of therapy with iodine, but this should then return to normal range (Best Practice NZ, 2010; NZ BP, 2005). Monitoring should occur prior to starting therapy, every 6 months during treatment and continue for a year after the cessation of the medication, due to its long half-life (Best Practice NZ, 2010).

Lithium can also affect the thyroid and lead to hypo- or hyperthyroidism, although the latter is rare (Best Practice NZ, 2010). Hypothyroidism induced by lithium is common and can occur abruptly. Baseline monitoring of TSH and fT_4 and annual monitoring of TSH are recommended (Best Practice NZ, 2010; NZ BP, 2005).

Consequences of Poorly Managed Thyroid Disorders

Patients whose thyroid disorders are not well managed may be at higher risk of developing associated health problems, including cardiovascular disorders and arrhythmias (Sawin et al., 1994), and have lower bone mineral density and quality (Ross et al., 1987). There has been clear evidence, for example, for poorer outcomes for patients with hypothyroidism and heart failure; hypothyroidism is associated with decreased inotropy, decreased cardiac output, reduced vascular compliance, and hyperlipidemia (Canaris et al., 2000; Heeringa et al., 2008; Iacoviello et al., 2008; Klein and Danzi, 2008; Rodondi et al., 2008; Ziman et al., 2012). The Colorado Thyroid Disease Prevalence study was a study of 25,862 individuals that aimed to determine the prevalence of abnormal thyroid function and the relationship between abnormal thyroid function and lipid levels and symptoms. The authors reported only 60% of patients taking thyroid medication had TSH levels in the appropriate range (Canaris et al., 2000). Additionally, there have been some (albeit preliminary) data that have pointed to subclinical hypothyroidism being associated with hyperlipidemia, cardiovascular disease, and low bone mineral density (Iacoviello et al., 2008; Rodondi et al., 2008; Ross et al., 1987). Hyperthyroidism is also associated negative health outcomes, including an increased risk of atrial fibrillation (Heeringa et al., 2008).

Diagnosis

Diagnostic tests are not warranted if there are no clinical symptoms. In a report by Bandolier (1997), people were categorized based on their clinical presentation as high, moderate, and low risk of hypothyroidism. Subsequently, these individuals' thyroid function was assessed; 78%, 2.9%, and 0.45% of people in the respective groups were found to have a thyroid disorder (NZ BP, 2005; White and Walmsley, 1978).

Serum TSH has been promoted to be the sole initial test for monitoring thyroid dysfunction (American Association of Clinical Endocrinologists, 2012; Best Practice NZ, 2010; NZ BP, 2005, 2007). In normal patients, when TSH is within the reference range (0.4–4.0 mU/L), the free-T_4 (fT_4; the metabolically available moiety of T_4 that is not protein-bound) will in most cases also be within the reference range, and there is no further need to check other hormone or antibody levels (Best Practice NZ, 2010; NZ BP, 2005, 2007).

TSH levels change with age, and some laboratory measurements will take age into account when reporting TSH reference levels (Best Practice NZ, 2010; NZ BP, 2005, 2007). For example, mild elevations in TSH may be normal in the elderly (American

Association of Clinical Endocrinologists, 2012). Due to the vague and often nonspecific symptoms that are associated with thyroid disorders, diagnostic tests are warranted if a thyroid disorder is suspected.

If TSH is not within the reference range, then further testing is warranted. If TSH is high, fT_4 should be checked and if this is normal, antibodies testing could be warranted. Low fT_4 is indicative of hypothyroidism. If TSH is low, then testing of both free-T_3 (fT_3) and fT_4 should be conducted. Elevated fT_3 and/or fT_4 could indicate hyperthyroidism. Normal fT_3 and fT_4 would warrant a clinical review and consider repeating testing in 6 months (Best Practice NZ, 2010; NZ BP, 2005, 2007).

There are some cases when initial testing of TSH alone is *not appropriate*. First, when the patient is suspected of having central hypothyroidism, due to pituitary gland failure (NZ BP, 2005). In this case, TSH will be normal, and fT_4 will be low (NZ BP, 2005). Patients who are suspected of being nonadherent to thyroxine replacement medication and those in early stages of therapy; these patients should also have both TSH and fT_4 tested (NZ BP, 2005). In the latter case, it will take approximately 2 months for the TSH and fT_4 to reach an equilibrium (Best Practice NZ, 2010; NZ BP, 2005, 2007). In the case of hyperthyroidism, positive TSH-receptor antibodies establish a diagnosis of Grave's disease (a disorder of the immune system that results in the overproduction of thyroid hormones). Radionuclide thyroid scanning is seldom warranted and can lead to further confusion of diagnosis (Best Practice NZ, 2010; NZ BP, 2005, 2007). Additionally, an endocrinologist's advice should be sought in those patients who are acutely ill and pregnant patients (Best Practice NZ, 2010; NZ BP, 2005, 2007).

Management of Hypothyroidism

In countries where there is sufficient dietary iodine, the major causes of hypothyroidism are Hashimoto's thyroiditis, thyroiditis (subsequent to hyperthyroidism), thyroidectomy, postpartum thyroiditis, irradiation, and medication related (Best Practice NZ, 2010; Garber et al., 2012; Hulisz, 2018; Kostoglou-Athanassiou and Ntalles, 2010). Hypothyroidism can also occur secondary to pituitary or hypothalamus disorders (Garber et al., 2012; Kostoglou-Athanassiou and Ntalles, 2010).

Symptoms

Hypothyroidism (high TSH, low-fT_4) has been described as an endocrine condition that occurs when the thyroid gland is underactive, resulting in a deficiency in the production of thyroid hormones (The National Institute of Diabetes, 2016; Yvette, 2012); this may subsequently affect integral systems within the body. Hypothyroidism is characterized by symptoms of goiter, bradycardia, fatigue, weight gain, constipation, menorrhagia, pale, dry skin and hair, and cold intolerance (American Association of Clinical Endocrinologists, 2015; Garber et al., 2012; Malaty, 2018; Roberts, 2004; The National Institute of Diabetes, 2016; Yvette, 2012). The most common symptoms of hypothyroidism are listed in **Table 1**. Hypothyroidism can be

Table 1 Common signs and symptoms of hypo and hyperthyroidism, table reproduction permission required unless modified (Best Practice NZ, 2010; NZ BP, 2005)

	Common signs and symptoms of hypothyroidism	*Common signs and symptoms of hyperthyroidism*
Symptoms highly indicative of condition	• Goiter • Delayed reflexes	• Goiter • Thyroid bruit (sound that can be heard over the thyroid mass) • Lid lag • Proptosis
Symptoms intermediately indicative of condition	• Fatigue • Weight gain/difficulty in losing weight • Cold intolerance • Dry, rough, pale skin • Constipation • Family history • Hoarseness	• Fatigue • Weight loss despite increased appetite • Heat intolerance/sweating • Fine tremor • Family history • Increased bowel motions • Fast heart rate/palpitations • Staring glaze
Symptoms that are lesser indicative of condition	• Coarse dry hair • Hair loss • Muscle cramps/aches • Depression • Irritability • Memory loss • Abnormal menstrual cycles • Decreased libido	• Nervousness • Insomnia • Breathlessness • Light or absent menstrual periods • Weight loss • Muscle weakness • Warm moist skin • Hair loss

differentiated into primary and secondary hypothyroidism (Garber et al., 2012). It is estimated that 95% of cases of hypothyroidism are of primary origin (Malaty, 2018). Secondary or central hypothyroidism is sometimes differentiated (into secondary and tertiary) depending on whether it relates malfunctions of the pituitary or the hypothalamus, respectively.

Rarely, a very severe form of hypothyroidism may occur called myxedema coma (Kostoglou-Athanassiou and Ntalles, 2010; Malaty, 2018). Patients present with low or normal temperature, shallow breathing, low blood pressure, low blood glucose, and unresponsiveness (DeEugenio and Smith, 2004). This can be caused by an infection, illness, exposure to cold, and from certain medications in patients who have untreated hypothyroidism (DeEugenio and Smith, 2004). This is a medical emergency and immediate hospitalization is required (DeEugenio and Smith, 2004).

Treatment

Confirmed overt primary hypothyroidism can usually be managed well with standard guideline treatment. In the case where there is an elevated TSH, but normal fT_4, this may indicate subclinical hypothyroidism. In those with mildly elevated TSH (up to 10 mU/L), in half of cases this normalizes itself and thus no immediate treatment is required. Instead, testing should be repeated in 6–8 weeks.

Subclinical hypothyroidism, where there is a substantially elevated TSH (>10 mU/L), is associated with adverse effects on the cardiovascular system. Therefore, treatment in these cases may be warranted.

Levothyroxine

Standard treatment for hypothyroidism is levothyroxine sodium (American Association of Clinical Endocrinologists, 2012; Best Practice NZ, 2010, in press; Garber et al., 2012; McDermott, 2009; Roberts, 2004); this is a synthetic form of T_4 used to replace the lack of endogenous T_4 and normalize blood levels. Levothyroxine treatment is usually warranted for life (Malaty, 2018; Truter, 2011). Regional guidelines vary slightly in terms of the starting and titration increments. Most adults will achieve euthyroidism with a dose of approximately 1.6 micrograms (μg)/kg/day orally (Best Practice NZ, 2010). Evidence has indicated that most patients should be started on the full replacement dose of levothyroxine (Malaty, 2018; Roberts, 2004) but should be given at the lower end of the anticipated dose requirement (Roberts, 2004). Usually, the initial dose is 50–100 μg/day (New Zealand Formulary, in pressa), and titration by 25–50 μg every 3–4 weeks (New Zealand Formulary, in pressa) is based on thyroid function tests. Some literature has indicated that ideal (lean) body weight, rather than actual body weight, is a better predictor of levothyroxine dose, and this is summarized and discussed by Jonklaas et al. (2014).

If patients are elderly or frail or in those with heart disease, a smaller initial dose of 25 μg/day should be used and titration by 12.5–25 μg every 6–8 weeks (Davoren, 2008; Kim, 2017; Malaty, 2018; New Zealand Formulary, in pressa; Roberts, 2004). In those patients who have undergone a thyroidectomy or radioiodine treatment for thyrotoxicosis but are otherwise healthy, an immediate dose of thyroxine at (or just below) their predicted daily replacement dose of 100–200 μg may be initiated (Davoren, 2008).

According to the American Association of Clinical Endocrinologists and the American Thyroid Association, treatment of special populations should be undertaken with an endocrinologist (Garber et al., 2012); these special populations include the pediatric populations, women who are pregnant or those planning to conceive, people with cardiovascular disease, and people with other endocrine diseases such as adrenal and pituitary disorders (American Association of Clinical Endocrinologists, 2012; Garber et al., 2012; Yvette, 2012). Specific guidelines for the management of thyroid disease in pregnant and postpartum women have been released by a number of endocrinology associations worldwide, for example, the American Association of Clinical Endocrinologists; however, these will not be discussed as they are outside the scope of this chapter.

Dosing can be administered once daily, due to the long half-life (approximately 7 days) (Davoren, 2008); dosing requirements may be necessary in the elderly, for a number of reasons (Kim, 2017). If there needs to be a dose adjustment at a smaller increment than available tablets, then alternate or variable day dosing should be used, as this alleviates the need for patients to need to cut tablets (Davoren, 2008). Tablets should not be cut in half, unless the manufactured brand states; otherwise, there are some brands that enable tablets to be crushed and sprinkled, for those patients who are unable to swallow—individual manufacturers advice should be sought (New Zealand Formulary, in pressa).

Levothyroxine is slowly incorporated into body organs; therefore, it usually takes up to 6 weeks before symptom improvement is observed (Davoren, 2008; Truter, 2011). However, many patients may experience improvement after 2–3 weeks of treatment (Davoren, 2008; Truter, 2011). The rate at which specific symptoms improve varies (Truter, 2011). Early in treatment, there can be an improvement in pulse rate, a reduction in weight and puffiness, while skin hair and voice tone may take a few months. A slower improvement occurs in cholesterol. Reduction in the size of the goiter may require high-dose thyroid hormone for a short period of time (Truter, 2011).

The recommendation is to administer levothyroxine an hour prior to breakfast (as bran and fiber may delay absorption) (Yvette, 2012), but in some cases, this may result in poor adherence (Jonklaas et al., 2014). Consistent daily dosing is adhered to with regard to meals (including types of foods consumed, especially in the case of foods that may affect absorption) and time of day should, therefore, be encouraged (Garber et al., 2012; Yvette, 2012). To date, no long-term studies have investigated the effect of adherence and timing regimens and the consequence on TSH levels (Jonklaas et al., 2014).

Levothyroxine is available generically and in a number of brands throughout the world. Many of these brands are not interchangeable (Best Practice NZ, 2010; Garber et al., 2012; Jonklaas et al., 2014).

In patients where unusually high doses of levothyroxine are required, the patient should be investigated for underlying gastrointestinal conditions (Jonklaas et al., 2014). A number of studies have identified conditions that could affect levothyroxine

absorption or serum TSH levels, for example, *Helicobacter pylori*-related gastritis. This is thought to be mediated via changes in acidity. The evidence for this has been summarized and discussed by Jonklaas et al. (2014). If the underlying condition is identified and treated, TFTs may need reviewing with the view to adjust the dosing of the levothyroxine (Jonklaas et al., 2014).

Monitoring of Therapy

After starting levothyroxine, patients should have their TSH measured every six to eight weeks until the levels become stable and within normal limits (0.4–4.0 mU/L) (Best Practice NZ, in press; Garber et al., 2012; NZ BP, 2005). Subsequent to the levels being attained, TSH should be checked every four to six months and then annually (Best Practice NZ, in press; NZ BP, 2005). Monitoring should become more frequent if the situation changes; for example, switching to a brand that is not bioequivalent (Best Practice NZ, 2010), if a drug that interacts with levothyroxine is added to the patient's medication regimen, for example, amiodarone, antacids, anticonvulsants, or if there is marked weight gain or planned pregnancy (NZ BP, 2005).

Poor Outcomes of Treatment

Levothyroxine is generally well tolerated (Roberts, 2004); however, it has a narrow therapeutic window (Roberts, 2004) and thus there is a substantial number of patients who are either being over and undertreated (Hulisz, 2011). Both over and undertreatment can cause adverse health consequences (Hulisz, 2011). As mentioned earlier, lack of adequate treatment can lead to cardiovascular disease (Hulisz, 2011). Overtreatment can lead to adverse effects including symptomatic thyrotoxicosis (Roberts, 2004) and can result in long-term sequelae, including atrial fibrillation, lower bone mineral density, and fracture and cardiovascular disease (Hulisz, 2011).

The Colorado Thyroid Disease Prevalence Study reported that 60% of people taking thyroid medication had TSH within reference values (Canaris et al., 2000). In a study in older Australian adults, abnormal TSH was found in 25% of people taking levothyroxine (Empson et al., 2007). High rates of abnormal measurements have also been reported by Canaris et al. (2000). These findings could be due to a number of reasons, which must be investigated in the patient: (1) adherence issues (Ramadhan and Tamilia, 2012), (2) a reduced absorption of levothyroxine, which could be due to drug–drug interactions or inconsistency with dosing in relation to food (Ramadhan and Tamilia, 2012), or (3) if patients switch from one brand to another that are not bioequivalent.

Adherence issues can be an important factor in poor response to treatment (Centanni et al., 2017), and due to the long half-life of the medication, missing a dose can have effects that last a number of days (Centanni et al., 2017). The pharmacist has a vital role to play in education of the patient (Hulisz, 2011), including why adherence is imperative for treatment. Explanation of the life-long nature of therapy, time to observe symptomatic changes, and consistency with dosing (emphasizing the relation to meals being consistent) is important not only at the introduction of therapy but also on an ongoing basis. Medication organizers, such as pill dosette boxes, may be of assistance in patients when adherence is an issue (Jonklaas et al., 2014).

Reduced gut absorption of levothyroxine is another reason for poor response. This may be due to drug–drug interactions, timing with meals, or a malabsorptive disorder, such as celiac disease and inflammatory bowel disease (Centanni et al., 2017; Jonklaas et al., 2014; Roberts, 2004). A study by McMillan et al. (2016) surveyed 925 individuals with hypothyroidism undergoing treatment and reported that a high proportion of patients do not take levothyroxine as directed. Patients should be advised to consulting the pharmacist if starting any new medication, including those purchased over-the-counter (OTC) medications (Hulisz, 2011) (including dietary supplements and iodine-containing products), and medications that have the potential to alter the absorption of levothyroxine, for example, calcium carbonate, cholestyramine, ferrous sulfate, proton pump inhibitors, and sucralfate (Roberts, 2004; Trifirò et al., 2015; Truter, 2011). Additionally, the metabolism of levothyroxine may be altered by some medications, including some antidepressants, antiepileptic drugs, and enzyme-inducing antibiotics (Roberts, 2004).

Explaining why brands cannot be interchanged to a patient is integral. If a prescriber decides to swap the brand, additional monitoring of thyroid levels will be required (Jonklaas et al., 2014).

Appropriate storage conditions of the levothyroxine should be explained, as this can lead to malabsorption if the preparation is affected (Centanni et al., 2017). The medicine should be kept below 25°C and away light.

In some patients, despite normalized TSH, ill health may persist. This may be due to the symptoms being unrelated to the thyroid, for example, depression. There have been reports, although there is a lack of evidence to prove this, that some patients have improved symptoms when TSH levels are in the lower end of the reference range (NZ BP, 2007). Reports have suggested that this appears to be safe, in young healthy patients, as long as the level does not become suppressed below 0.1 mU/L (Flynn et al., 2010; Walsh, 2016).

Other Therapies

Unlike current thyroid medications, which are synthetic, natural thyroid medications were once prepared from the thyroid glands of cows, hogs, and sheep (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011). These products provided both T_3 and T_4; however, the levels of T_3 and T_4 varied greatly (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011). In addition, as these medications were protein derived, they may be antigenic in allergic or sensitive patients (DeEugenio and Smith, 2004; Jonklaas and Talbert, 2011). The current use of these medications should not be encouraged (American Association of Clinical Endocrinologists, 2012; Best Practice NZ, 2010; Davoren, 2008; DeEugenio and Smith, 2004).

Liothyronine (triiodothyronine or T_3) is rarely used orally for maintenance therapy. Most patients respond well to T_4 alone, which is converted in the body to T_3. When a rapid response is required, T_3 may be used, that is, in severe hypothyroid states (New Zealand Formulary, in pressb).

Management of Hyperthyroidism

Hyperthyroidism and thyrotoxicosis are terms that are often used interchangeably (Topliss and Eastman, 2004). Hyperthyroidism is less common than hypothyroidism and is most frequently caused by Grave's disease (60%–80%) (Association et al., 2011; Best Practice NZ, 2010; Walsh, 2016), toxic multinodular goiter (nodules that develop in the thyroid gland and secrete thyroid hormone, also known as Plummer's disease) (Association et al., 2011; Best Practice NZ, 2010; Walsh, 2016), or toxic adenoma (Association et al., 2011).

Thyroiditis can also lead to hyperthyroidism; in thyroiditis, there is generally a three-stage course, that is, hyperthyroidism followed by hypothyroidism and finally euthyroidism. Depending on the type of thyroiditis the condition may resolve, or hypothyroidism may ensue and require treatment (Walsh, 2016).

It is essential in hyperthyroidism to establish the cause prior to the commencement of treatment, as this will alter the management (Association et al., 2011; Walsh, 2016).

Subclinical hyperthyroidism should be monitored as it often resolves without treatment (Meyerovitch et al., 2007), in some patients with persistent (i.e., longer than 3–6 months), subclinical hyperthyroidism treatment may be warranted to avoid altered skeletal health and atrial fibrillation (Association et al., 2011). Again, in persistent subclinical hyperthyroidism, the underlying cause should be identified (Association et al., 2011).

Rarely, a life-threatening condition called thyrotoxicosis (thyroid storm) can develop, even with treatment the mortality rate of thyroid storm is reported to be 30%. It presents as hyperthermia, severe tachycardia, disorientation, and severe agitation and may be accompanied with heart failure (Association et al., 2011; DeEugenio and Smith, 2004). This can lead to stupor and coma (Association et al., 2011; DeEugenio and Smith, 2004). This is a serious condition and requires treatment and monitoring in an intensive care unit. Treatment is supportive and thyroid specific and is discussed in detail in the Guidelines by the American Thyroid Association and American Association of Clinical Endocrinologists (Association et al., 2011; Jonklaas and Talbert, 2011).

Symptoms

In hyperthyroidism, there is low/nonexistent TSH and high fT_4 (Best Practice NZ, 2010; NZ BP, 2005). Clinical symptoms are characteristic (see **Table 1**) and include increases in blood pressure and heart rate, arrhythmia, enlarged thyroid (goiter; seen in both hypo and hyperthyroidism), bulging eyes, tremor, increased sweating, heat intolerance, irritability, anxiety, weight loss, and loss of sleep (Best Practice NZ, 2010; Hulisz, 2018; Jonklaas and Talbert, 2011; NZ BP, 2005; Walsh, 2016).

Treatment

There are three main avenues for treatment in patients with hyperthyroidism: surgery, antithyroid medications, and radioactive iodine. The route chosen depends on the cause of the hyperthyroidism. Furthermore, additional factors that affect the choice of treatment include preference in the region that the patient is being treated, that is, due to local guidelines, size and nature of the goiter, other medication or medical conditions, and (particularly in the case of patients with Grave's disease) patient preference (Best Practice NZ, 2010; Topliss and Eastman, 2004).

There are three treatment options for Grave's disease: (1) blocking the synthesis of thyroid hormones with antithyroid medication, (2) radioactive iodine, or (3) surgery (Association et al., 2011; Razvi and Perros, 2018; Topliss and Eastman, 2004; Walsh, 2016).

In toxic nodular goiter, radioactive iodine or surgery is generally the treatment of choice. Antithyroid medications are often not the treatment of choice, as it will need to be lifelong (Association et al., 2011; Pearce, 2018; Walsh, 2016).

If thyroiditis is the cause, often this does not need medication therapy, unless it is autoimmune thyroiditis and hypothyroidism may persist (Walsh, 2016). As mentioned previously, thyroiditis generally progresses in three parts: hyperthyroidism, hypothyroidism and then euthyroid (Walsh, 2016). TSH should be monitored, and if the hypothyroidism persists, then treatment should be commenced with levothyroxine (Association et al., 2011).

Symptom control may be necessary as an adjunct to treatment, and this is often attended to by the use of β-adrenergic blocking agents, for example, to alleviate tremor and tachycardia (Association et al., 2011; Best Practice NZ, 2010), as these medications are able to reduce the effects of T_4 on the sympathetic system (Michael et al., 2012).

Surgery

A thyroidectomy involves some or all of the thyroid gland being surgically removed. Patients must be rendered euthyroid prior to surgery with thionamide therapy (Association et al., 2011; Topliss and Eastman, 2004). In some special populations, this is the treatment of choice (Association et al., 2011; Best Practice NZ, 2010; Topliss and Eastman, 2004), including patients who are noncompliant to treatment, refuse to have radioactive iodine treatment, or where therapy fails, this may be used as an alternative

(Michael et al., 2012). Subsequently, the patient is likely to need thyroid replacement treatment thereafter (Association et al., 2011).

Antithyroid Medications

Antithyroid medications consist of thiouracils and sulfur-containing derivatives (thioamides: propylthiouracil and carbimazole). These medications work is by interfering with thyroxine synthesis in the thyroid gland (Razvi and Perros, 2018). The initial dose is dependent on the severity of the condition, and once a euthyroid state is achieved, the dose is lowered (Best Practice NZ, 2010). It has been reported that use for 12–18 months is the best course length for sustained remission in Grave's disease (Best Practice NZ, 2010; Razvi and Perros, 2018). Relapse can occur in approximately 50% of patients (Topliss and Eastman, 2004). Side effects of the medication include rash, fever, and gastrointestinal disorders. Rarely, agranulocytosis can occur (NZ BP, 2005).

Radioactive Iodine

This option is usually chosen when antithyroid medications are not effective (after relapse) or not able to be used (Topliss and Eastman, 2004). Additionally, this may be the treatment of choice in toxic nodular goiter (Pearce, 2006). Between 80% and 90% of patients become euthyroid after a single dose (Holm et al., 1981). There are some populations that this treatment is contraindicated in, for example, in pregnancy and breastfeeding, or of the patient is planning on becoming pregnant in the near future (Association et al., 2011; Pearce, 2006). The medication is administered as a single dose in a hospital environment (Association et al., 2011). Side effects include transient neck soreness, flushing, decreased sensation of taste, radiation thyroiditis, and potential exacerbation of ophthalmopathy (Pearce, 2006; Razvi and Perros, 2018). Worsening hyperthyroidism has been reported by some patients, which occurs shortly after the treatment due to thyroid hormone leaking from the damaged gland and, thus, may be administered an antithyroid drug prior to treatment or shortly afterward (Best Practice NZ, 2010).

Other Therapies

As mentioned, symptomatic treatment with beta-blockers is an option, for example, with propranolol (Best Practice NZ, 2010). This is sometimes useful at the start of therapy as it helps with palpitations, sweating, and anxiety (DeEugenio and Smith, 2004); however, it does not ameliorate the underlying condition. There are some populations in which these medications should be used with caution; for example, asthmatics (Association et al., 2011).

Monitoring

TSH may remain suppressed for 3–6 months after treatment with antithyroid medication begins (NZ BP, 2005); therefore, until TSH normalizes and the clinical presentation of symptoms has improved in the patient, it is recommended that thyroid function (TSH and fT_4) be monitored every 4 weeks (Best Practice NZ, 2010; NZ BP, 2005). Subsequently, the patient should be monitored every 2 months using TSH only (NZ BP, 2005). In some cases, patients will need to have the fT_3 monitored in addition, this is due to T_3 toxicosis and they should be under the care of an endocrinologist (Best Practice NZ, 2010).

Role of Pharmacist in Health-Care Team—Current and Future Roles in Pharmacotherapy and Management

The pharmacist can benefit the management of thyroid disorders in three main avenues: as an educator, an advisor, and potentially in an advanced role, with the latter being an avenue that still needs further research.

Understanding of the thyroid condition and its management is essential for patient engagement with their ongoing treatment. Pharmacists are in an ideal position, as the easiest to access health-care professional, to educate patients of these factors both when a patient is newly diagnosed and prescribed treatment, and on an ongoing basis when picking up repeat prescriptions for medications.

Suggestions for Counseling Patients with Hypothyroidism

The amount and type of counseling required to be provided to individuals will depend on the individual needs and their level of understanding; however, some suggestions include:

1. That there is no "cure" for hypothyroidism, but the condition can be appropriately and effectively managed using a synthetic version of the thyroid hormone (Yvette, 2012).
2. Treatment is in most cases lifelong but this should not prevent them from taking part in normal life activities (Yvette, 2012).
3. Adherence to treatment is crucial for effective treatment and this includes taking the medication at the same time each day in relation to food and other medications and not stopping taking the medication (even if they are feeling the symptoms are better) unless told to do so by their doctor. The recommendations for levothyroxine state that the medication should be taken with water on an empty stomach 30 min prior to food or at bedtime 4 h after their last meal. However, this may reduce adherence for some patients (Jonklaas et al., 2014). If the individual has been stabilized on a dose for some time, advising of a new routine in relation

to meals may significantly affect their levels and they will have to be dose-adjusted after tests by the prescriber. Patients should also not take the medication within 4 h of any fiber supplements or calcium, iron, multivitamins, aluminum hydroxide antacids, or any medications that bind bile acids.
4. If starting new medications (including ones that they can purchase without a prescription or herbal supplements), they should advise their prescriber and pharmacist that they are taking their medication for thyroid dysfunction, so that any interactions or considerations can be evaluated.
5. Individuals can be advised that usually the dose will be adjusted after blood tests, to ensure the right dose for the patient is being prescribed; these blood tests typically are every 4–8 weeks as that is the required period for hormone stabilization (Best Practice NZ, 2010).
6. It is helpful for individuals to be educated about the potential side effects of the medicine, as these can affect many vital systems within the body. This can be particularly worrisome for patients; therefore, being aware of which side effects to seek additional medical attention and how long to improvement of symptoms is integral to treatment. Patients should be advised to report any signs of palpitations, rapid weight loss, restlessness or shakiness, sweating, and insomnia to their prescriber straight away. Alarm symptoms, such as dizziness, lack of consciousness, slow heartbeat, and difficulty breathing should be reported to their emergency department (Yvette, 2012).
7. Lastly, patients should be advised that the brand of medication is very important; many brands are not interchangeable and therefore they must not switch brands, unless advised to do so by their prescriber (Jonklaas et al., 2014).

Main Factors to Include in Counseling for Hyperthyroidism

1. That hyperthyroidism can be appropriately and effectively managed using medication or surgery (Association et al., 2011).
2. Patients should be made aware of the time to symptomatic relief.
3. If symptomatic relief is prescribed by the doctor, it should be made clear which medication is for what purpose.
4. That even after clinical symptoms have resolved, it is important to continue to take the medication for the duration specified by the prescriber.
5. In addition to general side effects, all patients who are administered antithyroid medication should be told about the rare but serious complication of agranulocytosis and the appropriate management. If symptoms of fever, sore throat, or other infection develop, patients should stop treatment and seek immediate medical treatment (Best Practice NZ, 2010; NZ BP, 2005).
6. Monitoring will be conducted on a monthly basis, as this is the time necessary for there to be a change in hormone levels, once levels are within the reference range, the doctor may extend this to every other month (NZ BP, 2005).

When considering the importance of the pharmacist in patient education in thyroid disorders, only a small number of studies have explored this role. Singh et al. used a cross-sectional designed study to evaluate knowledge in patients diagnosed with hypothyroidism (Singh et al., 2014). They reported poor knowledge and misconceptions. In a separate study, better outcomes were associated with knowledge, appropriate use of medication, and dosage adjustment (Kannan et al., 2010). The pharmacist's role in this regard has been evaluated by a prospective case-controlled study of 118 individuals diagnosed with hypothyroidism (Maharjan and Chhetri, 2015). The authors found that education by the pharmacist in hypothyroidism improved patient knowledge, attitudes, and practice score. However, the study had a relatively small sample size and was based in one region of Nepal, limiting the generalizability of the results and no clinical outcomes were assessed (Maharjan and Chhetri, 2015). Future research could further explore knowledge, attitudes, and clinical outcomes to further evaluate this role.

The second major role of the pharmacist within the management of thyroid disorders is the role of the advisor. There is a huge potential for medication contribution to the development of thyroid disorders and also in affecting the management of thyroid disorders. As discussed previously, increasing age is associated with an increased prevalence of thyroid disorders; this also increases the likelihood that patients are on one or more medications. Pharmacists can act as an important resource within the health-care team to advise on which medications could be contributing to thyroid dysfunction, for example, amiodarone and lithium (Best Practice NZ, 2010). Additionally, pharmacists can also act in an advisory role to patients and other health-care professionals on the many interactions that could affect the management of these conditions and provide evidence-based advice on interactions and information about other complementary medicines in thyroid disorder. While no evidence has been reported specifically on the role of the pharmacist in the advisory role in thyroid disorders *in the community setting* to our knowledge, there has been a study by Ziman and colleagues that has evaluated the role of the pharmacist within a health-care team within outpatient pharmacy setting (Ziman et al., 2012). The pharmacist has been found to be a beneficial addition in this role (Ziman et al., 2012).

Traditionally, the role of the pharmacist has been the compounder and dispenser of medicines; however, more recently, due to many factors including an ageing population and subsequent increases in those with long-term conditions, their role is evolving. It has been said that the future role of the pharmacist will be a clinical one, including aspects of medication review and moving toward independent prescribing (Babar et al., 2018). Evidence for pharmacist's role in thyroid disorders in this respect is scant. There have been small-scale studies that have looked at an advanced role of the pharmacist in novel roles. Ziman et al. (2012) focused on the role of the pharmacist in the clinical context, in patients with heart failure and a thyroid dysfunction. They reported that there was a positive impact on patient adherence to thyroid testing in heart failure. This was a small study, but provides some baseline evidence to promote further research in this area (Ziman et al., 2012). Dong (1990) published a study that centered on pharmacist involvement in a thyroid clinic in a 500-bed university hospital. Within this hospital setting, there had been an established role

for a pharmacist within the thyroid clinic for 10 years. The report by Dong described how the pharmacist initiated, maintained, or modified the drug therapy of selected patients, under the guidance of a protocol approved by the chief endocrinologist (Dong, 1990). This study did state boundaries that the pharmacist operated within, that is, that major changes in the thyroid status and drug therapy, were always discussed with the chief endocrinologist. It was reported was that in a clinical audit, the role of the pharmacist was found to be effective (Dong, 1990). No economic assessment was made. To our knowledge, no further research since this has been published from this facility. Cleary, there are some grounds to warrant further research within this sphere. What needs to be addressed is what this role is, the guidance that this role would operate within, how to manage this expansion of scope, that is, whether this is through a pharmacist prescriber role within a dedicated team and the assessment of patient clinical outcomes and whether there is any clear benefit.

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Contraception and the Pharmacist's Role

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Learning Objectives

After reading this chapter, the reader should be able to:

1. Understand the different contraception options, their efficacy, contraindications, and precautions and adverse event profiles.
2. Consider the most suitable contraceptive choice for an individual patient based on the respective pros and cons of each method of contraception.
3. Be familiar with the efficacy of each contraceptive method and aware of the failure rate (even when used optimally).
4. Discuss the current and future roles of the pharmacist in the management of contraception, including the evidence for these roles.

Contraception is a large topic that is always changing, and there can be important differences in contraindications, precautions, and duration of use between products and countries. Therefore, this chapter aims to provide an introduction to the field. Product literature and up-to-date contraceptive Medical Eligibility Criteria (MEC) should be consulted. World Health Organisation (WHO), United States (US) and United Kingdom (UK) versions of MEC are readily available.

Key Concepts

Appropriate contraceptive choice is important for a significant proportion of women during their "childbearing" years. An increasing number of options each have their own pros and cons. The age of the woman, frequency of intercourse, other medical factors, and personal preference can influence the suitability of contraception.

In general, the longer the contraception is designed for, the more effective it is. Condoms, emergency contraceptive (EC) pills, and diaphragms are designed and used for single events and are less effective than ongoing hormonal contraception (Trussell, 2011). Oral contraceptives (OCs) (used daily) are less effective than the three-monthly progestogen injection, which is less effective than the long-acting reversible contraceptives (LARCs) of implants and intrauterine devices (IUDs). Finally, vasectomy and tubal ligation are the most effective of all.

Given the breadth of this topic, this chapter starts with an introduction to the area and the historical developments of contraception, before considering the various categories of contraceptives and their mechanisms of action, advantages and disadvantages and then a discussion of their effectiveness and usage. Given the increasing role pharmacists have with emergency contraception, this focuses most on the forms pharmacists can usually supply and their role in that supply. The chapter finishes with a noncomprehensive discussion of pharmacist-supply of contraceptives with a focus on professional interactions.

Introduction to Contraception

From the start of being sexually active and for the majority of the next 30 years or more (nearly a third of their life time), most women in many countries will be trying to avoid pregnancy. There are many options to help them do this, with variation in failure rates, ease of use, permanency, benefits, risks, and accessibility.

In the US, the age of first sexual intercourse has changed over time, dropping steadily to a low in the 1990s, then increasing by one year, with sexual intercourse experienced by 50% of people by their 18th birthday (Finer and Philbin, 2013). However, a reasonable proportion of 15 and 16 year olds (19% and 32%, respectively) has had sexual intercourse, and has barriers to accessing contraception. While less than a fifth of unintended pregnancies occur in adolescents, over 80% of pregnancies in ages 15–19 are unintended, and 64% in women 20–24 years old (Finer and Zolna, 2011).

Conception is highest in sexually active women aged in their 20s, with about a 25% pregnancy rate in a month without contraception (Johnson et al., 2012). It declines to about 20% per month around the age of 32 years then less than 5% per month by the age of 41 years and 1% per month by about 45 years. However, the messages about declining fertility may be leading to increased unplanned pregnancy rates in these groups (Finer and Zolna, 2011), and increasing termination rates in older age groups in England and Wales (contrasting to declining termination rates in under 25 year olds) (Abortion Statistics, 2017).

With the wide range of contraceptives available, high rates of unintended pregnancy (Finer and Zolna, 2014; Hohmann-Marriott, 2018) are surprising. Increasing use of LARCs should help given their high efficacy, but many women use options with lower efficacy, or underestimate their chances of pregnancy (Bellizzi et al., 2015). The range of contraceptives includes combined hormonal methods which contain an estrogen and a progestogen, including oral, transdermal, and vaginal rings. Progestogen-only methods include oral, injection, implant, or IUDs. Nonhormonal options include the copper IUD, barrier methods (condoms, diaphragms, cervical caps), and withdrawal and fertility awareness. Finally, there are permanent sterilization methods, male and female.

The WHO regularly provides updated Medical Eligibility Criteria (MEC) for the range of contraceptives. This may differ from the sponsor's licensed prescribing information. The UK and US produce their own MEC, which are more suited to developed countries (e.g., including bariatric surgery). These are important documents for appropriate prescribing of contraceptives with four levels of risk:

1. A condition for which there is no restriction for the use of the method.
2. A condition where advantages generally outweigh the theoretical or proven risks.
3. A condition where the theoretical or proven risks usually outweigh the benefits of using the method. The provision of a method requires expert clinical judgment or a specialist contraceptive provider since the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
4. A condition which represents an unacceptable medical risk if the method is used.

In general, MEC categories 1 and 2 are reasonable for provision, but 3 and 4 are not.

Pharmacists have an important role to play with contraception: in dispensing it pursuant to a prescription (with advice); in making recommendations for prescribers; and in recommending non-prescription contraception. In all cases there is a need to consider safety, adherence, education and patient-centered care.

History

Methods to avoid pregnancy, and sometimes sexually transmitted infections, have been described for hundreds of years (Amy and Thiery, 2015; Quarini, 2005). Early methods from the 17th century or earlier included male condoms made from animal intestines (reportedly used by Casanova), withdrawal, douching after intercourse, and sponges moistened with brandy or water, or paper inserted into the vagina. Cervical caps, IUDs, and fertility awareness became more common in the 1920s. Combined oral contraceptives (COCs) launched in the 1960s, initially contained 150 μg of mestranol (a pro-drug of ethinylestradiol, converting to about 70% of the mestranol dose) (Melo and Creinin, 2016). Gradual lowering of estrogen doses followed, as did development of new progestogens, progestogen-only pills, transdermal patches, and vaginal rings. Hormones were developed in longer-lasting forms, depot progestogen injections, and more recently in IUDs and implants. A goat's bladder female condom dates back to 150 AD, and 2000 years on, female condoms are marketed in some countries.

Nonpharmacological Contraceptive Options

Withdrawal of the penis before ejaculation reduces pregnancy risk because preejaculatory fluid has little or no motile sperm, but still has a one year failure rate of 22% (Trussell, 2011). Postcoital vaginal douching might heighten the risk of pregnancy by washing sperm into the uterus (Quarini, 2005).

Fertility awareness methods vary. Detection of cervical mucus changes has high levels of pregnancy (35% after 13 cycles), even where intensive training has taken place and with "perfect" use (Goldsmith, 2016). Adding body temperature monitoring reduces the failure rate, e.g., 2% over 13 months in clinical studies.

Breast-feeding on demand at least four hourly during the day, and at least six hourly at night, in the first six months postpartum has a 2% pregnancy rate (Alsharaydeh et al., 2017). Sterilization includes fallopian tube occlusion for women, and vasectomy for men.

Copper IUDs are discussed under LARCs.

Male Condoms

Condoms protect against pregnancy and sexually transmitted infections, and may prevent premature ejaculation (Batár and Sivin, 2010). Originally from animal membranes, rubber condoms became more popular and more available in the 19th century (Amy and Thiery, 2015). Nowadays, latex is usually used, with a teat end to capture the ejaculate to avoid a reflux of sperm. Polyurethane condoms (for latex allergy) and animal membrane condoms (skins) are also available (Amy and Thiery, 2015; Batár and Sivin, 2010). Polyurethane condoms may break more and be less effective than latex, and are not biodegradable. Animal membrane condoms are expensive and may not protect against STIs, nor be sufficiently robust for anal intercourse.

The challenge with condoms is ensuring they are used every time. Men and women have expressed dislike (Amy and Thiery, 2015). Effectiveness against STIs transmitted through skin-to-skin contact, such as human papilloma virus is less than for infections spread through fluid contact such as HIV, chlamydia, and gonorrhea (Amy and Thiery, 2015). Mineral oil lubricants, some vaginal candidiasis products, and excessive temperatures can damage latex condoms.

Female Barrier Methods

Female barrier methods, diaphragms, cervical caps, and female condoms, prevent spermatozoa reaching the egg. They are hormone-free for those with contraindications or wanting to avoid hormones, and for women who do not have intercourse often. They have unknown effectiveness in preventing most STIs, but the diaphragm provides some protection against HPV infection, and their use is low and in decline (Batár and Sivin, 2010).

Female condoms are a soft disposable sheath made of polyurethane with an outer ring, and inner ring inserted in the vagina up to eight hours before intercourse (Alsharaydeh et al., 2017; Amy and Thiery, 2015). They are expensive, can be noisy, can stick to male condoms, be uncomfortable and tricky to insert, and have low usage (Batár and Sivin, 2010).

Diaphragms (a latex shallow dome) and cervical caps (small and thimble shaped, fitting over the cervix) (Amy and Thiery, 2015), were popular in Europe and the US until the OC became available (Batár and Sivin, 2010). Diaphragms vary in size and need to be fitted by someone qualified for first usage, and after childbirth or significant weight changes (Batár and Sivin, 2010). They typically fold to be inserted, are used with spermicide owing to leakage of sperm, and are not felt during intercourse. The diaphragm remains in place for six to eight hours after intercourse, then is washed with lukewarm water and mild soap, rinsed, dried, and stored carefully. Checks for damage and replacement 1–2 yearly are important. Women with vaginal fistulae or latex allergy cannot use them, and toxic shock syndrome has been reported with delayed removal.

Cervical caps are very uncommonly used (Batár and Sivin, 2010). They also need fitting and are coated in spermicide, but can remain in place for more than 24 hours for repeated sexual intercourse. They are relatively rigid, may cause discomfort during intercourse, and insertion and removal can be difficult.

Spermicide-impregnated single-use sponges are available in some countries, but have reasonably high failure rates (Batár and Sivin, 2010).

Long-Acting Reversible Contraceptives

LARCs are contraceptives administered less frequently than once a month (The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014). They include IUDs (copper and hormonal), medroxyprogesterone acetate (MPA) injections and progestogen implants. Low opportunity for user error provides high efficacy. Their benefits and risks differ markedly from estrogen-containing contraceptives (Anon, 2016; Shoupe, 2016). Low use of LARCs arises from various reasons, including insufficient knowledge in women, cost concerns (Rose et al., 2011; Sweeney et al., 2015), insufficient familiarity and skill in providers, and overestimation by providers of women's adherence to OCs (Sweeney et al., 2015).

Medroxyprogesterone Acetate Injection

MPA injection, a progestogen, inhibits the secretion of gonadotropins, preventing follicular maturation and ovulation. It also thickens the cervical mucus limiting sperm penetration, and changes the endometrium, discouraging implantation (Pfizer Limited, 2018a; The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014). MPA is available as a deep IM injection (DMPA, Depo Provera® containing 150 mg medroxyprogesterone acetate) or the more recently available subcutaneous injection (Sayana Press®, 104 mg MPA) self-administrable with training (Pfizer Limited, 2018b).

Some African countries, e.g., Uganda, Malawi, and Swaziland have usage in 20%–30% of married or in-union women of reproductive age. High usage occurs in some South American and developing Asia Pacific countries, while other similar countries in these areas, and highly developed countries have minimal or no use.

MPA is initiated within the first five days of a normal menstrual cycle, or additional contraceptive cover is needed (Pfizer Limited, 2018a). The injections are administered every 12 weeks (Pfizer Limited, 2018a) (Depo-Provera) or every 13 weeks (Sayana Press) (Pfizer Limited, 2018b).

Unpredictable bleeding lessens satisfaction, so warn of changes (Hoopes et al., 2018). It cannot be discontinued immediately, and full fertility may take up to one year after discontinuation (Pfizer Limited, 2018a,b). Weight gain sometimes occurs, particularly in obese women under 18 years of age (The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014). A small loss in bone mineral density, particularly in the first year of use, typically recovers after discontinuation, but provides a caution for young women or those approaching menopause. The manufacturer advises that it is only indicated in women under 18 years of age when other contraceptive methods are considered unsuitable or unacceptable (Pfizer Limited, 2018b), and women at particular risk of osteoporosis should consider other contraceptives (Pfizer Limited, 2018a).

Amenorrhea (in 50% at one year) or reduced bleeding may be beneficial (The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014), particularly in women with heavy menstrual bleeding, dysmenorrhea or endometriosis pain, or in wheelchairs, and it can be used immediately postpartum. MPA users have nearly an 80% reduction in endometrial cancer (Shoupe, 2016).

Intrauterine Devices

IUDs are inserted into the uterus. The copper IUD shortens the sperm's survival and affects its passage into the fallopian tubes (Mishell, 2011a). It is made of polyethylene with fine copper wire, and lasts for 3–10 years (Anon, 2016), depending on the product. Few contraindications and precautions exist. Copper IUDs can be used when hormones are contraindicated, e.g., with breast cancer. Because copper IUDs can cause painful heavy bleeding, discontinuation is common (Alsharaydeh et al., 2017), and iron deficiency anemia is a precaution for use (Anon, 2016). About 5% of women will have the IUD displaced or expelled (Alsharaydeh et al., 2017).

IUDs should not be inserted if there is pelvic inflammatory disease or sepsis, and uterine perforation, bleeding, discomfort and infection can occur on insertion (Alsharaydeh et al., 2017).

The levonorgestrel (LNG) IUD prompts release of leukocytes and prostaglandins by the endometrium and thickens the cervical mucus, preventing proliferation of the endometrium, inhibiting sperm passage, and sometimes suppressing ovulation (Bayer PLC, 2018). It lasts 3–5 years depending on the product (Alsharaydeh et al., 2017). It has more contraindications and precautions than the copper IUD (Alsharaydeh et al., 2017; Anon, 2016), but causes lighter periods or amenorrhea, which can help in dysmenorrhea, and has very low failure rates (**Fig. 1**).

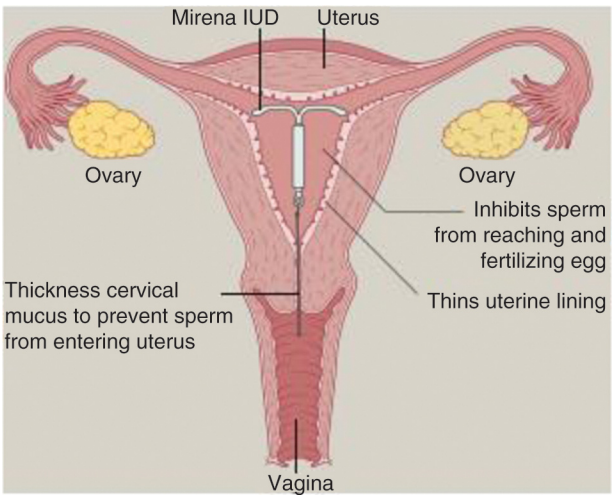

Figure 1 Mirena IUD. *Source: Reprinted from Alsharaydeh, I., Gallagher, M., Mahmood, T.A., 2017. Non-oral contraception. Obstet. Gynaecol. Reprod. Med. 27(5), 158–165, with permission from Elsevier.*

Progestogen Implants

The progestogen implant is increasingly used, with the lowest failure rate of all reversible contraceptives (Trussell, 2011), fewer contraindications and precautions than the COC (Anon, 2016), and high rates of continuation at 12 months (Diedrich et al., 2015; Trussell, 2011). It can be removed. Progestogen implants primarily prevent ovulation, and change the cervical mucus to inhibit sperm penetration (French and Darney, 2016). Currently there are two different progestogens used in small subdermal implanted rods, levonorgestrel or etonogestrel (a metabolite of desogestrel), with similar profiles (French and Darney, 2016). A higher dose is released initially, declining over time, and this is affected by bodyweight (Bayer OY, 2016; Merck Sharp and Dohme Limited, 2016).

The implant is inserted surgically, preferably by a person who has been appropriately trained. If inserted in the first five days of the menstrual period, no back-up contraception is needed (French and Darney, 2016). However, it can be inserted at other times if there is reasonable certainty that the woman is not pregnant and back-up contraception is used for seven days.

Check the latest product information for duration of effect (currently three (Merck Sharp and Dohme Limited, 2016) or five years (Bayer OY, 2016)), and recommendations in women who are "heavier." Migration of the implant is possible, particularly with deep insertion, manipulation of the implant or contact sports. At insertion and removal, vascular or nerve damage can occur (Alsharaydeh et al., 2017). Ovulation and fertility returns promptly after removal (Alsharaydeh et al., 2017).

Menstrual bleeds may change in frequency, intensity, and duration. About 20% of users become amenorrhoeic and a similar number have frequent and/or prolonged bleeding (Merck Sharp and Dohme Limited, 2016). Unscheduled bleeding is the most common reason for discontinuation (French and Darney, 2016).

Oral Contraceptives

One of the most commonly used forms of contraceptive is the OC. These are noninvasive, and allow short-term use with easy discontinuation when desired, e.g., with side effects or change in relationship status, without needing a health professional (Castaño and White, 2013). This does not help continuation though.

OCs contain an estrogen and a progestogen (COCs), or are progestogen-only pills (POPs) often referred to as the mini-pill. This section will first discuss the COCs and then the POPs.

The estrogen in COCs was initially mestranol, later replaced by ethinylestradiol, and with gradually reducing doses (Melo and Creinin, 2016). Ethinylestradiol is usually used in 20 μg to 35 μg strengths, and occasionally 50 μg. The lower estrogen dose is associated with greater break-through bleeding, but has been recommended if nausea or breast tenderness is attributed to the COC (Darney, 1997).

The originally used progestogens (first generation) in COCs included norethisterone (norethindrone) and lynestrol, however, attempting to improve the side effect profile, new progestogens were developed including LNG (second generation). Third generation progestogens, gestodene, desogestrel, norgestimate (Stegeman et al., 2013) were designed for lower androgenicity. The fourth generation progestogen, drospirenone is structurally related to spironolactone and has antiandrogenic activity (Melo and Creinin, 2016). COCs containing third and fourth generation progestogens may have higher thrombosis risks than with the second generation progestogens (Stegeman et al., 2013), although this is controversial (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). Cyproterone acetate is also a first generation progestogen and antiandrogen. It reduces hirsutism and acne, but increases the risk of thrombosis (Stegeman et al., 2013).

The COCs work primarily by preventing ovulation, and also thicken the cervical mucus to make sperm passage more difficult They reduce uterine and oviduct motility, hinder egg and sperm movement, and have effects in the endometrium that affect sperm survival (Mishell, 2011b).

Despite being one of the most widely used and widely studied medicines in the world, with good safety and well-defined contraindications and precautions, many women have misconceptions about effects on fertility and potential to cause cancer (Hamani et al., 2007; Küçük et al., 2012; Mishell, 1989). Myths perpetuated by media make it a surprise to learn that COC users live longer than never-users (Hannaford et al., 2010). COC users have a reduced risk of ovarian cancer of 40%–50%, and endometrial cancer of 40%–70% depending on treatment duration, with a significant effect remaining long after stopping (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Shoupe, 2016). Other benefits of COCs include reduced menstruation irregularities, cycle blood loss and anemia, and improving acne (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012; Melo and Creinin, 2016; Petitti, 2003).

Effectiveness is substantially lower than other forms of contraception, being prone to user error, particularly in adolescents (Melo and Creinin, 2016). Thus, some organizations, e.g., The American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics, recommend IUDs and the progestogen implant first-line, even in adolescents, rather than OCs (Melo and Creinin, 2016). Contraceptive failure is most likely with missed pills at the start of the cycle (Melo and Creinin, 2016). While contraindications, precautions, and drug interactions affect COC suitability for some women, most healthy young women can take them (Anon, 2016).

Side-effects include rare but serious effects (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012; Melo and Creinin, 2016; Petitti, 2003). These can include increased risk of thrombosis (risk depends on estrogen dose and progestogen), myocardial infarction, and stroke (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012; Petitti, 2003).

The risk of venous thromboembolism (VTE, including deep vein thrombosis and pulmonary embolism) is about 9–10/10,000 woman-years, twice the background risk, and highest in the first few months of use (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). This rate is lower than the 29/10,000 woman-years in pregnancy, and 300–400/10,000 woman-years immediately postpartum. Therefore, a personal history of VTE or known thrombogenic mutation is COC contraindications. Immobility is a risk factor and should be avoided, e.g., by changing contraception in cases of prolonged immobility. For flights over three hours, the woman should try to move regularly (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). For travel to high altitude areas for more than a week another contraceptive may be preferred. The risk of VTE increases as BMI increases, so a BMI of 30–34 kg/m^2 has an MEC of 2, while a BMI of 35 kg/m^2 or over has an MEC of 3 (Anon, 2016). Other risk factors may make the risks outweigh the benefits, see the MEC for details.

A 2015 Cochrane review found that COCs increase the risk of a myocardial infarction or stroke by about 60%, particularly in smokers, and with increasing estrogen (Roach et al., 2015). Increase in absolute risk is low (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). There was no association with the progestogen used. For women with a history of migraine, COCs at least double the risk of stroke, and even higher risk occurs in migraine with aura (Anon, 2016). Use in women with migraine with aura (even if long ago) is contraindicated. Other risk factors such as high blood pressure and obesity may increase myocardial infarction or stroke with the COC and the presence of some risk factors are contraindications. Even adequately controlled hypertension without other risk factors has an MEC of 3 (Anon, 2016). The risk is likely to outweigh the benefit with multiple risk factors such as smoking in women aged 35 years or over (Anon, 2016; Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). See the MEC for details.

Meta-analyses have shown a small elevated risk of breast cancer of 8%–24% with COCs (Anon, 2017). This disappears within 5–10 years of stopping (Iversen et al., 2017; The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014), and the Royal College of Obstetrics and Gynaecology (UK) states that *"use of COCs have not been found to be associated with increased mortality from breast cancer"* (The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014). The American College of Obstetricians and Gynecologists (ACOG) notes that the low baseline numbers of cancer in premenopausal women makes the absolute numbers small, and an increase of 20% equates to 1 additional case per 7690 women, or in women under 35 years, 1 in 50,000 (Anon, 2017). Because COCs prevent other cancers (endometrial, ovarian, and colon), overall cancer risk may be slightly lower in COC users (Anon, 2017). Alcohol increases breast cancer much more—British women drinking up to 250 mL of 12% wine daily have an extra 5 in 1000 lifetime risk of breast cancer versus nondrinkers (Hyde, 2017). Women with current or past breast cancer should not have COCs, but a family history of breast cancer is not a contraindication (Anon, 2016).

Cervical cancer might increase in COC users, but any increase disappears 5–10 years after stopping (Iversen et al., 2017; The Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit, 2014), and vaccination for human papillomavirus will make this disease rare in the future.

Research on links between COCs and depression are variable with some studies showing no effect (Duke et al., 2007; O'Connell et al., 2009). A recent Danish study found a 23% increase in first use of an antidepressant versus nonusers (Skovlund et al., 2016). Commentary on this latter study noted the increase would equate to 0.5% more women beginning hormonal contraception developing depression who might not have otherwise (Bitzer, 2017). In addition to other questions about the study, this commentator noted that increased use of antidepressants could occur because these women had more contact with health care services.

More minor side effects can include irregular bleeding, breast tenderness, nausea, and bloating. These can often be reduced with lower estrogen doses (Rosenberg et al., 1999), but this is associated with more breakthrough bleeding. Many of these side effects diminish with ongoing use. For example, women with irregular bleeding should continue the COC for three months before considering a change (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2012). COCs occasionally cause a small increase in blood pressure (Steenland et al., 2013).

The POP is used much less commonly than the COC, despite having a fewer contraindications and precautions and less risk of serious adverse effects. There are three different progestogens used: norethisterone, LNG, or desogestrel.

The POPs suppress ovulation, although this varies between the different progestogens—50%–60% of cycles with norethisterone, 72% in LNG users, and 97% for desogestrel users (Renner and Jensen, 2011). They make the cervical mucus thick, reducing sperm penetration. POPs also affect sperm and egg transportation by affecting tubal motility and cilia. Finally, they lead to an inactive endometrium, which possibly affects sperm transportation or implantation. They are taken daily with no break.

Norethisterone and LNG need to be taken within 3 hours of the due time; a dose over 27 hours after the last dose may reduce the effect on the cervical mucus (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2015). For desogestrel, up to 12 hours late is acceptable because of the greater suppressive effect on ovulation. With few contraindications (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2015), the POP is often suitable when the COC is not. It is often used for lactating women.

Mood changes have been reported with POPs (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2015), but a systematic review published in 2018 found no clear relationship between progestogen contraceptives and depression (Worly et al., 2018). Ectopic pregnancy may be a risk, and changes in bleeding patterns are common (Faculty of Sexual & Reproductive Healthcare Clinical Guidance, 2015).

Other Hormonal Contraceptives

Hormonal Vaginal Rings

The vaginal ring works in a very similar way to the COC with estrogen and progestogen for three weeks of a four week cycle. It releases 15 μg ethinylestradiol and 120 μg etonogestrel daily (Alsharaydeh et al., 2017). A ring is inserted (an applicator can be used, but is not essential) and then removed after three weeks for seven days allowing a withdrawal bleed before inserting a new ring. Alsharaydeh et al. (2017) and the product literature (Merck Sharp and Dohme Limited, 2018) report that the ring can release sufficient hormones for up to four weeks, providing extra cover for women who delay the removal (which is not recommended). The ring is considered to have similar effectiveness to the combined OC (Trussell, 2011). Women find the ring easy to insert and remove, it does not interfere with sexual intercourse, and satisfaction is high (Alsharaydeh et al., 2017). For the first use with no current hormonal use, the ring is inserted on day 1 of the cycle (first day of menstrual bleed), or days 2–5 if necessary, but then the woman may not be protected for the first seven days of use and needs contraceptive cover.

The vaginal ring can fall out, especially if poorly inserted, while removing a tampon, during sexual intercourse, or with severe or chronic constipation (Merck Sharp and Dohme Limited, 2018). It should be replaced within 3 hours to maintain contraception (Alsharaydeh et al., 2017; Merck Sharp and Dohme Limited, 2018). Vaginal discharge can increase occasionally, and vaginal infection may be a risk. Contraindications, precautions, interactions, and side effects are like the COC. However, it has the advantages of only needing to be remembered once a month, and achieving steady low hormonal levels which should aid tolerability.

The ring is refrigerated before dispensing, then stored at room temperature, up to 30 °C for up to four months (Merck Sharp and Dohme Limited, 2018).

Combined Hormonal Patches

The transdermal patch also releases estrogen and progestogen for three weeks, with seven days off and a withdrawal bleed (Alsharaydeh et al., 2017). It releases 203 μg of norelgestromin and 33.9 μg of ethinylestradiol every 24 hours. Contraceptive efficacy can be lower in women 90 kg or heavier (Janssen-Cilag Ltd, 2017).

The patch is applied weekly to clean, dry, hairless, intact health skin on the buttock, abdomen, upper outer arm or torso, where tight clothes will not rub (Janssen-Cilag Ltd, 2017). The site is rotated to minimize irritation. In the absence of previous hormonal treatment, the patch is started on day 1 of the cycle. See the product information for instructions on switching from other hormonal contraceptives. Complete or partial detachment may result in insufficient levels and contraceptive failure. See the product information for the action to take.

Alsharaydeh et al. (2017) reports 10% of users develop application site reactions, and that breakthrough bleeding is more common with the patch than COC in the first two cycles but not after that.

Effectiveness of Contraceptives

The failure rate of contraception is affected by a woman's underlying fertility, frequency of intercourse, the contraceptive method, and compliance (Goldsmith, 2016). A woman who has previously used hormonal contraceptives will have a lower failure rate than a new user, possibly through more awareness of correct use. Women who are satisfied with the OC have more correct use and fewer missed pills. Contraceptive failure is higher in people with low socioeconomic status, some ethnic groups, and obese women (who have been found to have lower compliance) (Goldsmith, 2016). Women need clear advice to understand the effectiveness of various contraceptives.

For women attempting to become pregnant, around 80%–85% will become pregnant within 12 months (Goldsmith, 2016; Trussell, 2011). In married women not trying to become pregnant, but also not using contraception, the 12 month rate of pregnancy is 46% (Goldsmith, 2016), but it is likely that these will be self-selecting for having low fertility (e.g., required help to become pregnant previously), or low frequency of intercourse (Trussell, 2011). The estimated rates of failure for various methods based on US data are outlined in **Table 1**. The data from Trussell (2011) reflects the first year after initiation (or restart) of the method, but these estimates arise from 1995 and 2002, so newer numbers are provided from a 2006–2010 US survey (Sundaram et al., 2017). The POP and the COC are combined in **Table 1**, primarily because the data comes from studies in which people reported being on "the pill" without identifying which pill. Trussell (2011) suggests that the POP might have a greater failure than the COC given the smaller window for taking it. A Cochrane review in 2011 found the different COCs to be comparable in preventing pregnancy (Lawrie et al., 2011).

Failure rates can vary. The failure rate for the implant is higher (0.23%) in women who are obese (Goldsmith, 2016). The MPA injection has recently been used subcutaneously, with an unknown failure rate, but a study over 24 months reported no pregnancies (Goldsmith, 2016). Condom users will sometimes use the EC when failure occurs, which drops the failure rate back to 1.0%–2.1% where used consistently. Latex condoms have lower failure rates than polyurethane condoms, possibly through less slippage or breakage (Goldsmith, 2016). The Choice study, in which women not on contraception chose an OC, vaginal ring, contraceptive patch, DMPA, implant, or IUD and were followed for three years, found a failure rate of around 5% for the group using the OC,

Table 1 Percentage of women experiencing an unintended pregnancy (Sundaram et al., 2017; Trussell, 2011)

	Sundaram et al. (2017) *From 2006 to 2010 data*	*Trussell (2011)* *During 1st year of use, mostly from 1995 and 2002 data*[a]	*Trussell (2011)* *During 1st year of use, mostly from 1995 and 2002 data*[a]
Method	*12 months of use (%)*	*Typical use (%)*	*Perfect use (%)*
No method		85	85
Fertility awareness-based methods		24	(0.4–5 depending on method)
Withdrawal	20	22	4
Female diaphragm		12	6
Male condom	13	18	2
Female condom		21	5
The pill (COC or POP)	7	9	0.3
Vaginal ring (Nuvaring)		9	0.3
Contraceptive patch (Evra patch)		9	0.3
Progestogen-only injectable (Depo-Provera)	4	6	0.2
Copper-bearing IUD		0.8	0.6
Levonorgestrel-releasing IUD (Mirena)		0.2	0.2
Progestogen implant (Implanon)		0.05	0.05
IUD or implant	1.4		
Female sterilization		0.5	0.5
Vasectomy		0.15	0.1

COC, combined OC; *IUD*, intrauterine device; *POP*, progestogen-only contraceptive.
[a]First year of use reflects when contraception has been initiated, not necessarily for the first time.

Table 2 Continuation at 12 months and three years with different forms of contraception

	12 months continuation (Trussell, 2011)	*12 months continuation (The Choice study) (Diedrich et al., 2015)*	*3 years continuation (The Choice Study) (Diedrich et al., 2015)*	*Other data*
OCs	67%	61%	31%	Sweden, at 6 months: COC 81% Desogestrel-only 71% (Josefsson et al., 2013)
IUD (copper or progestogen)	78%–80%	84%–87%	70%	
Progestogen implant	84%	82%	56%	Australia: 74% at 2 years (Harvey et al., 2009)
DMPA	56%	57%	33%	
Condoms	43%	N/A	N/A	

COC, combined OCs; *DMPA*, depot medroxyprogesterone acetate; *IUD*, intrauterine devices.

patch, or vaginal ring, at one year, increasing to around 9% at three years (Winner et al., 2012). The failure rate almost doubled in young women under 21 years. In comparison, the IUD or implant group had just under 1% failure rate at three years.

For adolescents, barrier methods are not usually recommended alone to prevent pregnancy because of higher failure rates compared with OCs, MPA, or LARCs, unless they are particularly mature and motivated, but even with perfect use pregnancy risk remains more elevated than other options (**Table 2**) (Greydanus et al., 2012).

Even after deciding to initiate DMPA, delaying initiation to rule out pregnancy can cause failure. In a US clinic, 7% of adolescents asked to return for the injection (day 1–5 of menses) became pregnant before returning. Despite needing no appointment, they took a median 28 days (average 104 days) to return, with 19% taking at least six months and 8% not returning (Ohlemeyer, 2003). In young women up to 26 years of age, immediate progestogen injection after a negative pregnancy test, regardless of the day of cycle, resulted in better progestogen injection continuation and significantly fewer pregnancies than using bridging hormonal contraception for 21 days then the injection (Rickert et al., 2007).

Immediate starting of contraception is recommended, particularly in young women, to avoid the risk of nonreturn to the clinic, or loss of motivation to use contraception (Whiteman et al., 2014).

The younger a woman starts having sex the longer it takes to initiate contraceptive use (Finer and Philbin, 2013). Furthermore, young women (e.g., up to 20 years old) have lower OC continuation rates than older women (Diedrich et al., 2015; White and Westhoff, 2011). A US study found that, despite most young women surveyed having used OCs, most did not like the idea of using them for themselves (Hoopes et al., 2018). DMPA was even less desirable to these women, few of whom had used it. The IUD and contraceptive implant were considered very acceptable by a larger group, although a significant minority considered these "very

unacceptable." Women seemed influenced by someone who had become pregnant on that particular contraceptive, and the views of friends and family. The young women in this study with a history of pregnancy were less interested in OCs and more interested in implants versus nulliparous women.

In women for whom a pregnancy may be particularly risky physically, e.g., stroke, certain cardiac conditions, some cancers, or transplant, the most effective methods of contraception should be used, i.e., LARCs (Anon, 2016). Women taking teratogenic medicines, e.g., oral retinoids, or methotrexate also have a particularly strong need for effective contraception, including for a period of time after discontinuation, depending on the medicine.

Continuation and Gaps in Therapy

Effectiveness depends on continuation, but the rates (**Table 2**) are based on consumers choosing their method, not being randomized to the different options. Self-reported continuation is overestimated, with a study finding 59% continuation at one year by self-report versus 38% by pharmacy claims (Triebwasser et al., 2015).

LARCs have higher rates of continuation generally as these are designed for use for years without needing to arrange interim prescriptions. It may reflect selection by women who wanted long-term contraception, e.g., being in a long-term relationship or particularly motivated to avoid pregnancy. Presumably it also reflects a lack of bothersome side effects. However, many women seeking short-term contraception do not want to try LARCs and those randomized to it had a discontinuation rate of 35% at two years, typically citing adverse effects (Hubacher et al., 2018). Around 6% of women fitted with an IUD postabortion had a repeat abortion within the next 24 months (Rose and Lawton, 2012).

A US study using administrative claims found when women started on hormonal contraception (first time or a restart), 55% refilled their prescriptions at three months indicating continuation (Murphy and Brixner, 2008).

For OCs, providing longer cycles (seven months (White and Westhoff, 2011) or one year (Foster et al., 2006)) significantly increases the continuation rate compared with shorter cycles of supply, particularly in women under 18 years (White and Westhoff, 2011). Longer supply also reduces the risk of pregnancy and abortion compared with shorter supply periods (Foster et al., 2011).

Availability without prescription might help continuation (Castaño and White, 2013). A study from El Paso, Texas, found women going to Mexico to get OCs without prescription had higher continuation rates than those going to local clinics (Potter et al., 2011). While counseling should help continuation, Castaño and White (2013) found no evidence for this. They reported that apart from one randomized controlled study with a positive effect on injection continuation, others had negative findings, but were limited by small sample sizes, variable interventions, and high loss to follow-up. Advising women when initiating the OC of the transient nature of most side effects might be helpful (Castaño and White, 2013).

US women's reasons for a gap in contraception use commonly include infrequent sexual activity; problems accessing or using methods, including cost, lack of time to get it, side effects, and not liking any method; ambivalence about becoming pregnant; or believing they could not get pregnant (Potter et al., 2011). Women who think they have experienced side effects are more likely to discontinue OCs, but also might switch to another OC or a less effective method (Castaño and White, 2013). Women without underlying concerns about hormones tend to switch to another highly effective contraceptive if they had side effects, while those with underlying concerns tended to stop contraception completely or move to condoms. In the mid-1990s, VTE reports resulted in many women discontinuing their OC, increasing abortions without any reduction in VTE incidence (Castaño and White, 2013). Women discontinuing IUDs or implants within three years commonly cite bleeding changes, or not liking how it made them feel. For OCs the most common reason was logistical reasons, e.g., remembering to take it, or barriers to access (Diedrich et al., 2015). DMPA discontinuers commonly cite side effects (Diedrich et al., 2015).

Missing occasional pills is common (e.g., 68% of women self-reported missing one or more pills in three months) (Smith and Oakley, 2005), and sometimes missing multiple pills inadvertently leads to discontinuation. While most missed pills do not increase pregnancy risk, some do, particularly where the woman runs out of tablets (Smith and Oakley, 2005). Poor OC compliance is associated with having no established routine for pill taking, not reading or understanding the written information provided, insufficient information from the health care professional, and perceived adverse effects (Smith and Oakley, 2005). The top reasons women missed a pill include being away from home, forgetting, not having a new pill pack, being late taking it, travel, work pressures, or school pressures (Smith and Oakley, 2005). Pharmacy could address these concerns through advance discussion with the woman about how she is going to remember taking it (e.g., mobile phone reminder, putting by the toothbrush, making it part of her routine), considering the unexpected night away or travelling (e.g., have a spare card in a wallet or at a house she stays at often), and how to ensure she does not run out. US women can get a free text reminder service for contraceptives (Castaño and White, 2013). To help maximize continuation and minimize gaps in therapy it is important to inform women about LARCs and offer from first starting contraception.

Use of Contraception Around the World

Contraceptive usage varies considerably by country (**Table 3**) (Department of Economic and Social Affairs Population Division, 2017). This is likely to reflect access including cost and health care worker availability, desire to avoid pregnancy within a population, social norms and other cultural effects. While variation is particularly marked between highly developed countries and

Table 3 United Nations contraceptive coverage data for women aged 15–44 or 15–49 in 9 countries (Department of Economic and Social Affairs Population Division, 2017)

	UK (2009)	*France (2011)*	*Columbia (2010)*	*US (2013)*	*Republic of Korea (2009)*	*Australia (2012)*	*Russian Federation (2011)*	*Ghana (2016)*	*Pakistan (2013)*
Use of any modern method	84%	77%	73%	70%	70%	65%	55%	26%	26%
Female Sterilization	8%	4%	35%	21%	6%	4%	1%	1%	9%
Male Sterilization	21%		3%	12%	17%	13%			<1%
Intrauterine device	10%	21%	8%	9%	13%	4%	14%	1%	2%
Implant	1%	2%	3%	1%		4%		7%	
Injectable	2%		9%	1%		1%		8%	3%
Oral contraceptive	28%	41%	8%	13%	2%	24%	13%	5%	2%
Male condom	27%	7%	7%	9%	24%	14%	25%	2%	9%
Traditional method	8%	6%	6%	4%	10%	3%	12%+	5%	3%

Dates provided above are the last date of data collection for the data in the table. Methods of data collection will vary between countries.

developing countries, there is also considerable variation between countries with similar development status. For example, IUDs are twice as commonly used in France than across the Channel in the UK, and Australia has much lower usage than either country.

Emergency Contraception

A copper IUD is 99% effective in preventing pregnancy if used within one week of unprotected intercourse (Alsharaydeh et al., 2017). However, oral hormonal methods are more convenient than an IUD insertion (Gemzell-Danielsson, 2010).

The Yuzpe method introduced in the late 1970s consisted of 0.1 mg ethinylestradiol and 0.5 mg LNG given within 72 hours post intercourse and repeated after 12 hours (Gemzell-Danielsson, 2010). Reduced side effects and higher efficacy saw LNG alone (at a higher dose) superseding the Yuzpe method (Cameron et al., 2017).

LNG can be given as 0.75 mg twice, 12 hours apart or as a single 1.5 mg dose (Gemzell-Danielsson, 2010) when administered within 72 hours of unprotected sexual intercourse. Failure rates increase with later dosing. In a large multicentre study, LNG had a pregnancy rate of 0.4% with dosing up to 24 hours after unprotected intercourse, versus 1.2% for 25–48 hours, and 2.7% at 49–72 hours (Task Force on Postovulatory Methods of Fertility Regulation, 1998). Overall, this represents prevention of 85% of the expected pregnancies. An increase up to 120 hours may have reduced effectiveness (Cameron et al., 2017; Gemzell-Danielsson, 2010) and is not licensed.

LNG appears to have no direct impact on sperm function or motility when used as an EC (Cameron et al., 2017; Gemzell-Danielsson, 2010; Gemzell-Danielsson et al., 2013). LNG can impact on follicular development, if used before the normal luteinizing hormone surge (Gemzell-Danielsson et al., 2013). Inhibiting the luteinizing hormone surge delays or prevents ovulation (Sznajder and Jamshidi, 2016). LNG mainly works by delaying ovulation long enough for any viable sperm to be rendered inactive (Cameron et al., 2017).

More recently available is ulipristal acetate (UPA) as a single 30 mg dose (Cameron et al., 2017). It is slightly more effective, and importantly can be used up to 120 hours after unprotected sexual intercourse (Cameron et al., 2017). A noninferiority study with LNG and UPA found a 1.8% observed rate of pregnancy with UPA (versus 5.5% expected rate), and 2.6% for LNG (versus 5.4% expected) (Glasier et al., 2010). There were 3 pregnancies in 106 LNG users 72–120 hours after sexual intercourse, versus none in 97 UPA users in the same time frame, a significant difference.

UPA is a progesterone receptor modulator that inhibits or delays ovulation and may have some effect on sperm function (Cameron et al., 2017). A theoretical concern has been noted when UPA is used by women already taking an OC. As UPA acts as a receptor modulator, this may make the progestogen contained in an OC unable to bind and therefore decrease the efficacy of the OC (Salcedo et al., 2013). Therefore, an additional barrier method is recommended for the remainder of the menstrual cycle.

LNG may be less effective in women with obesity (BMI $\geq$ 30 kg/m^2) than in normal/underweight women (Jatlaoui and Curtis, 2016). While the evidence is limited, there is some evidence to suggest that women over 80 kg are at increased risk of LNG failure and indeed experience pregnancy rates comparable to those with no contraception (Jatlaoui and Curtis, 2016). In these women, consideration of another method (i.e., UPA or IUD) may be appropriate.

Given the importance of "timely" access to emergency contraception (i.e., efficacy decreases the longer time from unprotected sexual intercourse), increasing access has been a key priority internationally. Pharmacy access may aid uptake due to the distribution of pharmacies, longer opening times and no appointment needed. For example, demand increased in Germany nearly 50% for the EC after reclassifying from prescription to nonprescription (Kiechle and Neuenfeldt, 2017). As early as 1997 community pharmacists in the USA were involved in increasing access (Anderson and Blenkinsopp, 2006), and by around 2000 many countries were supplying ECs via pharmacies (Anderson and Blenkinsopp, 2006). Service users rate pharmacists highly for quality of personal interaction and the quality of information provided (Anderson and Blenkinsopp, 2006). Young people have expressed positive

interactions accessing sexual health products from pharmacy and note specifically longer hours and accessible location (Gonsalves and Hindin, 2017).

A Canadian qualitative study found pharmacists poorly informed on the EC option of a copper IUD, and were unlikely to discuss it with patients, even with delayed presentation or bodyweight above 75 kg (Wong et al., 2017). Many felt reluctant to discuss bodyweight. Mystery shopping in private pharmacies in Kinshasa, Democratic Republic of Congo, found pharmacy staff were mostly knowledgeable and helpful, although some knowledge gaps existed, for example, in time window for use, and a fifth were out of stock of the EC (Hernandez et al., 2018).

Privacy is a common concern, with an Australian study finding many consultations took place at the dispensary counter, albeit that usually the mystery shopper found privacy to be maintained (Collins et al., 2018). More questions were asked when the counseling room was used than at the dispensary, although the number of counseling points did not differ. Some lacked knowledge about the new hormonal contraceptive, UPA, and regulatory matters (supply to a third party). The patient was usually not given a choice of LNG or UPA, despite increased efficacy with UPA.

In a small minority of cases, LNG was supplied outside of the 72 hour window in an Australian mystery shopping study, despite UPA being available (Collins et al., 2018).

Requests for emergency contraception also present an opportunity for pharmacists to provide ongoing contraception or education about it. In Jamaica, only 15% of women getting the EC pill who were not using regular contraception (except condoms in some cases) went on to regular contraceptive measures in the following 3–6 months (Chin-Quee et al., 2010).

Pharmacists' Roles with Ongoing Contraception

Pharmacists can have a variety of roles with ongoing contraception beyond dispensing prescriptions. This includes provision of information; continuation supply; initiation of oral contraceptives, transdermal contraceptives or vaginal rings; and administration or provision of injections.

Rural women in India had limited knowledge about contraceptive methods, which increased substantially following a pharmacist intervention (Chandrasekhar et al., 2018). A simple measure of a pharmacist providing a book improved knowledge immediately after the supply and three months later compared to before the intervention, versus a control group, in a study in Jordan (Akour et al., 2017). There may be other opportunities for contraception provision or advice in pharmacy, for example, a survey in Kuwait found that most pharmacists reported providing contraception advice to lactating women (Albassam and Awad, 2018), probably because they supply OCs without prescription (Shah et al., 2001).

Where hormonal contraceptives other than emergency contraception are available through pharmacy without prescription, the models can vary considerably. Requirements can include previous prescribing by a doctor, age restrictions, additional training by pharmacists, and use of screening tools (Gauld et al., 2016). Sometimes the availability expands through a continuation supply provision, as in Australia and the Netherlands, through reclassification as in New Zealand, or statewide legislation as in some states in the US. Some countries simply have pharmacy or drugstore availability (Grindlay et al., 2013; Ratanajamit et al., 2002).

While much research on the EC availability in pharmacy has been conducted, little research exists on the provision of other contraceptives by pharmacists without prescription. Two key pilot studies were conducted in London (UK) (Parsons et al., 2013) providing OCs and Washington State (US) (Gardner et al., 2008), providing OCs, contraceptive patches or vaginal rings (**Table 4**). In the London study, 11% of women surveyed said they would not have accessed contraception elsewhere, and users were often first-time hormonal contraceptive users. The London pharmacists were self-selecting, potentially being particularly motivated, received a lot of training, and knew they would be audited and mystery shopped. Therefore, this study may not represent a real-world model. In the Washington study, 9% of women were ineligible for supply, primarily because of blood pressure and/or bodyweight over the allowable limit. Some ineligible women did get supplied, typically those already taking it from another provider.

Another pharmacy study found that providing one month of POP to women at the EC consultation saw more women on contraceptives at 6–8 weeks later than those invited to take their empty EC pack to the family planning clinic (Michie et al., 2014).

Table 4 An overview of the two pilot studies conducted (Gardner et al., 2008; Parsons et al., 2013)

	London study	*Washington state study*
Pharmacists and pharmacies involved	16 pharmacists in 8 pharmacies trained; 7 pharmacists from 5 pharmacies provided the service	26 pharmacists in 8 pharmacies; all pharmacies recruited patients
Number of participants	741	214
Proportion of participants with previous use	41% had previously used OCs	87% had previously used hormonal contraceptives
Accuracy of the pharmacist on audit	100%	96% of supplies were within the guideline
Proportion supplied following an EC supply	45%	7%
Time in the consultation	19 minutes	23 minutes for an initial supply
Satisfaction ratings for women	All responding were satisfied or very satisfied	High or very high 98%

A US pilot saw pharmacists with additional training administer DMPA injections to women who were previous users (Maderas and Landau, 2007). Pharmacist enthusiasm or prioritization of the service, and a close relationship with and referrals from the local health clinic appeared to aid uptake, but some clinicians preferred their clinics delivered the injections.

Some real-life research exists of provision of ongoing contraception by pharmacists. One year after opening pharmacist-supply, only 11% of Californian pharmacies provided the service, but a further third expected to (Gomez, 2017). Barriers include lack of reimbursement by insurers and insufficient payment, time constraints, and liability concerns (Vu et al., 2017). Pharmacy purchase of OCs is common in Kuwait (Shah et al., 2001). A quarter of women started it without a physician's consultation. Most women sent another person to collect their OC, and instructions on usage or adverse effects in the pharmacy were rarely reported. OC discontinuation typically occurred with plans to become pregnant. The authors noted the high rate of obesity in women of child bearing age, and the need for improvements in pharmacy staff and packaging to provide better information. In Thailand (Ratanajamit and Chongsuvivatwong, 2001), mystery shopping and survey research with drugstores published in 2001 found deficiencies with history-taking and advice-giving with OCs, but good drug selection. EC provision also had room for improvement. Most drugstores are not pharmacist-owned, and there were some better practices seen with the pharmacists or staff in pharmacist-owned drugstores versus nonpharmacists and staff in drugstores not owned by pharmacists. An educational intervention improved the EC provision (Ratanajamit et al., 2002).

Further real world research is necessary to ascertain the safety, workability, and uptake with the various models.

Conclusion

Pharmacy has an important and increasing role to play in aiding safe and effective contraceptive choices and ensuring women are informed about contraception and how to use it effectively. There is a wide range of contraception, so pharmacists need to be well-informed, and access WHO, UK, or US MEC for the latest information on best practice recommendations.

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Management of Urologic Disorders and the Pharmacist's Role: Benign Prostatic Hyperplasia

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Introduction

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland due to proliferation of smooth muscle and epithelial cells within the prostatic transitional zone (McVary, 2010). The nonmalignant, uncontrolled growth of the prostate leads to bothersome lower urinary tract symptoms (LUTS). LUTS consist of both obstructive voiding symptoms and irritative storage symptoms. Common manifestations of obstructive symptoms include decreased force of stream, intermittent urinary stream, straining, hesitancy, post-voidal dribbling, and incomplete bladder emptying. Irritative symptoms present as increased daytime

frequency, nocturia, urgency, and urinary incontinence. BPH can also cause microscopic or gross hematuria. If left untreated, BPH may lead to more serious medical complications such as acute urinary retention, recurrent urinary tract infections (UTIs), bladder calculi, hydronephrosis, or renal insufficiency/renal failure.

Benign prostatic hyperplasia is the most common benign neoplasm found among men, which increases in incidence and prevalence with advancing age (McConnell et al., 1994). The prevalence of BPH increases from 8% in men aged 31–40, to approximately 50% in men aged 51–60, to over 80% in men older than age 80 (Berry et al., 1984). Black men are more likely to have BPH with moderate to severe LUTS than white men, while Asian men are less likely to have BPH-related symptoms (Martin et al., 2014). Other risk factors associated with an increased risk of BPH-induced LUTS include higher free prostate-specific antigen (PSA) levels, obesity, heart disease, diabetes mellitus, use of beta-blockers, and lack of physical exercise (Meigs et al., 2001).

The exact etiology of BPH remains incompletely understood although several theories exist. Due to the similarity between BPH and the embryonic morphogenesis of the prostate, it has been hypothesized that BPH may result from prostatic tissue reverting back to an embryonic-like state in which it is unusually sensitive to various growth hormones (McVary, 2010). Other possible explanations for the development of BPH may include a change in prostatic androgen receptors or an increase in the ratio of estrogen to androgen with advancing age (Chodak et al., 1992; Krieg et al., 1993). It is certain, however, that as men age, there will be an increase in the amount of prostatic stroma (fibroblast, myofibroblasts, and smooth muscle cells), which further increases the density of alpha-1 receptors in the prostate. Growth of the prostate stroma into the prostatic urethral lumen and increase in smooth muscle tone via the receptors within the prostate create a bladder outlet obstruction (BOO) that contributes to the clinical symptoms seen in BPH. Detrusor overactivity, due to bladder irritability from an overworked bladder trying to overcome an obstruction, is thought to cause irritative symptoms in LUTS.

Although symptoms of BPH are generally not life-threatening, they can be immensely bothersome and significantly affect quality of life (QOL). Thus, it is important to correctly diagnose BPH in order to provide the most effective therapy. The recommended diagnostic evaluation for BPH includes a patient history of LUTS, physical examination, urinalysis, PSA testing, and occasionally urodynamics. The patient's history should include the presence of obstructive and/or irritative symptoms. The severity of LUTS can be assessed using a self-completed questionnaire, such as the American Urologic Association Symptom Score (AUASS) or the International Prostate Symptom Score (IPSS) (Barry et al., 2017). Patients with scores of 0–7 have mild symptoms, 8–19 have moderate symptoms, and 20–35 have severe symptoms. A voiding dairy, which is utilized to record the frequency and volume of urination, may be useful in the evaluation of BPH, especially in men with nocturia or polyuria (>3 L/day) (McVary, 2010). During the physical exam, the bladder is palpated for distention and a digital rectal exam (DRE) is performed to evaluate prostate size, symmetry, and consistency. The presence of blood or a UTI can be detected by urinalysis. A serum PSA, which can be an indicator of prostatic volume, should only be obtained if the patient has greater than 10–15-year life expectancy and if a diagnosis of prostate cancer would modify management (Nickel et al., 2010). Uroflowmetry and post-void residual volume (PVR) are optional diagnostic tests that may be used to assess urine flow rates and identify obstruction. Cystoscopy may be indicated in patients undergoing surgery or in whom urethral stricture, bladder stone, or bladder cancer are suspected. Although BOO may appear severe on diagnostic tests, the degree of BOO or prostate size does not always correlate with the severity of BPH symptoms experienced by the patient.

Treatments for Benign Prostatic Hyperplasia

The primary goals of treatment are to improve patient QOL by relieving LUTS, slowing disease progression, and preventing secondary complications. The need for therapy depends on the severity of symptoms (as assessed by the AUASS or IPSS), its effect on the patient's QOL, and the extent of urinary tract damage. The treatment options for BPH include behavioral modifications, phytotherapy, medicine, and surgery.

Medical Therapy

Behavioral Modification

The American Urologic Association (AUA) recommends that patients with mild LUTS (AUASS or IPSS <8) or patients with moderate to severe LUTS (AUASS or IPSS >8) who are not bothered by their symptoms should be managed with watchful waiting or active surveillance and reexamined yearly. Patients with symptoms that are beginning to affect their QOL but have no evidence of complications (e.g., recurrent infections, urinary retention, or renal insufficiency) may be monitored and treated conservatively with behavioral modifications. Patients should be advised to avoid substances that make urinary symptoms worse. Reducing consumption of spicy food, acidic food, caffeine, and alcohol in the diet may help minimize urinary symptoms. Certain medications that exacerbate symptoms (e.g., diuretics) or induce urinary retention (e.g., alpha-agonists, antihistamines) should also be avoided. If nocturia is a major symptom, men should avoid diuretics in the evening, decrease fluid intake in the evening, and elevate legs an hour before bedtime (to help redistribute and eliminate excess fluid before sleeping) if they have lower extremity edema (McVary, 2010). Lastly, men can try voiding in a sitting position rather than standing or use the double voiding technique to help empty the bladder more completely (de Jong et al., 2014). These lifestyle modifications may be helpful for all patients, regardless of

BPH severity. LUTS may also be relieved by clean intermittent self-catheterization (CIC). This is an appropriate option for men who fail to respond to medical therapy and are not candidates for surgical therapy.

Phytotherapy

The use of phytotherapy (plant-based or herbal medications) for BPH treatment may benefit some men. The current AUA guidelines do not recommend using alternative medicines for the management of LUTS secondary to BPH, due to the lack of data on safety and efficacy of these agents (McVary, 2010). Saw palmetto (*Serenoa repens*) is the most widely used and studied phytotherapy for BPH. The extract from its berries is believed to have antiandrogenic effects, 5-alpha-reductase inhibition, and antiinflammatory effects. However, there is currently conflicting data concerning the efficacy of this extract, with most studies stating saw palmetto has no benefit in the treatment of BPH (Barry et al., 2011; Tacklind et al., 2009). Other phytotherapies marketed for BPH treatment include African plum tree (*Pygeum africanum*), stinging nettle *(Urtica dioica*), pumpkin seed (*Cucurbita pepo*), South African star grass (*Hypoxis rooperi*), and rye grass pollen (*Secale cereale*). The extract from the bark of the African plum tree, which is suggested to inhibit fibroblast proliferation and have antiinflammatory and antiestrogenic effects, has been demonstrated to improve urinary symptoms two times more than placebo and increase maximum urinary flow (Q_{max}) rates (Wilt and Ishani, 1998). Pumpkin seeds have also been shown to have antiinflammatory effects and reduce urinary urgency and frequency in men with LUTS (Damiano et al., 2016). Cernilton, which is extracted from rye grass pollen, has shown to provide symptomatic improvement in BPH, but does not affect urinary flow rates, PVR, or prostate volume (Wilt et al., 1998). Its proposed mechanism of action involves alpha-blockade and 5-alpha-reductase inhibition. Beta-sitosterol, a sterol found in these many of these phytotherapies, has been identified as the ingredient that improves LUTS in men with BPH (Wilt et al., 1999). While some men find benefit in using phytotherapies, there may be a considerable placebo effect with these agents.

Oral Medications

If LUTS continue to negatively affect the patient's QOL despite conservative management, initiation of medical therapy may be indicated. Pharmacotherapy can be considered in men with moderate to severe BPH symptoms (AUASS or IPSS ≥8) who do not have an absolute indication necessitating surgery. Before medically treating BPH, the severity of the patient's symptoms and the potential side effect of therapy should be weighed. Oral medications commonly used for treatment of BPH include alpha-adrenergic antagonists (alpha-blockers), 5-alpha-reductase inhibitors (5ARIs), anticholinergic agents, phosphodiesterase-5 (PDE-5) inhibitors, or combination therapy (**Table 1**).

Alpha-Blockers

Action and Indications

American Urologic Association guidelines recommend the use of alpha-blockers as first-line treatment for moderate to severe symptomatic BPH. Alpha-blockers work by inhibiting alpha-1 adrenergic receptors on the smooth muscle cells of the bladder neck, prostate, and prostatic urethra, leading to the reduction in urethral resistance and bladder obstruction. Alpha-blockers prevent the sympathetic activation of these receptors by the neurotransmitter norepinephrine. Alpha-1 adrenergic receptors consist of 3 subtypes: alpha-1A, located in the smooth muscle of the prostate, bladder neck, seminal vesicles, and vas deferens; alpha-1B, located in blood vessels; and alpha-1D, located in nasal passages, bladder, and spinal cord. Alfuzosin (Uroxatral), doxazosin (Cardura), tamsulosin (Flomax), terazosin (Hytrin), and silodosin (Rapaflo) are long-acting alpha-blockers approved by the US Food and Drug Administration (FDA) for BPH treatment. Alfuzosin, doxazosin, and terazosin are nonsubtype selective alpha-blockers, while tamsulosin and silodosin are selective alpha-1A blockers.

Efficacy

All five alpha-blockers appear to have equal efficacies when administered at the appropriate doses (Jung et al., 2017; McVary, 2010). The alpha-blockers allow for long-term improvement in IPSS and urinary flow rates, decreasing 30%–40% and increasing 16%–25%, respectively (Djavan and Marberger, 1999). Alpha-blockers have also proved to be more effective in improving maximal urine flow and nocturia than finasteride, a 5ARI (Tacklind et al., 2010). Maximal urinary flow rates can be achieved within 8 h of the first dose of a selective alpha-1A blocker and up to 4 weeks with nonselective alpha-blockers. Urinary improvements may be evident within a few days and maximal improvement may take up to 1–3 months (Marks et al., 2013). While older alpha-blockers, such as terazosin and doxazosin, are more cost-effective choices, they require dose titration over several weeks and administration at bedtime to avoid hypotension. Alpha-blockers such as doxazosin can also prevent the progression of BPH (by 39% compared to placebo) (McConnell et al., 2003).

Side Effects

While similar in their efficacies, alpha-blockers can be distinguished by their side-effect profiles due to their differences in affinity for the various alpha-1 receptor subtypes. Some adverse effects experienced by patients include fatigue, nasal congestion, dizziness, orthostatic hypotension, syncope, and retrograde ejaculation. Agents that block alpha-1B receptors can cause hypotension,

Table 1 Oral medications for treating BPH

Class	*MOA*	*Generic name*	*Brand name*	*Selectivity*	*Titration/used for HTN*	*Supplied*	*Directions*	*Maximum daily dose*	*Adverse effects*
α-blocker	Relax smooth muscle in the bladder neck and prostate by inhibiting α-receptors	Alfuzosin	Uroxatral	α-1 non-selective	No/No	Tabs: 10 mg	po q day after a meal	10 mg	Fatigue, nasal congestion, dizziness, orthostatic hypotension, syncope, retrograde ejaculation
		Doxazosin	Cardura	α-1 non-selective	Yes/Yes	Tabs: 1, 2, 4, 8 mg	po q day	8 mg	
		Silodosin	Rapaflo	α-1A selective	No/No	Caps: 4, 8 mg	po q day with a meal	8 mg	
		Tamsulosin	Flomax	α-1A selective	Sometimes/No	Caps: 0.4 mg	po q day after a meal	0.8 mg	
		Terazosin	Hytrin	α-1 non-selective	Yes/Yes	Tabs: 1, 2, 5, 10 mg	po q HS	10 mg	
5α-Reductase Inhibitor (5-ARI)	Reduce prostate volume by inhibiting 5-α reductase enzyme and	Dutasteride	Avodart	Types 1 and 2	No/No	Caps: 0.5 mg	po q day	0.5 mg	Erectile dysfunction, decreased libido, decrease volume of ejeculate, gynecomastia
		Finasteride	Proscar	Type 2	No/No	Tabs: 5 mg	po q day	5 mg	
Phosphodiesterase-5 Inhibitor (PDE5I)	Decrease bladder, prostate, and urethra smooth muscle tone by increasing intracellular cGMP	Tadalafil	Cialis	Type 5	No/No	Tabs: 5 mg	po q day	5 mg	Headache, flusing, back pain, nasal congestion, myalgia, dyspepsia, diplopia, blurry vision, impaired color vision
Anticholinergic Agents	Reduce bladder smooth muscle contractions via inhibiting muscarinic receptors	Tolterodine	Detrol	M receptor non-selective	No/No	Caps: 2, 4 mg	po q day	4 mg	Urinary retention, blurry vision, dry mouth, constipation, cognitive impairments
α-blocker + 5-ARI	Combination MOA of α-blocker and 5-ARI	Dutasteride + Tamsulosin	Jalyn	Type 1 and 2 5α-Reductase Inhibitor + α-1A adrenergic receptor inhibitor	No/No	Caps: 0.5 mg dutasteride + 0.4 mg tamsulosin	po q day after a meal	0.5 mg dutasteride + 0.4 mg tamsulosin	Combination side effects of α-blocker and 5-ARI

dizziness, and syncope. Doxazosin and terazosin cause more hypotension than alfuzosin, tamsulosin, and silodosin (Marks et al., 2013; Roehrborn et al., 2003). However, the hypotensive side effects of doxazosin and terazosin may be favorable in patients with both BPH and hypertension. Agents that block alpha-1D receptors may cause nasal congestion.

Combination of Alpha-Blockers and 5ARIs

The combination of an alpha-blocker and a 5ARI is an appropriate and effective treatment for patients with LUTS and demonstrable prostatic enlargement (>40 g) (McVary, 2010). This combination treatment is also ideal for patients with severe symptoms (AUASS or IPSS >20) or those who do not have an adequate response to maximal monotherapy. Jalyn (0.5 mg dutasteride and 0.4 mg tamsulosin) is the combination pill approved for use in the United States. Based on their respective mechanisms of action, alpha-blockers provide rapid relief of urinary symptoms, and 5ARIs alter the underlying disease process.

The Medical Therapy of Prostate Symptoms (MTOPS) trial and the Combination Avodart and Tamsulosin (CombAT) trial demonstrated that both agents used together improved voiding symptoms (as measured by IPSS) and Q_{max} more than either agent alone (McConnell et al., 2003; Roehrborn et al., 2010). The MTOPS trial also revealed that the combination of both agents is better at preventing the progression of BPH and the need for prostate surgery compared to monotherapy alone. Doxazosin and finasteride reduce the progression of BPH by 39% and 34%, respectively, but together reduce it by 66%. It was also found that men with a PSA >1.5 ng/mL and a prostate volume >40 g benefited the most with the combination of alpha-blockers and 5ARIs (Füllhase et al., 2013). The CombAT study demonstrated a durable 4-year improvement in urinary symptoms with combination therapy.

Combination of Alpha-Blockers and Anticholinergics

When irritative symptoms (i.e., urgency, frequency) in men with BPH do not resolve despite treatment with alpha-blockers, adding an anticholinergic agent may help improve those symptoms. The combination of an alpha-blocker and anticholinergic is ideal for patients with low PVR and irritative symptoms that persist with alpha-blocker monotherapy. It has been shown that this combination provides a greater improvement in QOL, IPSS, urgency, frequency, and nocturia than with either agent alone (Filson et al., 2013). Benefits from the combination can be maintained for at least 1 year (Drake et al., 2015).

Recommendations and Warnings

Care should be taken when prescribing alpha-blockers in patients using a PDE-5 inhibitor, such as sildenafil or vardenafil. The hypotensive effects of alpha-blockers, especially doxazosin or terazosin, can be potentiated with the use of PDE-5 inhibitors. It is recommended that patients space these medications apart by at least 4 h (Viagra, 2014). Furthermore, alpha-blocker monotherapy should be avoided in men with BPH and concurrent cardiovascular comorbidities due to increased risk of congestive heart failure, angina, coronary revascularization, and stroke (Coordinators for the ACRG, 2002).

5-Alpha-Reductase Inhibitors

Action and Indications

5ARIs block the conversion of testosterone to dihydrotestosterone (DHT). DHT, the principal prostatic androgen, contributes to prostatic growth (Bartsch et al., 2000). Instead of reducing smooth muscle tone like alpha-blockers, 5ARIs work by improving LUTS by decreasing prostatic volume. There are two 5-alpha-reductase isoenzymes: type I, found predominately in extra prostatic tissues (i.e., sebaceous glands and liver), and type II, found predominately in genital tissues (Bartsch et al., 2000). Type II 5-alpha-reducatase increases the concentration of DHT in the prostate, hair follicles, and other androgen-sensitive tissues. Finasteride (Proscar) and dutasteride (Avodart) are the only 5ARIs approved for BPH treatment. Finasteride inhibits only type II 5-alpha-reductase and dutasteride inhibits both type I and type II 5-alpha-reductases. However, both medications lead to greater than 80% reduction in intra-prostatic levels of DHT (McVary, 2010).

Efficacy

AUA guidelines recommend the use of 5ARI monotherapy to prevent the progression of BPH and reduce the risk of urinary retention and future prostatic surgery. Due to its primary effect on prostate size, 5ARIs should not be used in men without prostatic enlargement. Prostatic enlargement can be measure by volume measurement (>30 g), PSA level, or DRE (Barry et al., 2017). The Enlarged Prostate International Comparator Study (EPICS) demonstrated that both dutasteride and finasteride are similar in efficacy. 5ARIs have shown to reduce prostate volume by 20%, improve symptom score by 20%, increase Q_{max} by 10%, reduce the risk of urinary retention by 50%, decrease PSA by 50%, and reduce the risk of surgical treatment by 50% (Gormley et al., 1992; Roehrborn et al., 2004). These agents may also help stop hematuria that can occur in BPH (Foley et al., 2000). The Proscar Long-Term Efficacy and Safety Study (PLESS) demonstrated that treatment with finasteride in men with a PSA ≥1.4 and prostate volume >40 g could maintain improved symptom scores, Q_{max}, and prostate volume for more than 4 years. Men with these specific characteristics are appropriate candidates for 5ARIs. In contrast to alpha-blockers, 5ARIs require long-term treatment for efficacy. It usually takes 6–9 months before the prostate size is reduced enough to notice symptom improvements (Wieder, 2010). However, 5ARIs are a reasonable alternative for patient who cannot tolerate alpha-blocker side effects, especially hypotension, and still desire medical therapy. The main difference between finasteride and dutasteride is the serum half-life, which is 6–8 h versus 5 weeks,

respectively. Patients should, therefore, be aware of the possible prolonged duration of side effects after cessation of dutasteride. Finasteride is also indicated for male pattern hair loss (androgenic alopecia).

Side Effects

The side effects of 5ARIs are generally sexual. Adverse effects include erectile dysfunction (ED) (<5%), decreased libido (<4%), decreased volume of ejaculate (<3%), and gynecomastia (<1%) (Gormley et al., 1992). However, it has been shown that adverse sexual effects are only increased during the first year of therapy (Wessells et al., 2003). Another potential side effect of 5ARIs includes increased risk of self-harm and depression, particularly during the initial 18 months of treatment (Welk et al., 2017). 5ARI therapy should be discontinued if depression develops.

Combination of 5ARIs and Alpha-Blockers

As discussed previously with alpha-blockers, the combination of 5ARIs and alpha-blockers is an appropriate treatment for men with severe LUTS (AUASS or IPSS >20), enlarged prostates (>40 g), and inadequate response to monotherapy.

Recommendations and Warnings

Women, especially those who are pregnant or may become pregnant, should not handle crushed or broken tablets as they may be absorbed and cause potential harm to a male fetus. Another concern with the use of 5ARIs is the increased risk of high-grade prostate cancer. However, it has also been found through the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial that 5 ARIs can reduce the incidence of prostate cancer. Based on these findings, the FDA recommends evaluating men for prostate cancer before initiating 5 ARIs but does not approve them for the prevention of cancer.

Anticholinergic Agents

Action and Indications

Anticholinergic agents work by competitively inhibiting the binding of neurotransmitter acetylcholine to muscarinic receptors in smooth muscle throughout the body, including the bladder. Involuntary bladder contractions are under the control of the parasympathetic nervous system, which is hyperactive in overactive bladder (OAB). Of the five subtypes of muscarinic receptors (M1–M5) found in the bladder, M2 and M3 receptors make up the majority, while M3 receptors are the predominate type associated with bladder contraction (Caulfield and Birdsall, 1998). Inhibition of the M3 receptors in the bladder reduces detrusor overactivity. Anticholinergic medications are considered first-line therapy for OAB, which often coexists with BPH. Thus, the irritative symptoms (i.e., frequency, urgency, nocturia, and urinary incontinence) of BPH can be reduced with the use of these agents. The AUA recommends anticholinergic agents as alternative monotherapy in men with LUTS secondary to BPH who have predominately irritative symptoms without elevated PVR. Anticholinergic agents approved for use in OAB include tolterodine, oxybutynin, darifenacin, solifenacin, fesoterodine, and trospium. However, none are currently approved by the FDA for the treatment of BPH.

Efficacy

Anticholinergic monotherapy has demonstrated to be safe and efficacious in men with predominantly OAB symptoms (Athanasopoulos et al., 2011). Studies have shown that these agents can reduce AUASS or IPSS by 6 points. With anticholinergic monotherapy, patients with smaller prostatic volume, higher IPSS, and higher Q_{max} have greater treatment success rates (Liao et al., 2013). Although PVR tends to increase significantly, patients rarely develop acute urinary retention (<3%) (Kaplan et al., 2011). It has been found, however, that risk of acute urinary retention is highest in the first month of treatment. Anticholinergics may improve urinary symptoms within 1 week, but maximal improvements are usually achieved by 3 months (Kaplan et al., 2011). The durability of effectiveness cannot be assessed due to lack of studies with greater than 12 weeks of follow up.

Side Effects

Due to the wide distribution of muscarinic receptors throughout the body, anticholinergic agents have a broad side-effect profile. In the bladder, inhibition of M receptors can cause severe urinary retention. Outside of the bladder, M receptors are located in the eyes, salivary glands, intestines, heart, and brain. Inhibition of M3 receptors in the eyes causes pupil dilation, which leads to blurry vision. Inhibition of M3 receptors in the salivary glands reduces saliva production leading to dry mouth. Dry mouth is the most common side effect experienced with anticholinergics. It can be decreased, however, with the use of extended release rather than immediate release formulations. Inhibition of the M3 receptors in the intestines reduces motility, which leads to constipation. Inhibition of M2 receptors in the sinus nodes of the heart can cause tachycardia.

Combination of Anticholinergics and Alpha-Blockers

As discussed previously with alpha-blockers, the combination alpha-blocker and anticholinergic therapy may be used in patient with predominantly irritative symptoms with concomitant BOO. The addition of an alpha-blocker is recommended in patients who have persistent LUTS with anticholinergic monotherapy.

Recommendations and Warnings

Contraindications to the use of anticholinergics include urinary retention, gastric retention, intestinal obstruction, angle closure glaucoma, and myasthenia gravis. Due to the peripheral side effects and need for prolonged use to achieve maximal benefits, many patients become noncompliant. Management of bothersome side effects, such as dry mouth and constipation, may help maintain patient compliance. Dry mouth can be managed with oral lubricants, sipping water, sucking on sugar-free hard candy, chewing sugar-free gum, or avoiding alcohol-based mouth wash. Constipation can be managed by increasing fluid and fiber intake, stool softeners, laxatives, and regular exercise. Side effects may also be reduced by using M3-specific anticholinergics, such as darifenacin and solifenacin, but these agents have been noted to have higher rates of constipation (Chapple et al., 2008).

Phosphodiesterase-5 Inhibitors

Action and Indications

PDE-5 inhibitors block the degradation of cyclic guanosine monophosphate (cGMP) by cGMP-specific PDE-5 in smooth muscle cells. This increases levels of cGMP leading to relaxation of smooth muscle in the bladder neck, urethra, and prostate and in their vascular supply. PDE-5 inhibitors are first-line treatments for ED. There is a concomitant increase in the prevalence of ED and LUTS secondary to BPH in aging men, which may be due to a shared pathophysiology (Kaplan and Gonzalez, 2007). It has been found that sexual dysfunction is strongly related to the severity of LUTS due to BPH (Rosen et al., 2003). Although AUA guidelines do not mention PDE-5 inhibitors for the management of BPH, European Association of Urology (EAU) guidelines state that PDE-5 inhibitors (i.e., tadalafil, sildenafil, and vardenafil) are appropriate to use for the concomitant treatment of BPH and ED. Tadalafil (Cialis) is the only PDE-5 inhibitor approved by the FDA for BPH. PDE-5 inhibitors are ideal for men who have both obstructive symptoms and ED.

Efficacy

A meta-analysis demonstrated significant improvements in IPSS despite no difference in urodynamic parameters in men with symptomatic BPH after >12 weeks of treatment with tadalafil compared to placebo (Liu et al., 2011). Compared to alpha-blockers, PDE-5 inhibitor monotherapy also showed significant improvements in IPSS and Q_{max}, while being the only treatment to improve ED and QOL in men with BPH (Oelke et al., 2012). Tadalafil can improve IPSS by greater than 25% within 1–4 weeks of use in most patients (Oelke et al., 2015). Maximal improvements in LUTS may take up to 2 months. Long-term safety and effectiveness of these agents have not been assessed in men with symptomatic BPH with concurrent ED.

Side Effects

The most common side effects with PDE-5 inhibitors include headache and facial flushing, which is due to the vasodilatory effect of these agents. Other less common side effects include nasal congestion, back pain, myalgia, dyspepsia, diplopia, blurry vision, and impaired color vision (blue or purple hues). While extremely rare, priapism, loss of vision, and loss of hearing may occur. Most side effects experienced by patients often decrease or resolve after several weeks of use.

Combination of PDE-5 Inhibitors and Other Benign Prostatic Hyperplasia Medications

PDE-5 inhibitors may be combined with other BPH medications when monotherapy is inadequate in treating BPH-related symptoms. The combination of PDE-5 inhibitors and alpha-blockers has shown to significantly improve IPSS, Q_{max}, and ED more than with alpha-blockers alone (Gacci et al., 2012). The combination of PDE-5 inhibitors and 5ARIs has also shown to improve symptom scores more than with 5ARIs alone (Elkelany et al., 2015).

Recommendations and Warnings

PDE-5 inhibitors should be avoided in men with extreme hypotension (blood pressure <90/50) or hypertension (blood pressure >170/110), men who are taking drugs that prolong the half-life of PDE-5 inhibitors, or in patients with retinitis pigmentosa. PDE-5 inhibitors are contraindicated in men taking nitrates for chest pain since these agents potentiate the effect of nitrates and may cause life-threatening hypotension. Caution should be taken when co-administering PDE-5 inhibitors with alpha-blockers as hypotension may occur when taken together. It is recommended to start a PDE-5 inhibitor at the lowest dose if the patient is stable on an alpha-blocker, and vice versa. In addition, a dose of sildenafil >25 mg should not be taken within 4 h of taking an alpha-blocker (Viagra, 2014).

Surgical Therapy

While being a highly invasive option, surgery is the most effective treatment for BOO due to BPH. It is strongly indicated in patients with acute urinary retention, recurrent UTIs, refractory gross hematuria, recurrent or large bladder stones, hydronephrosis, or renal insufficiency from BPH. Patients with an enlarged median lobe are unlikely to respond to medical therapy and should be treated surgically. In addition, patients who fail lifestyle modifications and combination medical therapy after 12 months should be considered for surgical management. AUA guidelines state that surgical intervention is an appropriate treatment option for patients

with moderate to severe LUTS. While initial medical therapy is recommended in these men, patients may choose to pursue surgery as the primary treatment. In general, the decision to proceed with surgery depends on the effectiveness of medical therapy, the development of complications from BPH, and patient preference. Surgical therapies for BPH include minimally invasive, endoscopic, open, and robotic surgery.

Endoscopic Approaches

Transurethral Resection of the Prostate

TURP is considered the "gold standard" surgical therapy for treating BPH. Obstructing prostatic tissue is resected transurethrally via a resectoscope with an electrical loop, allowing urine to flow more easily. It is most suitable for men with prostate volumes <80 g. This procedure is performed in an operating room under general or spinal anesthesia.

Most patients experience substantial improvements with TURP. Compared to medical therapy with alpha-blockers, TURP has the most significant improvements in IPSS (15 vs. 6 points) and Q_{max} (11 vs. 2 mL/s) (Wieder, 2010). Despite the great results, the procedure is associated with a significant risk of morbidity (11.1%) and a small risk of mortality (0.10%) (Reich et al., 2008). The most common postoperative complication is bleeding, which may be reduced with the use of bipolar TURP (compared to monopolar TURP) or the preoperative administration of a 5ARI (McVary, 2010). There is also a risk of blood transfusion and prolonged hospital stay. Other complications include bladder wall injury, bladder neck stenosis, urinary incontinence, ED, or retrograde ejaculation. Transurethral resection syndrome (TUR syndrome), which comprises of hyponatremia and water intoxication due to excess fluid absorption, is a possible adverse effect that may lead to hypertension, mental confusion, nausea, vomiting, and visual changes.

Endoscopic Laser Treatments for Benign Prostatic Hyperplasia

Holmium Laser Enucleation and Holmium Laser Resection of the Prostate

The holmium:yttrium-aluminium garnet (Ho:YAG) laser is a pulsed solid-state laser, which is absorbed by water and any tissue containing water. Secondary to the laser's wavelength (2140 nm), the depth of the penetration is limited to 3–4 mm. The procedure uses the laser to enucleate the prostatic adenoma within the tissue planes. The Laser cuts and instantaneously provides tissue hemostasis. Secondary to excellent hemostatic properties and the fact that the procedure uses isotonic saline solution, the procedure is ideal for men with BPH and larger prostate glands. A Compared to TURP, HOLEP has similar symptoms improvement, potency, continence, and major morbidity but shorter hospitalization and catheterization. HOLEP may also be safely performed in men being treated with anticoagulant and/or antiplatelet agents (El Tayeb et al., 2016; Westenberg et al., 2004).

Open Simple Prostatectomy

An open simple prostatectomy is the most radical surgical option available and the standard of care for large (>80 g) prostate glands. It involves surgical removal of the inner core (transition zone) of the prostate, leaving behind the peripheral zone.

Similar to TURP, an open simple prostatectomy provides better improvements in IPSS (10 vs. 6 points) and Q_{max} (14 vs. 2 mL/s) than with medical management (Wieder, 2010). However, it is the most invasive procedure and is associated with an increased risk of longer hospital stay, larger amounts of blood loss, and possible blood transfusions (McVary, 2010). The side-effect profile is similar to TURP with the exception of an increased risk of bladder neck stenosis and urinary incontinence (Wieder, 2010).

Role of Pharmacist

The process leading to the diagnosis and management of BPH is often initiated following symptomatic presentations to general practice. Medical therapy is the first step of management. Patients who do not respond to this medical therapy are subsequently refereed for specialist urology assessment. There are no studies, which have specifically assessed the pharmacist's role in this setting. However, the pharmacist can play a key part in ensuing successful implementation of treatment, provide continuous monitoring, and evaluate for ongoing response. Pharmacist-initiated patient education with regard to timing of administration, drug interactions, and side effects can maximize the likelihood of successful medical therapy. In addition, as mentioned earlier in the chapter, BPH is a progressive condition and despite initial response to treatment, a proportion of patients will continue to deteriorate. As healthcare professionals who interact with patients on regular basis, the pharmacist should enquire about recurrence of symptoms and make subsequent recommendations for further medical assessment.

BPH is almost exclusively diagnosed in older men who are often concurrently treated with multiple other therapeutic agents. The pharmacist is in a prime position to assess and review possible drug interactions. Medication side effects are often the main reason for poor compliance and consequently lead to failure of medical therapy for BPH.

Lastly, pharmacists should be aware of all available options for management of BPH and LUTs. They should be able to reassure their patients that failure of one agent or combination therapy does not translate to life-long symptoms and that surgery remains an option for many men with LUTs.

Conclusion

BPH is undoubtedly one of the most prevalent conditions seen in elderly men, especially as the population is rapidly aging. While it is not usually a life-threatening condition, BPH can significantly impact a patient's QOL and may eventually lead to complications such as renal failure. While surgical management is extremely effective in relieving LUTS due to BPH, medical management has emerged to become the predominant method for treating BPH. Thus, pharmacists play a crucial role in the management of patients with BPH.

Due to the comorbidities and polypharmacy often associated with BPH, pharmacists need to ensure that patients are adequately educated on the disease process associated with BPH and receiving the optimal treatment for their symptoms. There are many drug classes that have shown to be effective in treating LUTS in BPH, but it is important to consider the patient's symptoms, risk of disease progression, coexisting conditions, and other medications before deciding on which medical therapy to pursue. Alpha-blockers are recommended as first-line treatment for patients with BPH. 5ARIs are only recommended in men with prostatic enlargement. PDE-5 inhibitors can be used in men with concomitant ED. Lastly, anticholinergics are recommended in patients with symptoms of OAB. These classes of medications may be combined depending on severity of the disease and the presence of concurrent symptoms.

Phytotherapy may also have a potential benefit in patients with BPH, but these products have not shown to be entirely safe and efficacious in controlled studies. Pharmacists may also counsel men with BPH on behavioral modifications and screen their profiles for medications that can exacerbate LUTS. If patients are unsuccessful with behavioral and medical management, surgery may be an appropriate option. It should also be emphasized to patients that nonadherence to medical therapy may increase the need for surgery. The ultimate goal of BPH treatment is to reduce LUTS and improve QOL. Pharmacists are essential in the management of patients with BPH by ensuring their therapy is safe and effective, providing realistic treatment expectations, and stressing medication compliance.

Glossary

Phytotherapy Phytotherapy is the study of the use of natural extracts as medicines or health-promoting agents. Phytotherapy medicines differ from plant-derived medicines in standard pharmacology

LUTS (lower urinary tract symptoms) LUTS is a term used to describe a number of symptoms related to issues related to the lower urinary tract (urethra, prostate, and bladder). LUTS are grouped into obstructive symptoms (during voiding) or irritative (also called storage e.g., frequency, urgency) symptoms.

IPSS Score The International Prostate Symptom Score (I-PSS) is based on patient answers to seven questions (scored from 0 to 5) concerning urinary symptoms and one question assessing quality of life. The total score (0–35) indicated the severity of the symptoms.

Bladder outflow obstruction (BOO) BOO is a blockage of urine flow from the bladder which can lead to LUTS symptoms. This is often related to BPH.

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Management of Erectile Dysfunction and the Pharmacist's Role

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Learning Objectives

After reading this chapter, the reader should be able to:

1. Define erectile dysfunction, and understand its prevalence, common causes, and effect on the sufferer.
2. Discuss the management of erectile dysfunction including lifestyle and pharmacological management, and risk management for pharmacological treatment.
3. Discuss the current and future roles of the pharmacist in the identification and management of erectile dysfunction, including the evidence for these roles.

Key Concepts

- Erectile dysfunction (ED) is a common condition, increasing in prevalence with age.
- ED can be an early indicator of more widespread cardiovascular disease, with the small vessels being occluded earlier.
- The risk of ED increases with many medical conditions, such as diabetes, hypertension and hyperlipidemia, and the use of some medicines.
- ED can be from physical causes (e.g., blood vessel occlusion), and from psychological causes, such as depression, or performance anxiety. Even where the cause of ED is physical, a psychological component is common, for example, with reduced confidence in their sexual performance.
- Treatment options include vacuum devices intercavernosal injections and intraurethral pellets.
- PDE5 inhibitors are considered first line therapy. These inhibit PDE5, preventing the breakdown of cyclic guanosine monophosphate. This causes smooth muscle relaxation, and increased blood flow which compresses the veins and maintains an erection.
- Contraindications to the use of PDE5 inhibitors include use of nitrates or alkyl nitrites, use with a recent myocardial infarction (MI), stroke, or life-threatening arrhythmia, particularly low or high blood pressure, unstable angina, angina with sexual intercourse, severe cardiac failure, loss of vision in one eye, and hereditary degenerative retinal disorder.
- PDE5 inhibitors are the most commonly counterfeited of all medicines, and many herbal products can be adulterated with PDE5 inhibitors, sometimes combined with other pharmaceuticals.

- Sourcing PDE5 inhibitors without health professional involvement is common, particularly in younger men (under 40 years), mostly through internet purchase.
- In some countries, pharmacists may be able to supply PDE5 inhibitors without a prescription.
- Protocols or checklists should aid safe supply, and help identify men needing a medical check-up. Advice is an important aspect of this supply.
- There are still many considerations that need to be evaluated for the advanced role of the pharmacist in this field and more research needs to be undertaken to evaluate the scope, protocols, and effectiveness.

This chapter particularly concentrates on aspects of ED that are most relevant to the pharmacist. It focuses on potential causes, particularly conditions or medications where pharmacists might be able to make a difference, on counterfeit medicines and remedies with undeclared ED prescription medicines, and on counseling points. It also provides information on pharmacists' models of care for ED outlined in the literature.

Introduction to Erectile Dysfunction

Erectile dysfunction (ED) is a very common complaint in men, particularly associated with increased age, and arising from many medical conditions, medicines, and psychological factors. It can have a profound impact psychologically and on relationships. While there are a variety of mechanical devices and locally administered options, the treatment of ED was "revolutionized" with the advent of sildenafil in 1998. This "Viagra" era and the associated "little blue pill" have heralded a new stage of ED conversation and therapy options. This has led to ED becoming increasingly discussed, with over 100 million men thought to have sought treatment for ED since then (Perelman and Watter, 2016).

Erectile Dysfunction—An Overview

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain a penile erection adequate for satisfactory sexual performance (NIH Consensus Conference, 1993; Tsertsvadze et al., 2009).

Sexual stimulation leads to the release of nitric oxide from nerve endings and the endothelium of the penis, stimulating an increase in levels of cyclic guanosine monophosphate (cGMP), which causes relaxation of the cavernosal smooth muscle. This causes dilatation of the cavernosal arterioles allowing blood to flow into the corpus cavernosum. It is this increased blood flow that causes the engorgement of the penis and results in an erection. Cyclic guanosine monophosphate is degraded by phosphodiesterase 5 (PDE5) (Andersson, 2018).

Prevalence and Etiology

ED is a common condition, increasing by age (Feldman et al., 1994; Schouten et al., 2005). The prevalence varies by study according to definition, sampling, and survey tools. In men under 40 years, various studies have suggested a prevalence of 1%–10%, from 40 to 49 years the prevalence has been found to be 2%–9%, increasing then to 20%–40% in men 60–69 years, and 50%–100% above 70 years (Shamloul and Ghanem, 2013). However, some men with ED are unperturbed by it, with a Dutch study finding only around a quarter of men with ED particularly concerned by their ED, with greater concern in those with more significant ED (Schouten et al., 2005).

While ED can be caused by organic causes in which the physiology is affected, or by psychological causes such as performance anxiety or relationship issues, in many cases it is a mix of both (Hatzimouratidis et al., 2016).

> "In men aged <60 years and in men with diabetes or hypertension, ED can be a critical warning sign for existing or impending cardiovascular disease and risk for death." (Meldrum et al., 2011)
>
> "ED significantly increases the risk of CVD, coronary heart disease, stroke, and all cause mortality, and the increase is probably independent of conventional cardiovascular risk factors." European Association of Urologists 2018 (Hatzimouratidis et al., 2016)

ED can be "the canary in the coal mine," being an important independent marker of heightened cardiovascular (CV) risk (Hatzimouratidis et al., 2016; Meldrum et al., 2011; Shah et al., 2016). Vascular ED is strongly linked with cardiovascular disease, often coexisting with silent CV disease. It shares the same risk factors of obesity, smoking, dyslipidemia, physical inactivity, and diabetes. ED symptoms typically occur before CV symptoms, and have an independent association with CV disease and CV events. In men presenting to an emergency department with chest pain and angiographically confirmed coronary artery disease (CAD), half had ED, with ED occurring before CAD symptoms in 67%, by a mean of 39 months (Montorsi et al., 2003). Therefore it is recommended that all men with vascular ED have a CV risk assessment, unless done recently (Shah et al., 2016). We want patients to consult doctors early when it occurs so they can be checked for CV risk and preventative measures started early if necessary, helping both their CV risk and their ED.

Smoking increases the risk of getting ED, up to twofold, with a dose dependent relationship (longer duration and higher frequency increases the risk) (Kovac et al., 2015). Men quitting smoking before middle age can have some improvement in their

ED, and improvement in erectile function can be seen even after a short smoking absence (Kovac et al., 2015). However, regaining erectile function is less likely if the ED was severe and/or the man over 50 or 60 years of age. There is good evidence to advise men to quit smoking early to protect their erectile function.

Men with hypertension, with no other medical conditions, have at least double the risk of ED compared with men without hypertension, with longer and more severe hypertension increasing the incidence further (Meldrum et al., 2011).

Comorbidities are common, for example, a Spanish study (Martín Morales et al., 2010) found many men getting ED medication had hypertension (64%), diabetes mellitus (43%), hypercholesterolemia (55%), hypertriglyceridemia (34%), or depression (38%). Men with diabetes are three to four times as likely as men without diabetes to have ED (Burke et al., 2007; Maiorino et al., 2014; Colson and Roussey, 2013), with risk increasing with age, and a longer duration of disease (type 1 or 2). ED occurs 10–15 years earlier in men with diabetes, who tend to have more severe ED and are less likely to respond to oral therapy. Microvascular and macrovascular damage, and concomitant conditions that diabetes is often associated with, are likely to contribute to this increased risk.

Panel 1

Contributing factors to erectile dysfunction include (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016; Meldrum et al., 2011; Rai and Terry, 2018):

- Sedentary lifestyle
- Obesity
- Cigarette smoking
- Cycling more than three times per week
- Atherosclerosis
- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Metabolic syndrome
- Degenerative disorders, e.g., Parkinson's disease, multiple sclerosis
- Stroke
- Multiple sclerosis
- Hormones, e.g., testosterone deficiency, hyperprolactinemia, excess or insufficient thyroid hormones or cortisol
- Pelvic surgery
- Radiotherapy or brachytherapy for prostate cancer
- Penile trauma or abnormality, e.g., from priapism, Peyronie's disease
- Excessive alcohol
- Recreational drug use
- Spinal cord injury
- Renal failure
- Poor health
- Depression
- Relationship difficulties
- Performance anxiety
- Disorders of sexual intimacy

ED is common in men on opioid replacement therapy, with around half of such men being sexually inactive or having ED, increasing in prevalence as the dosage increases (Lugoboni et al., 2017). In Parkinson's disease, 43%–79% report ED (Bhattacharyya and Rosa-Grilo, 2017).

Some medicines may cause ED (Panel 2).

Panel 2

Drugs known to cause erectile dysfunction (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016; NICE, 2017; Aronson, 2016)

Beta blockers
Thiazide and thiazide-like diuretics
Spironolactone
Disopyramide, flecainide
Tricyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Venlafaxine
Chlorpromazine, haloperidol, thioridazine
Risperidone, clozapine, ziprasidone

Digoxin
Amiodarone
Cimetidine, ranitidine
Finasteride
Antiandrogens, e.g., flutamide, cyproterone acetate
Gonadorelin and analogues
Corticosteroids
Bromocriptine
Interferon alfa
Sulfasalazine
Opioids
Naltrexone
Recreational drugs

Some care may need to be taken about mentioning ED as a possible side effect of a new medicine started as at least some of the effect is psychological. Men taking atenolol 50 mg per day for three months were twice as likely to have ED when told about possible side effects than when only told that they were getting atenolol (Silvestri et al., 2003). They were even less likely to report ED when they did not know what they were given (3%), and placebo seemed nearly as effective as sildenafil in solving the problem, further suggesting a psychological component.

More lipophilic beta blockers may be more likely to cause ED, and new generation beta blockers, e.g., nebivolol less likely (Aronson, 2016). Meyler's Side Effects of Drugs (Aronson, 2016) suggests that the likelihood of ED with thiazides is elevated but still reasonably low.

Sexual dysfunction including ED is common with antidepressants, with ED occurring in 14%–40% of men taking selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors, depending on the agent, but most of those suffering do not report it to their doctor (Montejo et al., 2001). In most people the problem will not resolve spontaneously. While some people are not particularly concerned with this adverse effect, others may be particularly bothered by it and there is a risk of discontinuation of their antidepressant as a result.

Psychological factors such as depression, anxiety, performance anxiety, and relationship difficulties often cause ED (Perelman and Watter, 2016). Even where the cause of ED is physical, a psychological component is common with reduced confidence in their sexual performance, avoiding sex and sometimes avoiding affection, with negative impacts on the relationship. A partner may have doubts about their attractiveness or the man's fidelity. Couple's therapy is often recommended.

Diagnosis

Diagnosis is based on the man's report of his erectile difficulties, and considering potential causes discussed above such as medication, relationship issues, underlying disease, alcohol or drug misuse, or cigarette smoking (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016; Bella et al., 2015). A medical and sexual history is required. ED can be confused by some men with other problems including premature ejaculation. Testosterone blood tests are indicated if there is evidence of hypogonadism (e.g., low energy, low libido, and cognitive impairment). Lower Urinary Tract Symptoms (LUTS) should be asked about. A physical examination check is recommended. Blood pressure, heart rate, lipids, and glucose should be measured. Questionnaires can be used, particularly to aid evaluation of the response to therapy. Sensitivity and privacy are important, as is understanding patient expectations of what is normal with respect to erectile function.

Men commonly take an extended period of time before discussing their ED with a health professional (Martín Morales et al., 2010), and some may never do it. Spanish men who had sought treatment for ED from a health professional took on average 26 months from their first symptoms of ED. This reluctance to discuss the concern with a doctor can result in men never seeking treatment or using the internet (Sugita and Miyakawa, 2010; Shaeer, 2013) to acquire treatment. Some groups are particularly reluctant, for example, only 6% of men with ED on opioid replacement are treated for ED, despite its association with reduced quality of life in this group (Lugoboni et al., 2017). Doctors often do not raise the topic of sexual disorders, and patients may be embarrassed or unsure as to the reaction of the doctor (Perelman and Watter, 2016).

Most men with diabetes who have ED have never discussed it with their doctor, despite its association with lower quality of life, a less satisfactory sexual life, and a higher level of depressive symptoms in men with type 2 diabetes, and doctors generally do not ask men with diabetes about it (De Berardis et al., 2002).

Quality of Life

Quality of life is affected by ED. It can affect the man's relationship with his partner and is associated with reduced self-esteem (Cappelleri et al., 2006; Paige et al., 2001; McCabe and Althof, 2014). Men with untreated ED have lower self-esteem and confidence

than men without (Cappelleri et al., 2006). Quality of life in diabetics (De Berardis et al., 2002) and in men on opioid replacement (Lugoboni et al., 2017) is also negatively affected by ED, particularly with increasing severity of ED. Treatment can help (see treatment below).

Management of Erectile Dysfunction

Lifestyle Measures

Modifiable risk factors should be addressed (Hatzimouratidis et al., 2016; NICE, 2017), e.g., quitting smoking, and weight loss, either before treatment or alongside treatment. Where ED may be associated with an underlying condition, e.g., hypertension or diabetes, control of the condition is important. For men doing long distance cycling (more than three hours per week), trialing a period without cycling is recommended.

Exercise increases nitric oxide release, both acute exercise (for 48 hours), and daily exercise (for longer), and men who exercise have a much lower risk of ED (Meldrum et al., 2011). Weight loss and increased physical activity can help ED (Hatzimouratidis et al., 2016; Meldrum et al., 2011). Meldrum et al. (2011) suggested that more frequent sexual intercourse may help prevent ED through the greater effect on the blood vessels of an erection compared with other exercise.

Pharmacological Treatment

Use of ED medicines is common, increasing with age, until peaking around 65–69 years (Bjerkeli et al., 2018). A Swedish study found 5.3% of men aged 45–64 years had filled a prescription with an ED medicine in 2016, and 9.2% of 65–79 year old men (Bjerkeli et al., 2018).

There is a high rate of discontinuation with ED medicines generally, and particularly for ethnic minorities (Perelman and Watter, 2016). In some cases this is likely to occur because of relationship changes, or inadequate consideration to psychological factors. Other reasons for failure of ED treatment include not waiting long enough for the medicine to work, that the onset of effect might have been delayed by food (**Table 1**), or their alcohol consumption might have affected their erectile function.

PDE5 Inhibitors

These medicines are regarded as first-line treatments by the European Association of Urology (Hatzimouratidis et al., 2016). They inhibit PDE5, stopping the breakdown of cyclic guanosine monophosphate. This causes smooth muscle relaxation and increased blood flow which compresses the veins with the outgoing blood, therefore trapping blood in the penis, and helping maintain the erection (Hatzimouratidis et al., 2016). This is only of use when the individual is sexually stimulated.

The first of these to be introduced was sildenafil, which remains very popular. It is used for on demand dosing, has a fairly short half-life, and its effect is slowed by food. With a long half-life, tadalafil provides longer cover than the others, and has a low once daily dose that can help LUTS also. However, tadalafil has a longer onset of action. Vardenafil is most affected by drug interactions, but its onset is reasonably quick and not particularly affected by food unless it is a high fat meal. Avanafil is the newest agent, and is very specific for PDE5, minimizing the frequency of side effects.

PDE5 inhibitors provide an erection sufficient for intercourse in most men with ED, having a success rate of 65% or more, depending on the dose (**Table 2**) (Shamloul and Ghanem, 2013). PDE5 inhibitor use in men with ED improves self-esteem, confidence, quality of life, their relationship with their partner, and their sex life (Cappelleri et al., 2006, 2008; McCabe and Althof, 2014; O'Leary et al., 2006; Leoni et al., 2013). Partner satisfaction is typically high for PDE5 inhibitors (Gil et al., 2001; Althof et al., 2006; Conaglen and Conaglen, 2012).

Table 1 Comparison of the PDE5 inhibitors (Pfizer, 2016; Lilly, 2017; Bayer, 2018; Menarini, 2018)

	Strength	*Dose*	*T_{max}*	*Half-life*	*Comments*
Sildenafil	25 mg, 50 mg, 100 mg	25–100 mg one hour before sexual activity, starting with 50 mg	Median 60 minutes	3–5 hours	T_{max} is delayed about one hour by food
Tadalafil	2.5 mg, 5 mg, 10 mg, 20 mg tablets	10–20 mg prior to sexual activity; or 2.5–5 mg once daily for continuous use	Median 2 hours	17.5 hours	No effect of food on the absorption
Vardenafil	5 mg, 10 mg, 20 mg	5–20 mg 25–60 minutes before sexual activity	Median 60 minutes	4 hours	A high fat meal delays absorption 1 hour
Avanafil	50 mg, 100 mg, 200 mg	50–200 mg 15–30 minutes before sexual activity, starting with 100 mg	Median 30–45 minutes	6–17 hours	A high fat meal delays the T_{max} 1.25 hours

Table 2 Percentage of a general ED population reporting improved erections after 12 (tadalafil and vardenafil) or 24 weeks' (sildenafil) treatment[a] (Hatzimouratidis et al., 2016)

	Sildenafil	*Tadalafil*	*Vardenafil*
Lowest dose	25 mg 56%		5 mg 66%
Moderate dose	50 mg 77%	10 mg 67%	10 mg 76%
High dose	100 mg 84%	20 mg 81%	20 mg 80%
Placebo-response as comparator	25%	35%	30%

[a]Not head-to-head studies.

The recommended doses typically start in the middle of the dose range, and increase or reduce as necessary, with a maximum of one dose per day. While there is a dose-response relationship, the middle dose is effective in nearly as many men as the upper dose is.

Failure of the PDE5 inhibitor can occur where the medicine is counterfeit (see below) and the drug is absent or subtherapeutic, or with insufficient dose, insufficient sexual stimulation, or taking the drug too close to the time of sexual activity (noting also the potential effect of food for some agents) (Hatzimouratidis et al., 2016). It is recommended that six attempts are made occurs before failure is decided. Up to 35% of men fail with PDE5 inhibitors, with failure more likely in men with diabetes mellitus, severe ED, history of pelvic surgery or severe neurological or vascular disease (Shamloul and Ghanem, 2013; Suetomi et al., 2008).

Adverse events are typically mild (Shamloul and Ghanem, 2013), and vary in incidence between the agents (Hatzimouratidis et al., 2016). The most common events are headache, flushing, dyspepsia, and nasal congestion. The European Association of Urology (EAU) Guidelines (Hatzimouratidis et al., 2016) report that avanafil is more highly selective for PDE5 inhibition versus other PDE subtypes, as compared to other PDE5 inhibitors. Frequencies of many of the side effects reported in clinical studies appear to be lower for avanafil than the rates reported for the other medicines, noting this data is not from comparative studies between the different agents. There is some other variation between the different PDE5 inhibitors, for example, the reported rates of dyspepsia (12%) appear higher for tadalafil than the reported rates for the other PDE5 inhibitors, and back pain (6.5%) and myalgia (5.7%) can occur with tadalafil but are not reported on for the others. Abnormal vision (differences in blue/green color discrimination) occurs particularly with sildenafil and vardenafil, but affects a small minority of men, at under 2%. Reports of some side effects for vardenafil seem more frequent than that reported for the other agents, for example, headache (16%), flushing (12%), and nasal congestion (10%).

Non-arteritic anterior ischemic optic neuropathy (NAION) has been identified as a possible side effect of PDE5 inhibitors, but the evidence is not clear (Aronson, 2016). The EAU Guidelines (Hatzimouratidis et al., 2016) report "no increase in myocardial infarction rates in patients receiving PDE5 inhibitors" in clinical trials. However, they have contraindications as noted in Panel 3.

Panel 3

Contraindications to PDE5 inhibitor use (Hatzimouratidis et al., 2016; Pfizer, 2016; Bayer, 2018; Lilly, 2017)[1]

- A myocardial infarction, stroke, or life-threatening arrhythmia in the last 3–6 months[1]
- Resting blood pressure <90/50 mmHg, or >170/100 mmHg or uncontrolled hypertension[1]
- Unstable angina, angina with sexual intercourse
- Severe cardiac failure[1]
- Loss of vision in one eye because of the risk of non-arteritic anterior ischemic optic neuropathy (NAION)
- Hereditary degenerative retinal disorders, e.g., retinitis pigmentosa
- Severe hepatic impairment (some agents)[1]
- Severe renal impairment (some agents)[1]
- Nitrate and alkyl nitrite usage
- Men with cardiac disease for whom sexual activity is inadvisable
- Men with uncontrolled arrhythmias[1]
- See also interactions

[1] Most contraindications are common to all PDE5 inhibitors, but see the summary of product characteristics for each medicine as there is some variation, e.g., with degree of cardiac failure and renal impairment.

Drug interactions vary a little between the agents. All PDE5 inhibitors are contraindicated with nitrates owing to the potential for an unpredictable, and potentially dangerous, drop in blood pressure. While being fairly selective, with a substantially greater effect on the penis than elsewhere, PDE5 inhibitors cause a fall in blood pressure of about 10 mmHg

(Preston, 2018). Stockley's Drug Interactions reports that as nitrates increase the cyclic guanosine monophosphate production, PDE5 inhibition causes cyclic guanosine monophosphate to increase and nitric oxide enters the circulation increasing vasodilation and reducing the blood pressure. The half-life of the agent is relevant, with a nitrate not given for 24 hours after sildenafil, versus 48 hours after tadalafil, and 12 hours after avanafil. Nicorandil and alkyl nitrites ("poppers") are also contraindicated with PDE5 inhibitors.

Cytochrome P450 3A4 is the major isoenzyme involved in metabolism of each of these PDE5 inhibitors (Pfizer, 2016; Lilly, 2017; Bayer, 2018; Menarini, 2018). Therefore, their clearance is reduced by CYP3A4 inhibitors and increased by CYP3A4 inducers to varying degrees discussed below. Grapefruit juice has a more modest effect than other CYP3A4 inhibitors, but some caution is advised (Preston, 2018).

For sildenafil, concomitant administration of the CYP3A4 inhibitor erythromycin results in nearly three times the exposure to sildenafil, and the manufacturer recommends a starting dose of 25 mg (Pfizer, 2016). However, for ritonavir, which is a highly potent CYP3A4 inhibitor, the fourfold increase in the C_{max}, and considerable prolongation of half-life and 11-fold increase in exposure (AUC), means this combination is not advised. CYP3A4 inducers can reduce the blood levels of sildenafil. Although CYP2C9 is a minor isoenzyme involved in sildenafil metabolism, CYP2C9 inhibitors seem to have no effect on sildenafil levels. Sildenafil's inhibition of some CYP isoenzymes appears to be too weak to affect other drugs.

While cytochrome P450 3A4 is also the major isoenzyme involved in tadalafil metabolism, the effect on C_{max} is minimal and the tadalafil exposure is not increased as much as for sildenafil, e.g., ritonavir increased the exposure to tadalafil by twofold (Lilly, 2017). The manufacturer advises caution. Rifampicin, a potent CYP3A4 inducer, reduces the AUC by 88%.

CYP3A4 is also the major isoenzyme for vardenafil metabolism (Bayer, 2018), and the effect on vardenafil pharmacokinetics is much greater than for sildenafil or tadalafil. Ritonavir caused a 13-fold increase in C_{max} and 49-fold increase in AUC for vardenafil 5 mg. Ketoconazole increased the AUC of vardenafil by 10-fold. Potent CYP3A4 inhibitors should be avoided with vardenafil.

A small QT prolongation has been reported for vardenafil (8 ms for 10 mg) (Preston, 2018). While the manufacturer states that the clinical impact of these changes is unknown, it suggests avoidance of vardenafil in patients with risk for prolonged QT, e.g., hypokalemia, concomitant use of Class IA antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., sotalol, amiodarone) (Bayer, 2018). Some studies have reported 6 ms with 50 mg of sildenafil, but other studies have not (Preston, 2018), and the manufacturer provides no cautionary advice (Pfizer, 2016).

Alpha-blockers taken with PDE5 inhibitors can cause postural hypotension in some people. Caution is advised, it is recommended that the patient is stable on the alpha-blocker first, initiate with the lowest dose and the patient should be advised what to do if postural hypotensive symptoms develop (Pfizer, 2016; Bayer, 2018; Menarini, 2018) (lie down, raise the legs, and when feeling better get up slowly) (Preston, 2018). Dose separation is sometimes recommended, depending on the alpha blocker. The manufacturer recommends avoiding concomitant use with doxazosin owing to the significance and duration of the hypotensive effect (Lilly, 2017).

Riociguat is used for pulmonary arterial hypertension, and it is contraindicated with PDE5 inhibitors owing to hypotensive effects (Pfizer, 2016; Lilly, 2017; Bayer, 2018; Menarini, 2018).

Vacuum Erection Devices

These devices use negative pressure on the penis shaft, helping draw blood into the corpora cavernosa (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016; Yuan et al., 2010). After achieving an erection, a constricting ring is placed at the base of the penis, preventing blood flow from the penis, and maintaining the erection. The erection can take half a minute to seven minutes to achieve. There is no additional arterial blood flow into the penis, and to prevent ischemia the constriction ring is removed within 30 minutes. With practice, over 90% of men will get an erection, and 85% of men with a spinal cord injury. Satisfaction rates have been variously reported as 35%–68%, possibly reflecting a need for more patient education in some studies. The erections feel cold and not natural, with numbness, and the devices can cause pain and delayed ejaculation. They are not recommended in men prone to priapism or with penile abnormalities. Vacuum devices can be used in conjunction with other ED therapies. Following radical prostatectomy, early use of vacuum devices aided early return of spontaneous erectile function, preservation of penile size (shrinkage is common after radical prostatectomy) and early return to sexual life.

Intercavernous Injections

Although intercavernous injections have a high success rate and work quickly, they are typically recommended only where oral drugs have failed (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016). Men need to be taught how to use the injection in a clinic, and the summary of product characteristics provide recommended administration information for each injection, e.g., to vary the site of injection. The erection occurs about 10 minutes after the injection, with no need for sexual stimulation first. Satisfaction for the man and partner can be very high, but some men do not continue with these injections, with side effects, fear of needles, lack of spontaneity, inconvenience, poor response, and fear of complications common.

Medicines used include alprostadil (a form of prostaglandin E_1), papaverine, and phentolamine, sometimes in combination therapy. Alprostadil injections cause pain for about half of users, in about a tenth of their alprostadil injections, but is typically mild (Shamloul and Ghanem, 2013; Hatzimouratidis et al., 2016; Aronson, 2016). Systemic effects include hypotension and syncope.

More significant side effects include fibrosis (2%), which can require temporary or permanent cessation of this therapy, and priapism (1%). Priapism can cause damage to the penis and needs medical attention. Combination intercavernous injections have been used to aid effectiveness at lower doses.

Contraindications include conditions with a predisposition to priapism, e.g., sickle cell anemia, leukemia, multiple myeloma, or deformations of the penis (Pfizer Limited, 2017).

Other Therapies

Where testosterone measurements show low levels, testosterone replacement therapy can provide an improvement in ED (Shamloul and Ghanem, 2013).

Alprostadil used as intraurethral pellets has an advantage of the avoidance of needles and good safety, with no contraindications to use (Moisidis et al., 2016). The pellets have a success rate of 59%–78%, but have considerably higher doses than intracavernosal injections because of systemic uptake. They take about 5 minutes to achieve an erection. Sudden drops in systolic blood pressure occur in about 5% of men, sometimes with loss of consciousness, and there is commonly pain and a burning sensation on insertion.

Penile implant surgery is a third-line option, with high satisfaction of patients and partners (Shamloul and Ghanem, 2013). Possibilities include a semi-rigid implant, an inflatable implant or a hydraulic implant.

Herbals

While herbal medicines have been used historically for enhanced sexual performance (Shamloul, 2010), very few studies have been conducted to substantiate claims. Some herbals have been specifically studied for ED and include *Panax ginseng*, *Butea superba*, *Epimedium*, *Tribulus terrestris*, *Securidaca longipedunculata*, *Piper guineense*, and yohimbine (Ho and Tan, 2011). Three of these have been evaluated in human studies, *Panax ginseng*, *Butea superba*, and yohimbine, and while there is some evidence of benefit, the studies conducted were not robust enough to be considered definitive (Ho and Tan, 2011; Ernst et al., 2011). Yohimbine can cause hypertension, among other side effects (Aronson, 2016).

It is recognized that the use of herbal medicines for ED continues to grow worldwide, but concern has been raised about the negative impact of these medicines from a safety perspective (Bhagavathula et al., 2016). This is further complicated by the adulteration of these products with medicines (including PDE5 inhibitors, see "Counterfeit" section) (Skalicka-Woźniak et al., 2017).

Counterfeit Products and Undeclared Ingredients

PDE5 inhibitors are the most commonly counterfeited of all medicines, perhaps unsurprisingly given it is more profitable than supplying heroin (Jackson et al., 2010). In Japan, it was estimated that the counterfeit products supplied were over double that of the legitimate market (Sugita and Miyakawa, 2010). Counterfeit PDE5 inhibitors may contain different strengths to that stated on the label, for example, in Indonesia (Taher and Setiawati, 2013) 6% contained more than the labeled strength. Some may contain none of the ingredient on the label (Bate and Hess, 2010), although this appears less common. While counterfeiting is common with internet purchases, in some countries counterfeit products can be widespread. An Indonesian study (Taher and Setiawati, 2013) found all sildenafil purchased from street peddlers was counterfeit, while half of the drugstores supplied counterfeit tablets, and 7% of pharmacies provided counterfeit tablets. Packaging and package inserts were typically very similar to the original packaging. A man was hospitalized in Australia with hypoglycemia after he used a counterfeit medicine labeled Cialis purchased in Vietnam, which contained sildenafil and glibenclamide (Chaubey et al., 2010). Men were hospitalized and some died in Hong Kong after having sexual enhancement remedies containing sildenafil and glibenclamide, purchased from a variety of sources including pharmacies, friends, and peddlers (Poon et al., 2009).

Sourcing PDE5 inhibitors without health professional involvement is common, particularly in younger men (under 40 years), mostly through internet purchase (Jackson et al., 2010). Many of these men think they can get the same medicine from the internet as on prescription. Although most men with ED recognize ascertaining the legitimacy of an internet site for medicines is difficult (Young, 2013), and many men recognize safety limitations of internet-bought medicines (Jackson et al., 2010), over a third of men with ED would consider buying ED drugs from one (Young, 2013), and a minority of men with prescriptions get them that way (Jackson et al., 2010). There are multiple ways pharmacy can help address this. The first measure is to ensure a comfortable and positive experience for a man picking up this prescription, e.g., ensuring privacy and fast, friendly and helpful service, and consider offering delivery. Pharmacists can increase awareness, advising men getting a prescription for an ED product that getting them from any other sources, e.g., buying when travelling or buying from the internet has dangers such as inappropriate amounts of the medicine, no medicine, or other ingredients. Finally, encouraging authorities to allow pharmacists to supply PDE5 inhibitors without a prescription is likely to minimize the inconvenience of a prescription barrier.

A similar danger comes from complementary remedies with undeclared PDE5 inhibitors. This is a common situation with remedies for sexual enhancement available for sale in local stores and through the internet and highlighted by regulators or

researchers all over the world (Bonner, 2016; Medsafe, 2013; Haggan, 2018; Podder et al., 2014). One danger arises from the undeclared PDE5 inhibitors, sometimes in excessive strengths. A second danger is the inclusion of other pharmaceutical ingredients such as chloramphenicol, oxytetracycline, fluoxetine or sibutramine, and sometimes other contaminants. Pharmacists need to be wary of sexual enhancement supplements offered for supply through the pharmacy, and could usefully warn men to avoid their use, particularly men on nitrates.

Advice

The topic is sensitive. Pharmacists need to ensure any conversations about the products take place in a private area where the conversation cannot be overheard. The medicine should not be obvious to others in the pharmacy, i.e., should be in a bag before being taken out to the patient to avoid other people seeing it. Sometimes the medication will not be known to be used by a spouse or partner, and pharmacists need to respect patient confidentiality. There have been cases of a spouse picking up other repeat medicines for their male partner being asked if they want the sildenafil also, breaching confidentiality, and inadvertently raising questions about an extra-marital relationship.

Lifestyle advice is important, as discussed earlier, e.g., improved diet, weight loss if overweight, increasing exercise, stopping smoking, limiting alcohol or recreational drugs, and reducing stress. Having ED might be quite motivating to put some lifestyle changes in place.

Advice about avoiding use with interacting medicines is important, particularly nitrates and alkyl nitrites (recreational drugs also known as 'poppers'). It is also important to ensure men know about the risks of counterfeit products and complementary remedies with undeclared ingredients.

It is helpful to know about side effects, headache, flushing, and a potential effect on color vision, for example, with PDE5 inhibitors. Priapism with PDE5 inhibitors is extremely unlikely, but more likely with intercavernosal injections. These can cause long-term damage, and need medical attention.

For men taking a PDE5 inhibitor for the first time, advice about the potential for hypotension can be helpful.

Where the pharmacist can supply ED medication without prescription, it can be helpful to have the partner involved in the consultation also. It might benefit the relationship if the man mentions to his partner that he is using the medicine.

Where the man has come to the pharmacy to seek advice, remember that it may have taken considerable courage to raise the issue, and take care to be sensitive to this. For example, let him know that this is a very common problem and has effective solutions. Ideally the man should also mention his ED to his doctor as it provides important information to the doctor on cardiovascular risk. However, where a man does not wish to do this, a medical check-up is usually indicated to ascertain if he has elevated cardiovascular risk or diabetes, for example, that needs identifying and treating. The underlying cause should be considered, e.g., depression, anxiety, relationship issues, performance anxiety, medication, excessive alcohol consumption or recreational drugs.

Advise with a PDE5 inhibitor that sexual stimulation is still required to achieve an erection, and that it needs to be taken in advance of the need (see table 1 above). Food can sometimes delay the effect. A man can try it on their own first to get confidence that it will work. This will help reduce the potential for performance anxiety at the time which can be enough to stop the medication from being sufficiently effective. Typically the first dose used is in the middle of the dose range, with an increase recommended if the response is insufficient. Treatment failure is confirmed if it does not work on six different attempts, and referral to the doctor or for relationship counseling will be appropriate there, depending on the likely cause.

The Role of the Pharmacist in the Healthcare Team—Current and Future Roles in Pharmacotherapy and Management

Pharmacists have multiple roles with management of ED, advising patients about appropriate use of ED medicines, being aware that ED may cause compliance issues with other medicines, raising with patients at risk the possibility of ED, and, in some countries, providing ED medicines without a prescription.

ED might affect compliance, for example, in diabetes, depression, hypertension, and hyperlipidemia (McLaughlin et al., 2005). While pharmacists can mention to men that ED can happen with certain medicines, note the concerns with atenolol mentioned earlier (Silvestri et al., 2003). An open question about whether or not there are any side effects that are troubling them might be a useful start. Where non-compliance seems likely, further mention of the potential for ED, and that it can be managed if it does occur, might be useful. Addition of a PDE5 inhibitor might resolve the ED and allow them to continue their medication (McLaughlin et al., 2005). A US study from a healthcare claims database found initiation of sildenafil in men with poor adherence to antidepressants, antihypertensives, lipid-lowering agents, or oral hypoglycemics was associated with improved medication adherence (McLaughlin et al., 2005).

When dispensing medicines for ED, pharmacists should be ensuring the safety, being aware of potential interactions, and providing advice to maximize safe and effective use. This may include lifestyle advice, and reminding men to manage their other conditions or lifestyle factors that might have caused the problem. For example, with men who have diabetes and ED, lifestyle measures and PDE5 inhibitors are recommended, and better glycemic control might assist (Maiorino et al., 2014).

Non-Prescription Supplies

In some countries, pharmacists may be able to supply PDE5 inhibitors without a prescription.

In the UK, PDE5 inhibitors have been supplied by pharmacists through patient group directions in some pharmacies, starting with a pilot in three pharmacies with sildenafil in 2007 (Mayor, 2007). Under this model, pharmacists needed to have additional training and could supply only to men fulfilling certain criteria, with the criteria varying a little according to the patient group directive. Various PDE5 inhibitors have been available in a range of strengths through this mechanism.

In 2017, Pfizer reclassified sildenafil in the UK to a pharmacy-only medicine, allowing supply of up to eight tablets of 50 mg. This should broaden the number of pharmacies supplying it compared with the patient group direction. There is a non-compulsory screening tool with questions that consider medical conditions, interactions, and cardiovascular health.

In NZ, following a reclassification in 2014 initiated by a local generic company, Douglas Pharmaceuticals, pharmacists who have undergone additional training could supply sildenafil up to 100 mg to men who fit specific criteria, with the help of a screening tool. Pharmacists without the training and pharmacy assistants cannot supply the medicine without a prescription. Under the model the consultation at the initial non-prescription supply includes questions about medical history, and measuring of blood pressure and pulse, repeated annually. Most pharmacies charge for this consultation on top of the price of tablets (Braund et al., 2018). If the man goes to a different pharmacy the full initial consultation is needed again. Repeat sildenafil requests without a prescription by the same man at the same pharmacy include questions about changes in medical history and medication. Under this model, men typically return to the same pharmacy, providing continuity of care. Pharmacists inform the man's general practitioner unless he opts out of this.

In Poland, a reclassification also by a local generic company, Adamed, saw sildenafil 25 mg able to be supplied from pharmacies. The man is expected to only use it without a prescription if he meets certain criteria which he can use the screening tool to ascertain.

A Europe-wide attempt in 2008 to reclassify sildenafil was met with concern and withdrawn by the applicant, and attempts in Australia to reclassify vardenafil and sildenafil were rejected in 2017.

Where sildenafil is legally available without prescription, the models of supply, strengths available and criteria for supply differ. For example, men under 35 years old or over 70 years old cannot get the medicine in NZ, while the UK and Poland allow supply to men 18 years or above, with no upper age limit, in line with the age for the prescription product license. The strength available without prescription is 25 mg in Poland, 50 mg in the UK (or higher under patient group direction), and up to 100 mg in New Zealand. Screening tools have been found to increase the amount and consistency of patient assessment for other supplies by pharmacists (Schneider et al., 2013), so may also help here.

Availability from the pharmacist might help discourage purchase from the internet, and help address unmet need, where men do not access any treatment from the doctor but will access it from the pharmacy. Reduced internet supplies could benefit men through minimizing risk of counterfeit products, and enabling discussions with a health professional which could result in a medical referral where appropriate, reduce the risk of use in men with contraindications or precautions, and result in a more informed patient, given the opportunity for discussing appropriate use and lifestyle advice.

In some countries supply by pharmacists without a prescription is common, despite no official reclassification, for example, in Chile (Mennickent et al., 2005), Spain, and Greece (Martin Morales, 2013). In Spain men very commonly first discuss their ED with a pharmacist rather than a doctor (Martín Morales et al., 2010).

There is a small amount of literature on the role of pharmacists with ED.

An observational study in Spain (Martín Morales et al., 2010) compared men prescribed a PDE5 inhibitor with men requesting ED advice or treatment without a prescription. Men without a prescription were significantly younger and more likely to smoke than those getting it on prescription, but otherwise the groups did not differ statistically, for example in comorbidities, ED severity or how long they took to see a health professional for their ED. Smoking and comorbidities were very common in both groups.

In NZ post-reclassification, qualitative interviews with 35 pharmacists found that pharmacists providing the service were happy to undergo additional training, and were generally comfortable with the supply (Braund et al., 2018). Their experiences of supply indicate this service differs considerably from usual non-prescription supplies. The estimated consultation time was typically 15–20 minutes. Many pharmacists estimated that over 50% of initial consultations resulted in medical referral without supply, but asked questions first that most likely would cause referral. The acceptance of this new model with longer consultations, use of a screening tool and informing the doctor may reflect the fact that pharmacists are usually charging for their consultation. It may also reflect the ability to build rapport with the patient, and the opportunity some took for a longer discussion on cardiovascular risk and psychological factors. However, an audit of 90 pharmacies conducted by the Ministry of Health in 2017 (Medicines Control, 2017) indicated some failings with the service, with some pharmacists not keeping the expected records, and some supplies to men outside of the appropriate criteria. Some confusion on the supply criteria was seen in the qualitative research (Braund et al., 2018), which could be the cause of the audit failings. It shows the importance of having reminders from professional pharmacy organizations on pharmacists' responsibilities with a new service, and follow-up research to identify potential concerns or improvements.

In NZ, market growth post-reclassification (Gauld, 2017) suggested pharmacists were addressing unmet need, although that leveled off in time. Customs-intercepted sildenafil entering the country declined post-reclassification (**Fig. 1**), although it is unknown what effect reclassification had versus other factors.

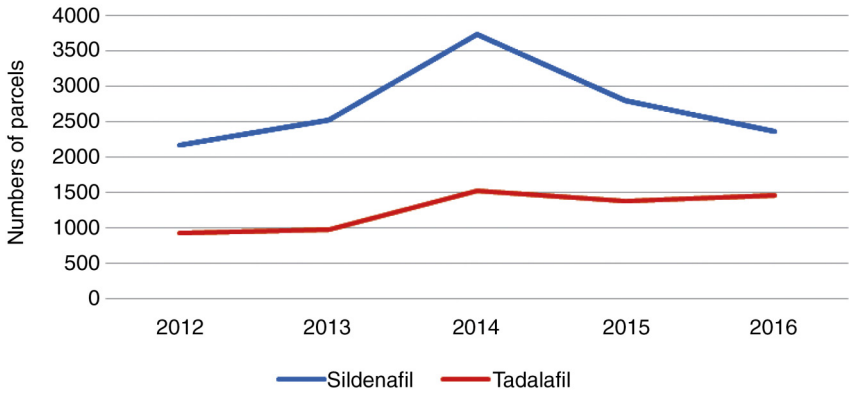

Figure 1 Customs interceptions of sildenafil and tadalafil in New Zealand before and after the reclassification (sildenafil tablets became available through pharmacists in October 2014). *Source: Medsafe, 2016.*

A conference abstract (Weber and Burch, 2006) from the US mentions the utilization of a pharmacist-run ED group clinic which reduced the wait time for the clinic from six months to less than 30 days, and reported high satisfaction in the clinic from patients. Another conference abstract (Orrico et al., 1998), used pharmacists to assist the doctor in determining the correct dose of sildenafil, reduce the risk of adverse effects, minimize the cost of therapy by titrating to the lowest dose and splitting tablets, and conduct an outcome review. Over 500 patients were seen by the pharmacist, many of whom responded to 50 mg of sildenafil.

Conclusion

ED is a common condition that men may not seek medical help on. While it has many potential causes, it is an important indicator of cardiovascular disease. Various treatments are available, with PDE5 inhibitors being used first-line, alongside lifestyle advice. Intracavernosal injections and penile implants are other options. Counterfeiting and complementary remedies with undeclared remedies are common problems with ED management, with deaths reported previously.

Pharmacists in some countries have played a greater role with supply of PDE5 inhibitors without a prescription under legitimate supply models. Such models vary from leaving assessment to the patient, through to requiring pharmacists to undergo extra training and adhere strictly to a screening tool. Research is needed to ascertain the safety of this model, and whether or not it reduces the likelihood of men acquiring the medicine from internet supply or other dubious routes.

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Management of Urologic Disorders and the Pharmacist's Role in Urinary Incontinence

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Objectives

After reading this chapter, one should be able to:

- Understand the different types of urinary incontinence and recognize contributing factors.
- Identify drugs used to treat incontinence and understand their mechanisms of action.
- Give lifestyle advice to patients suffering from incontinence.
- Understand the role pharmacists can play in making medication management recommendations for patients suffering from incontinence.

Anatomy

The urinary tract is made of the following important structures that are necessary to understand when learning about and managing urinary incontinence (Fig. 1).

Physiology

Normal Urinary Functioning

Urine is a liquid by-product that is produced by animals after they have metabolized the foods and water and other compounds they have put into their bodies. Urine flows from the kidneys through the ureters to the bladder. As urine fills the bladder, its muscular walls will stretch. Thus, when the volume of urine inside the bladder reaches around 180–250 mL, the urge to urinate should be experienced through signaling via the nervous system. At 500 mL, a very strong urge to urinate should be experienced. When a person feels this urge to urinate, they will initially send signals to the bladder structures to hold the urine in, and when appropriate (i.e., they have reached the toilet), they will then allow the brain's signaling pathways to relax the urethral sphincter muscles and contract the detrusor or bladder muscle and push urine out. In addition to the above-mentioned structures involved in normal urine functioning,

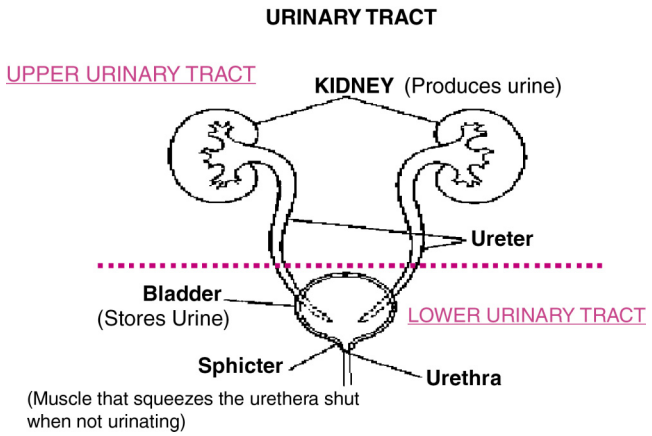

Figure 1 Urinary tract.

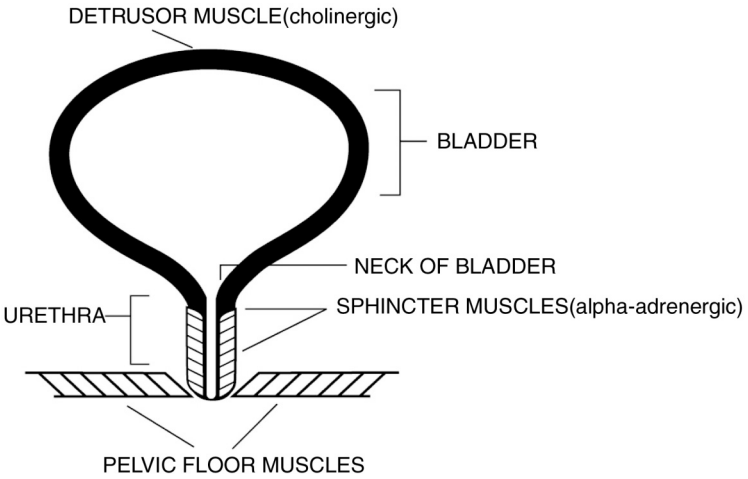

Figure 2 Important structures involved in urinary continence.

the pelvic floor muscles that support the urethra, rectum, and vagina in females are also an important to assist in supporting the urethra and maintaining adequate pressure to retain urine in the bladder, until the person voluntarily wants to empty their bladder/urinate (Campbell et al., 2002; Hickling et al., 2015) (Fig. 2).

Definition and Prevalence of Incontinence

Urinary incontinence refers to the involuntary loss of urine from the bladder. It is a condition where one has the inability to control the storage or release of urine (Moles, 2003a).

The prevalence of incontinence is markedly different between males and females. A review article published in Urology on prevalence (Nitti, 2001) reported that the prevalence of urinary incontinence among females is approximately 20%–30% in young female adults up to age 35 rising to 30%–50% in the elderly. Some studies, however, in specific populations showed prevalence rates of between 10% and 75% for stress incontinence, between 9% and 33% for urge incontinence, and between 14% and 61% for mixed urge and stress incontinence (Nitti, 2001). In contrast, the prevalence in men is markedly lower with rates quoted between 3% and 11% (Nitti, 2001).

Overall Principles on How Incontinence Occurs

Looking at the diagram presented in Fig. 2, incontinence occurs when the pressure inside the bladder exceeds the pressure at the urethral sphincter. One can think of the urethral sphincter like a tap. There are several ways that these pressure imbalances could

occur, and these will determine the type of incontinence that one is suffering from. For example, the pressure inside the bladder could exceed the pressure at the tap if the tap was weakened by medications that relax the sphincter muscles, or the sphincter muscles are not as well supported by the pelvic floor. In addition, the pressure inside the bladder may exceed the pressure at the tap if there is a downward force applied to the detrusor muscle. If there was a blockage at the tap, initially this would lead to urinary retention; however, as the bladder continues to fill with filtrate from the kidneys, eventually as it overfills, the pressure inside the bladder will exceed the pressure at the tap, again leading to incontinence (Moles, 2003a). Each of these underlying mechanisms of incontinence will be discussed in the next section of this chapter.

Types of Incontinence

There is a variety of different types of incontinence. It is important to understand the type of incontinence suffered, as it will assist in explaining the factors that are leading to or precipitating the incontinence and of course allow one to implement the correct nondrug and or drug interventions to treat the incontinence. The following types of incontinence, their symptoms, causes, and treatment will be discussed in this chapter: stress incontinence, urge incontinence, overflow incontinence, and nocturnal enuresis.

Stress Incontinence—Symptoms and Causes

Stress incontinence is a condition in which there is an involuntary loss of small amounts of urine when pressure within the abdomen increases suddenly. For example, when a female coughs, sneezes, laughs, jumps, or runs, she leaks a small amount of urine; this is stress incontinence (Yarnell et al., 1981).

Stress incontinence in women is often precipitated by pregnancy and childbirth. Pregnancy and childbirth often weakens the pelvic floor muscles as the baby pushes on these muscles. Once the pelvic floor muscles are weakened, the urethra is less supported allowing the pressure at the tap to be weakened. During activities that push down on the bladder such as coughing, sneezing, or jumping, the pressure inside the bladder may start to exceed the pressure at the tap leading to small involuntary losses of urine. In addition, estrogen helps to maintain the thickness of the urethra lining to keep the urethra sealed after passing urine; however, during menopause, estrogen is produced in lower quantities and as a result of this loss of estrogen, some women experience stress incontinence during menopause (Brunner, 2017).

Medications may also contribute to stress incontinence. As the urethral sphincter muscles are under alpha adrenergic control, alpha blocking medicines, which may be used for blood pressure, will relax the sphincter muscles and may precipitate stress incontinence (Moles, 2003a).

Urge Incontinence—Symptoms and Causes

Urge incontinence can be described as storage failure. It is due to uninhibited contractions of the bladder also known as detrusor instability (Arnold et al., 2012). This is the most common type of incontinence in the elderly (Thirugnanasothy, 2010). The patient suffering from urge incontinence feels a sudden and strong need to urinate but can often not make it to the toilet completely in time, hence having involuntary loss of urine. In a properly functioning bladder, the detrusor muscle remains relaxed as the bladder gradually fills up; however, if you have urge incontinence, then the bladder for some reason may feel fuller than it actually is, sending a strong signal to urinate, when in fact it may not be that full. This results in the bladder contracting too early when it is not very full, and not when one wants it to (Moles, 2003a).

The cause of urge incontinence is not fully understood; it is more common in females and gets worse as one ages (Thirugnanasothy, 2010). Symptoms may get worse at times of stress and may also be made worse by caffeine and alcohol, which both have diuretic effects. Urge incontinence may also occur as a result of constipation; an enlarged prostate gland in males is simply the result of a long history of poor bladder habits. In some cases, the cause of an overactive bladder is unknown. Medicines may also precipitate or aggravate urge incontinence. For example, medicines that lead to constipation may aggravate urge incontinence, and medicines that are diuretic in nature could aggravate urge incontinence (Moles, 2003a).

Mixed Incontinence—Symptoms and Causes

Mixed incontinence is more common in older females and is exactly as its name suggests, it is a mix of stress and urge incontinence. Patients suffering from mixed incontinence therefore have both of the conditions described above where they lose small amounts of urine when coughing and sneezing for example, and they also have an overactive detrusor muscle where a strong urge to urinate may be experienced and they are unable to make it to the toilet in time (Moles, 2003a).

Overflow Incontinence—Symptoms and Causes

Overflow incontinence is somewhat different from the other two types discussed (stress and urge), as it is caused by emptying failure due to an outlet obstruction (Dmochowski, 2005). This incontinence is therefore actually associated with chronic retention as the bladder is unable to empty properly. As the bladder continues to fill and fill, eventually the pressure inside the bladder will exceed the

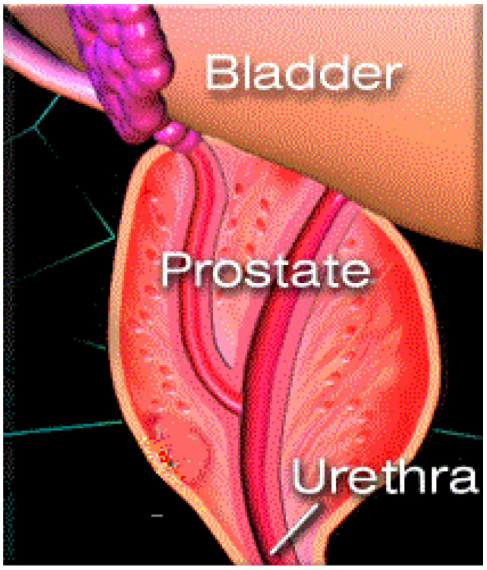

Figure 3 Prostate gland.

pressure at the tap and frequent leakage of small amounts of urine occurs as a result (Moles, 2003a). The main cause of outlet obstruction is an enlarged prostate (Arnold et al., 2012).

The prostate gland is typically the size of a walnut and it surrounds the urethra (**Fig. 3**).

Benign growth of the prostate tissue is not uncommon as males age. Benign prostatic hyperplasia (BPH) is thought to be due to changes in circulating male hormones and usually does not occur until males are above 40 years. Dihydroxytesterone, a metabolite of testosterone, causes the tissue to grow (Moles, 2003b).

As the prostate tissue that is surrounding the urethra grows, it begins to obstruct normal urine flow and eventually results in retention. Symptoms suggesting incomplete bladder emptying include: feeling the need to strain when passing urine, a weak or slow stream of urine, feeling that you are unable to completely empty your bladder, needing urinate frequently at night, dribbling more urine after going to the toilet.

Medications that relax the detrusor muscle may also exacerbate overflow incontinence. This is because the detrusor muscle is under cholinergic stimulation. If an anticholinergic medicine is taken, then this means that the detrusor muscle will not be able to contract with as much force, again leading to overfilling of the bladder. Again, when the bladder overfills, eventually, the pressure inside will exceed the pressure at the tap leading to involuntary loss in urine (Moles, 2003b).

Nocturnal Enuresis—Symptoms and Causes

Nocturnal enuresis is also known as bedwetting (O'Flynn, 2011). It involves involuntary urination while one is asleep. A person is said to have nocturnal enuresis when he or she continues to wet the bed at an age after bladder control usually occurs. For most girls, they will have achieved full bladder control by age six and for most boys, they will stay dry by age seven. By ten years of age, 95% of children are dry at night. The remaining 5% have nocturnal enuresis. Most commonly, bedwetting is from a developmental delay rather than a mental or physical illness (O'Flynn, 2011).

Primary nocturnal enuresis (PNE) is the most common form of bedwetting and would be defined by a child wetting the bed on an average of at least two nights a week with no long periods of dryness or to not sleep dry without being taken to the toilet by another person. In contrast, secondary nocturnal enuresis occurs after a person has had an extended period of dryness at night (usually six months or more) and then they revert to bedwetting. Secondary enuresis may be triggered by emotional stress, or a physical condition such as a urinary tract infection.

What causes a child to have nocturnal enuresis is not fully understood. However, there are some common principles that may be involved, including an overactive detrusor muscle, excessive urine volume, and a lack of arousal when the bladder is full. The later involves a neurological developmental delay and is thought to be due to a nervous system that is slow to process the feeling of a full bladder. An overproduction of urine could also be associated with insufficient production or response to antidiuretic hormone (ADH). ADH regulates urine production by increasing water reabsorption in the kidney. At night, ADH usually signals to the kidneys to make less urine, but in some bedwetters, they do not produce enough ADH or the ADH response is insufficient; hence, they end up with excessive urine production (Eggert and Kühn, 1995). Chronic constipation can also push on the bladder exacerbating nocturnal enuresis.

Management of Incontinence

Due to the different mechanisms involved in the different types of incontinence, there are a number of different treatments that are specific to a particular type of incontinence. In some instances, a medication treatment of one type of incontinence could exacerbate a different type of incontinence, so getting the medicines correct and understanding the underlying principles are essential.

Looking at Fig. 2, one can see that the detrusor muscle is predominately under cholinergic control. This means that giving a cholinergic medicine should contract the detrusor muscle, which could be of some help in overflow incontinence but would be detrimental for a patient with urge incontinence. On the other hand, an anticholinergic medicine would be helpful for urge incontinence but detrimental for overflow. Similarly, an alpha adrenergic stimulant could be theoretically of benefit for stress incontinence but detrimental for overflow and an alpha blocker could be helpful in overflow but exacerbate stress incontinence. These principles are useful when conducting comprehensive medication review services, as there may be a plethora of medicines that could help or hinder one's incontinence. The next sections will go through each type of incontinence and its preferred management.

Stress Incontinence—Management

The first-line treatment for stress incontinence is strengthening the pelvic floor through pelvic floor muscle training. If this fails, then surgery may be considered. As well as these treatments, lifestyle modifications are also recommended to decrease the pressure placed on the urethral closure mechanisms. This includes losing weight, avoiding constipation, and treating chronic cough.

Pelvic floor exercise can be performed by both men and women. The floor of the pelvis is made up of layers of muscle and other tissues. These layers stretch like a hammock from the tailbone at the back, to the pubic bone in front. Pelvic floor muscles support the bladder and bowel in both men and women, as well as support the uterus in women. The urine tube and the back passage all pass through the pelvic floor muscles as well as the vagina in females. Your pelvic floor muscles help you to control your bladder and bowel. They also help sexual function. It is vital to keep your pelvic floor muscles. Recommendations for conducting such exercises can vary between guidelines, but in general each person needs to follow steps similar to those outlined in the box below (Continence Foundation Australia, 2018a).

1. Identify your Pelvic Floor Muscles
   a. Sit or lie down with the muscles of your thighs, buttocks, and stomach relaxed.
   b. Squeeze the ring of muscle around the back passage as if you are trying to stop passing wind. Now relax this muscle. Squeeze and let go a couple of times until you are sure you have found the right muscles. Try not to squeeze your buttocks.
   c. When sitting on the toilet to empty your bladder, try to stop the stream of urine, then start it again. Do this to learn which muscles are the right ones to use—but only once a week. Your bladder may not empty the way it should if you stop and start your stream more often than that.
   d. If you do not feel a distinct "squeeze and lift" of your pelvic floor muscles, or if you cannot slow your stream of urine as talked about in point 3, ask for help from your doctor, physiotherapist, or continence nurse. They will help you to get your pelvic floor muscles working right. Women with very weak pelvic floor muscles can benefit from pelvic floor muscle training.
2. Begin Training
   a. Squeeze and draw in the muscles around your back passage and your vagina at the same time. Lift them UP inside. You should have a sense of "lift" each time you squeeze your pelvic floor muscles. Try to hold them strong and tight as you count to 8. Now, let them go and relax. You should have a distinct feeling of "letting go."
   b. Repeat "squeeze and lift" and let go. It is best to rest for about 8 s in between each lift up of the muscles. If you cannot hold for 8, just hold for as long as you can.
   c. Repeat this "squeeze and lift" as many times as you can, up to a limit of 8–12 squeezes.
   d. Try to do three sets of 8–12 squeezes each, with a rest in between.
   e. Do this whole training plan (three sets of 8–12 squeezes) each day while lying down, sitting, or standing.
   f. While doing pelvic floor muscle training:
      - keep breathing;
      - only squeeze and lift;
      - do NOT tighten your buttocks; and
      - keep your thighs relaxed.

Surgery involves the use of a synthetic mid-urethral sling or autologous fascial slings. If these fail, then implantation of an artificial urinary sphincter can also be tried (Kim et al., 2014).

With respect to medications to treat stress incontinence, several drugs have been trialed but there are none that are approved for the management of stress incontinence (Saks and Arya, 2009). The off-label use of alpha adrenergic agents such as pseudoephedrine or ephedrine is sometimes seen, as these agents theoretically contract the sphincter muscles, which are under adrenergic control (Saks and Arya, 2009). Duloxetine, a serotonin and noradrenalin reuptake inhibitor, indicated for depression, has more recently been trialed for its use in treating stress incontinence (Saks and Arya, 2009). Compared to placebo, Duloxetine has been shown to be favorable in decreasing stress incontinence episodes (Norton et al., 2002) and after prolonged use (30 months), it has been rated by women to be more effective than prior to starting treatment (Bump et al., 2008). However, many

women in the later trail discontinued treatment with Duloxetine; hence, long-term benefits of duloxetine as a treatment strategy for stress incontinence are yet to be proven, and the indications for this medicine are yet to be widened (Bump et al., 2008; Saks and Arya, 2009).

In females who are postmenopausal, the use of topical estrogen may be considered if the incontinence appears to be related to atrophic changes. In this case, it is recommended that topical estrogens are applied initially every night for the first 1–2 weeks and then once to twice weekly (Therapeutic Guideline, 2018).

Urge Incontinence—Management

As urge incontinence is caused by an overactive detrusor, the therapeutic treatments are twofold. First, a person may undergo bladder training to try to learn to hold onto urine longer before voiding. Second, medications are used to relax the detrusor muscle so that it is less likely to be overactive when signals are sent to the brain to indicate that the bladder is getting full.

With respect to bladder training, the aim is to help the patient gain better control and reduce frequency and withhold the need to void and increase the volume voided when one visits the toilet (Continence Foundation Australia, 2018b). Most bladder training is performed by a physiotherapist or a specialist continence advisor and may take up to 3 months of weekly appointments and the maintenance of a bladder diary to see improvements.

In addition to bladder training, medication treatment is often needed for patients with urge incontinence. Traditionally, medications with anticholinergic actions have provided the mainstay of treatment.

Anticholinergics reduce bladder contractility and increase the bladder capacity by relaxing the detrusor muscle. Benefits vary between individuals and in general have been reported to decrease incontinence episodes by one event per 48 h compared to placebo. Some of the anticholinergics used include: Oxybutynin, Solifenacin, Tolterodine, and Darifenacin. Propantheline is to be used but is no longer recommended. Medications with anticholinergic activity should be used with caution in the elderly as they are more prone to adverse effects including blurred vision, dry mouth, constipation, confusion, and urinary retention. Please note that while urinary retention in this case is the aim of therapy, patients need to ensure that they are still able to void (Arnold et al., 2012).

There is no evidence that any one anticholinergic is superior to another with respect to bladder control. Oxybutynin may cause the highest incidence of dry mouth, whereas Solifenacin has been reported to cause higher incidence of constipation. Solifenacin has been reported to increase the QT interval at high doses (Hesch, 2007).

Mirabegron is a newer agent that works in a similar way by relaxing the detrusor muscle and increases bladder capacity. Mirabegron, however, is a $Beta_3$-adrenarecptor agonist. Due to its action on Beta receptors, it is contraindicated in severe uncontrolled hypertension as blood pressure can increase after ingestion. It is also metabolized through the CYP3A4 pathway; hence, patients taking CYP3A4 inhibitors may be advised to take lower doses or avoid its use. Its use in renal impairment is also precautionary and lower starting doses maybe required (Warren et al., 2016). As this agent is relatively new at the time of writing, there is limited evidence as to what cut-off renal function should be used; hence, the manufacturer recommends avoiding its use in patients with an eGFR of less than 15 mL/min/1.73 m^2 (Australian Medicines Handbook, 2018). This new agent may be appropriate for patients who cannot tolerate the anticholinergic agents due to side effects or additive effects with concomitant medications.

One other medical intervention for urge incontinence is the use of Botulinum toxin. This may be used if other oral medications such as anticholinergics or Mirabegron are not tolerated or ineffective. As this may lead to a large reduction in bladder contractility, there is a risk of urinary retention, and hence this should only be used if a person is capable of self-insertion of a urinary catheter if required. Due to this reason, the use of Botulinum toxin in urge incontinence is limited (Orasanu and Mahajan, 2013).

Overflow Incontinence—Management

As overflow incontinence is caused via voiding dysfunction, usually due to outlet obstruction, such as benign prostatic hypertrophy, the treatment is centered around relaxing urethral smooth muscle, or decreasing prostate size, for urine flow to be less restricted.

The mainstay of drug treatment therefore includes alpha adrenergic receptor blockers that relax urethral and prostate smooth muscle and 5-alpha-reductase inhibitors, which inhibit the conversion of testosterone to dihydrotestosterone that has influence on benign prostate growth. If the overactive bladder syndrome is secondary to bladder outlet obstruction, then there may be a role for combinations of both the 5-alpha-reductase inhibitor and the alpha blockers (Moles, 2003b).

Prostate size is the most important factor influencing drug choice. Symptomatic relief, however, requires continuous treatment. Selective alpha-blockers can improve symptoms within 48 h (full effect in 4–6 weeks) and also improve urinary flow rates. They appear to be effective regardless of prostate size. The most commonly used alpha blockers include terazosin, doxazosin, tamsulosin, alfuzosin, silodosin, and prazosin. The most important side effects of alpha blockers are dizziness and low blood pressure after sitting or standing up. Some alpha blockers will interact with phosphodiesterase 5 (PDE5) inhibitors used to treat erectile dysfunction and may cause marked decreases in blood pressure. Tamsulosin and Alfuzosin are generally more acceptable to be prescribed to patients who use PDE5 inhibitors (Gillis and Wilde, 1997).

5-Alpha-reductase inhibitors are more likely to be prescribed when the prostate gland is greater than 30–40 cm^3. Treatment with these agents usually needs to be for greater than 6 months to observe a decrease in prostate size and may not exhibit full effects until after 12–18 months of treatment. The most commonly used 5-alpha-reductase inhibitors are Finasteride and Dutasteride.

Saw Palmetto (*Serenoa repens*) is a herbal product that is often marketed to assist men with symptoms of BPH. It should be noted, however, that a Cochran systematic review found that this product is no more effective than placebo in improving urinary symptoms (Tacklind et al., 2012).

Nocturnal Enuresis—Management

First-line treatment is usually non-drug in nature and involves ensuring a normal daily fluid intake, creating a typical toileting pattern and avoiding caffeine in drinks and chocolate, especially in the evening period. Enuresis alarms that are placed under the sheets that detect very small amounts of fluid are also often very successful.

With respect to medication management, Desmopressin, an analogue of antidiuretic hormone, is the first-line drug therapy in children above 6 years of age. Desmopressin comes in a variety of formulations; however, the oral tablet or sublingual form may be preferred over the nasal spray due to an increased risk in hyponatremia; however, all formulations are approved for use in children and the sublingual and tablet form can be harder for children to use appropriately. Usually, Desmopressin will be trialed for 1–3 months and then withdrawn to assess for relapse (O'Flynn, 2011).

If the above treatment measures fail, then imipramine may be used for its anticholinergic effects; however, this should be under specialist supervision due to its side-effect profile, which can be more predominant in small children.

Incontinence Appliances and Pads

Based on the above treatment options including medication and surgery for different types of incontinence, it should be noted that incontinence pads and pants are usually never the only option despite the fact they are less invasive. Incontinence pads are widely available; however, they should perhaps only be acceptable for patients who are not suitable for drug or surgical intervention (e.g., the frail elderly).

Role of the Pharmacist

The pharmacist has a key role to play in managing patients who suffer from all types of incontinence. As medications can both contribute to causing incontinence and assist in its management, a thorough understanding of medicines pharmacology and effects and adverse effects is required (Moles, 2003a, 2003b).

Often, an initial task in assisting a person with incontinence is to take a thorough medication history. As a pharmacist, you can easily ask a few questions related to bowel habits, urinary symptoms being suffered, a history of urinary tract infections, questions about your patient's lifestyle, as well as what medications they are taking, and a history of when the problem began. You can then try to relate some causal factors to the symptoms described.

Some example questions are listed in below Table.

1	How long have you had bladder problems?
2	When was it that it started to get worse?
3	Do you have any other problems when urinating? (pain or burning?)
4	What are your bowel habits usually like? Any constipation? How long has that been a problem?
5	Tell me a bit about your diet, what do you eat most days? And drink? Do you have coffee, tea, or alcohol? How often?
6	And what about your medications, how long have you been taking each one, and how have they been going?
7	Any other problems you wish to talk about, other medical conditions, or any other medications?
8	What are you doing currently to manage your issue?

After you have gathered the information about the patient, including their medication history, it is important to review their medications, alcohol and caffeine intake, and bowel habits to see if any of these factors can aggravate the issue.

You should be very particular about looking for medications/substances that increase volume such as diuretics, caffeine, and alcohol, cause constipation or sedation such as opioids and anticholinergic medicines, and those that have a direct effect on the function on the bladder (as listed above). Patients may need referral back to the GP and a comprehensive medication review should be performed.

Your role in medication review is to identify drugs/substances that may be aggravating incontinence. For example, medications with anticholinergic side effects would be a cause for concern in a patient with overflow incontinence, and alpha blockers would be a reason to consider alternative antihypertensive agents in a patient with stress or mixed incontinence. This intimate knowledge of the pharmacology of medicines provides the pharmacist a vital role in assisting physicians and patients manage their condition.

Furthermore, when dispensing medicines to treat incontinence, a large part of our role will be in providing advice about the new medicine. We have a role in discussing how the medicine will work, how to take the medication, and importantly the side effects that may be common. In addition to this usual advice, realistic expectations on what to expect should be delivered along with written information.

Pharmacist can also provide practical tips such as: Asking the patient to keep a bladder diary to help record the effectiveness of treatment or performing pelvic floor exercises to strengthen the urethral sphincter muscles. These are particularly useful for urge and stress incontinence, respectively. Other lifestyle factors should also be discussed such as: managing contributing factors to their bladder issues such as urinary tract infections, constipation, excessive fluid intake, unstable diabetes, obesity; or consumption of alcohol or caffeine-containing drinks.

Finally, providing protective pads may also be helpful in managing incontinence, especially in people with cognitive impairment or limited mobility, but as mentioned previously, these are rarely to be used as the patient's only solution to his or her problem (Moles, 2003a).

An Example Case Study of the Medication Review Process

Mrs. Reynolds is a 65-year-old customer who enters your pharmacy and comes to the counter with a packet of incontinence undergarments. She is an overweight lady with five children and four grandchildren who always comes to your pharmacy to collect her Prazosin prescription for hypertension, alongside her Hydrochlorothiazide and Amiloride prescription. She also takes Amitriptyline at night for depression and to aid her sleep. She explains that she has "lost some control over her waterworks" and this has been getting worse in the last few months. She says that sometimes she "all of a sudden needs to go to the toilet, but doesn't always make it in time," and often if she coughs or laughs, she leaks small amounts of urine. She appears a little embarrassed but comments that it is just part of getting older and there is nothing anyone can do about it.

Is this true? How can the Pharmacist Help?

As a pharmacist, we are able to provide Mrs. Reynolds with incontinence aids, but more importantly, we can organize and conduct a comprehensive medication review. In this case, some of the issues a pharmacist may consider include:

- Age itself is a factor that needs to be taken into consideration. Decreased elastin reduces bladder capacity, and sensations from the bladder may be delayed; therefore, an elderly person may have reduced reserve and increased vulnerability to incontinence, but it must be noted that it is not an inevitable part of normal ageing.
- Mobility may also impact on incontinence; if a patient's mobility is restricted, then the time taken to reach the toilet may be a factor.
- Certain medications may exacerbate incontinence and commonly those indicated include sedatives, diuretics, anticholinergic agents, caffeine, and alcohol.
- Urge incontinence may be caused by neurological conditions such as Parkinson's, multiple sclerosis, or Alzheimer's, and these should be medically assessed.
- Alternatively, symptoms may arise from increased sensory input from the bladder due to local causes, such as a urinary tract infection or constipation.
- Excessive fluid intake, alcohol, caffeine, and other diuretics can exacerbate urge incontinence.
- Stress incontinence is often associated with weak pelvic floor muscles caused by trauma during childbirth and atrophy of the pelvic floor after menopause as estrogen levels fall.
- In addition, constipation and obesity are predisposing factors to stress incontinence by contributing to an increase in pressure in the bladder.

It is likely that the alpha blocker prazosin is relaxing the urethral sphincter and exacerbating her stress incontinence. Furthermore, her diuretic is adding to the urine volume. In addition, while the amitriptyline may actually assist her urge incontinence, it may be causing constipation and its sedative effects can also be problematic. Providing an evidence-based recommendation of an angiotensin converting enzyme (ACE) inhibitor as a first-line antihypertensive agent to replace the current antihypertensive could be a good start to assisting Mrs. Reynolds.

As illustrated in this short case, the pharmacists' role in this area can be quite extensive and their unique knowledge of the pharmacology of medicines, alongside the physiology involved in incontinence, means they are well placed to assist patients with urinary incontinence.

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Management of Rheumatology Disorders and the Pharmacist's Role: Gout and Related Conditions

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Learning Objectives

By the end of this chapter, the reader will be able to:

- Describe the main concept, etiopathogenesis, and typical clinical presentation of gout and other crystal-induced arthropathies.
- Discuss various pharmacological approaches and select a suitable therapy for acute gout and hyperuricemia.
- Design a patient-oriented care plan to ensure effective therapeutic outcomes.
- Educate patient regarding various aspects of gout and its therapy.
- Identify and manage adverse drug effects and drug interactions associated with pharmacotherapy of gout.

Introduction

Gout refers to a spectrum of diseases characterized by elevated serum uric acid (hyperuricemia) and deposition of monosodium urate (MSU) crystals in joints causing attacks of acute inflammatory arthritis. It might further advance to soft tissue deposits of urate crystals (tophi), interstitial renal disease, and uric acid nephrolithiasis (Khanna et al., 2012a). Acute attack typically affects a single joint (monoarticular) and often involves the first toe (podagra); however, other joints such as insteps, ankle, knee, fingers, wrist, and elbow can also be affected (Dalbeth et al., 2016).

Epidemiology

The global prevalence of gout ranges between 0.1% and 10% with an incidence rate of 0.3–6.0 cases per 1000 person-years (Kuo et al., 2015). Gout is more prevalent in developed countries (Kuo et al., 2015). In the United States, an estimated 3.9% of population had gout during 2007–08 (Zhu et al., 2011). The population-prevalence of gout is 1.1% in China (Liu et al., 2015). A

combined prevalence of 1.4% has been reported for gout in Germany and the United Kingdom (Annemans et al., 2008). Whereas, the prevalence of gout is 0.9% in France (Bardin et al., 2016).

Gout is more common in men, and its incidence increases with age (Burke et al., 2016). The cumulative incidence of gout among older adults (up to 65 years) is 8.6% in men and 2.5% in women, which increases up to 11.8% in men and 5% in women by the age of 75 years (Burke et al., 2016). Whereas, the prevalence in individuals above 80 years of age is around 10% in men and 6% in women (Ragab et al., 2017).

Etiology and Pathophysiology

Gout is associated with hyperuricemia, that is an abnormally elevated level of serum uric acid (>7 mg/dL). Uric acid is the end product of purine catabolism. Various enzymes are involved in the production of uric acid; however, xanthine oxidase plays a pivotal role (Schlee et al., 2018a). Uric acid is considered a waste product that has no known physiologic role in the body. Its major portion (2/3) is excreted in urine, whereas the remainder is eliminated through the gastrointestinal (GI) tract (Ragab et al., 2017; Richette and Bardin, 2010).

The main cause of hyperuricemia is reduced uric acid excretion by the kidney (>90% cases) that is genetically determined. Renal excretion of uric acid is also reduced by certain drugs such as thiazide or loop diuretics, cyclosporine, pyrazinamide, ethambutol, low-dose aspirin (<2 g/day), ethanol, levodopa, and cancer chemotherapy (Ben Salem et al., 2017).

Hyperuricemia may be caused by overproduction of uric acid. Some rare enzyme abnormalities such as deficiency of HGPRT (hypoxanthine-guanine phosphoribosyl transferase) and increased activity of PRPP (phosphoribosyl pyrophosphate synthetase) are associated with hyperuricemia. It may also occur in myeloproliferative and lymphoproliferative disorders due to increased breakdown of tissue nucleic acids. Cancer patients undergoing chemotherapy are also prone toward hyperuricemia because of lysis and breakdown of cellular matter (Ragab et al., 2017).

Under normal conditions, uric acid is present in the solubilized state. Upon exceeding 7 mg/dL, it achieves a saturated state and precipitates to form crystals (Schlee et al., 2018a). The deposition of MSU crystals in synovial fluid of various joints leads to a self-limiting pain and inflammation. The inflammatory response is initiated upon phagocytosis of MSU crystals by the synoviocytes which releases various pro-inflammatory mediators such as the cytokines, interleukin-1, interleukin-8, and tumor necrosis factor alpha. Chronic inflammation in the joint(s) may lead to loss of cartilage and erosion of the bone (Dalbeth et al., 2016; Ragab et al., 2017; Teng et al., 2006).

Clinical Features

In acute gout, the most frequent clinical presentation is "podagra" that refers to inflammation and pain in the first metatarsophalangeal joint (big toe) (Schlee et al., 2018b). Gout typically affects a single joint, but some patients may present with inflammation and pain involving multiple joints or periarticular soft tissue of the lower or upper extremities. The affected joint appears swollen, tender, warm, and dusky red. Gout attack involves severe pain that peaks at 2–6 h. It is rapid, intense, and localized to the affected joint. The attack usually occurs during night because water diffuses out of the synovial fluid when a person is in supine position leading to crystallization of MSU. Gout attack may be accompanied with fever, malaise, and even delirium when larger joints (knee) are affected (Schlee et al., 2018b). The frequency of gout recurrence varies considerably. Some patients may never experience a repeated attack of gout, while others may experience recurrent gout attacks within a year (Grassi and De Angelis, 2012).

Persistent hyperuricemia and frequent gout attacks lead to chronic gout. Patients with chronic gout may present with continuous joint pain and joint deformation that can cause functional impairment. In chronic cases, gout attack is less intense that can be precipitated by stress, trauma, alcohol ingestion, surgery, or uric acid lowering therapy (Grassi and De Angelis, 2012; Schlee et al., 2018b). Elderly patients may have an atypical presentation of gout involving multiple joints (polyarticular) which resembles that of rheumatoid arthritis (Schlee et al., 2018b).

Uncontrolled progressive gout may lead to the development of kidney stones, nephropathy, and tophi. Tophi often develops in hands, wrists, elbows, and knees that can lead to irreversible joint deformities and loss of functionality (Grassi and De Angelis, 2012; Ragab et al., 2017; Schlee et al., 2018b).

Diagnosis

Diagnosis is usually based on physical examination, presence of signs and symptoms, and response to therapy. Serum uric acid level provides crucial information about the risk or severity of gout, but it alone cannot predict the presence of gout as many patients with hyperuricemia do not develop gout. Arthrocentesis (joint aspiration) is the procedure of choice for the detection of MSU crystals in joint fluids in order to confirm the diagnosis of gout (Dalbeth et al., 2016; Schlee et al., 2018b).

Treatment

The primary goal of pharmacotherapy of acute gout is to resolve pain, preserve joint function, and improve the patient's quality of life. In chronic cases, the main goal is normalization of serum uric acid level (below 6 mg/dL) in order to prevent future episodes and complications.

The American College of Rheumatology (ACR) guidelines are widely used for the management of gout (Khanna et al., 2012a,b). However, other guidelines are also available and applicable to specific regions and situations (see Further Reading for detail).

Acute Gout

Management of acute gout mainly focuses on reduction of inflammation and pain (Fig. 1). Different anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids can be used to treat an acute attack (Khanna et al., 2012b; Richette et al., 2017). The selection of therapy depends on disease presentation (severity of the attack, duration since onset, and number of joints involved), previous drug use, and patient's factors. Typically, NSAIDs are the recommended first choice. If they are contraindicated, colchicine, or corticosteroids are alternative options (see Table 1 for drugs' doses and cautions). Usually monotherapy with one of the above drugs is used in most of the cases. However, combination-therapy or investigational drugs may be used in severe cases (Fig. 2). Moreover, an individualized approach is recommended for each patient in case of comorbidities such as chronic kidney disease, diabetes mellitus, hypertension, and heart diseases (Khanna et al., 2012b; Richette et al., 2017).

NSAIDs are effective in the treatment of acute gout. They are well-tolerated and have a good safety profile for short-term use. Although some NSAIDs (naproxen, indomethacin, and sulindac) are specifically approved by the US Food and Drug Administration (FDA) for the treatment of gout, others are similarly effective and can be used in full doses to treat an acute attack

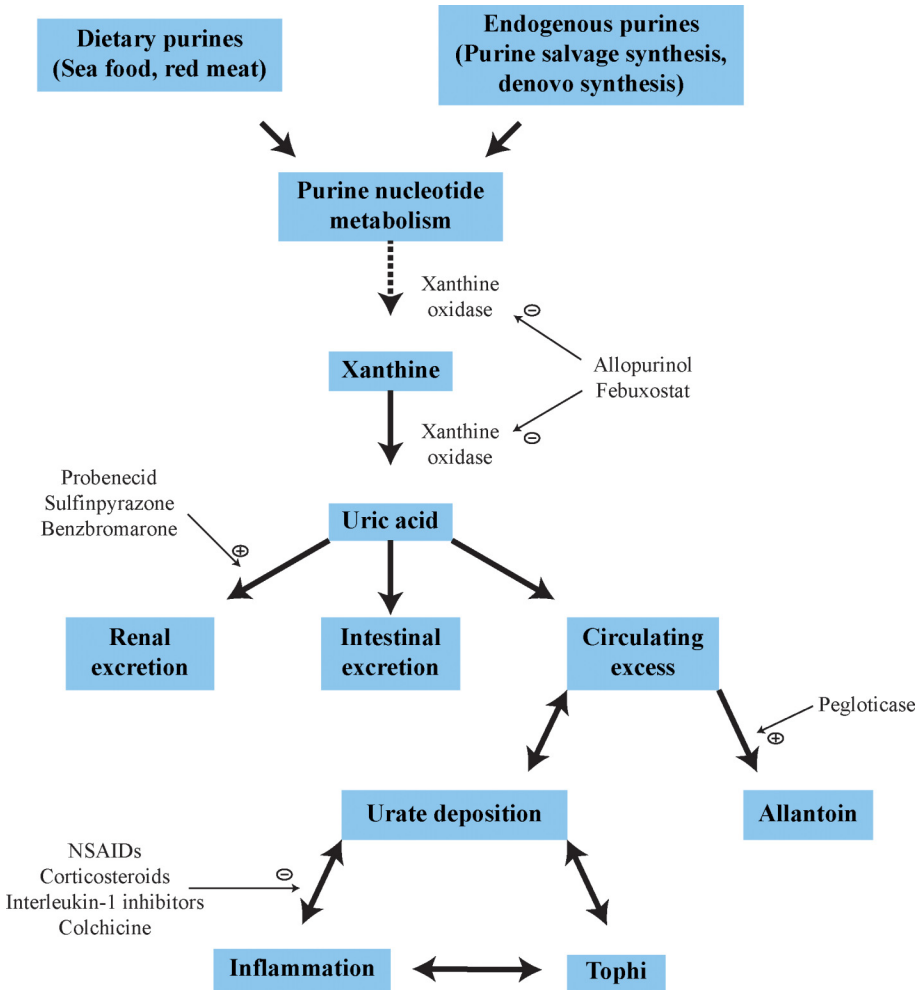

Figure 1 Drugs' site of action in the management of gout.

Table 1 Recommended doses, dose adjustment and cautions of drugs used for the treatment of acute gout

Drugs	*Adult dosage*	*Dose adjustments*	*Cautions*
Naproxen	750 mg oral followed by 250 mg thrice daily until attack has subsided	*Renal impairment:* Avoid if CrCl is <30 mL/min *Hepatic impairment and geriatrics*: Use lowest effective dose	Avoid in patients with peptic ulcer disease and active bleeding Use with caution in patients with CHF, dehydration and renal impairment Consider co-administration with a PPI when long-term treatment in individuals at high-risk for GI bleeding is necessary
Indomethacin	50 mg oral thrice daily until pain is tolerable; taper dose and discontinue based on pain response	*Renal impairment:* Not recommended unless benefits outweigh risks *Geriatrics:* Use lowest effective dose	
Diclofenac	50 mg oral thrice daily; or initial 100 mg oral thrice daily, followed by 50 mg oral thrice daily	*Hepatic impairment:* Initiate at lowest effective dose, discontinue if not efficacious; use not recommended in severe impairment *Geriatrics:* Use with caution and lowest effective dose *Renal impairment:* Use not recommended in severe impairment	
Ibuprofen	400–800 mg oral three or four times daily	*Renal impairment:* Use lowest effective dose	
Sulindac	200 mg oral twice daily for 7 days	*Renal and hepatic impairment*: Monitor patient closely and use lower dose	
Celecoxib	Initiate with 800 mg oral then 400 mg 12 h later followed by 400 mg twice daily for 7 days	*Renal and hepatic impairment:* Avoid in severe impairment *Hepatic impairment:* Reduce the dose by half in moderate hepatic impairment; in severe impairment, better to avoid *Geriatrics:* Use lowest effective dose *Slow cytochrome metabolizers:* Use alternate therapy	Increases risk of cardiovascular events such as myocardial infarction
Colchicine	1.2 mg oral at first sign of flare followed by 0.6 mg 1 h later (max 1.8 mg over 1 h)	*Renal impairment:* Severe (CrCl <30 mL/min), 0.3 mg/day orally initially; increase dose with adequate monitoring. Do not repeat course more than once every 2 weeks *Hepatic impairment:* Severe, consider dose reduction (in gout prophylaxis), do not repeat course more than once every 2 weeks (in gout flare) *Concomitant strong cytochrome and P-glycoprotein inhibitors*: Dose adjustment recommended	Intravenous use should be avoided because of increased toxicity
Prednisolone	0.5 mg/kg/day for 5–10 days followed by discontinuation or 0.5 mg/kg/day initially for 2–5 days, followed by tapering over 7–10 days	–	Use with caution in DM and CHF. Rebound flare may occur if prophylaxis not continued for 4–7 days
Triamcinolone	Initial, 2.5–15 mg as a single intra-articular injection, additional doses can be adjusted between 20 and 40 mg and administered as necessary	–	
Anakinra	100 mg subcutaneously daily for 3 consecutive days	*Renal impairment:* Administer every 48 h if CrCl is <30 mL/min	Opportunistic infections may occur. Avoid use with live vaccines
Canakinumab	Single dose of 150 mg subcutaneously	–	Opportunistic infections may occur. Avoid use with live vaccines

CHF, chronic heart failure; *CrCl*, creatinine clearance; *DM*, diabetes mellitus; *GI*, gastrointestinal; *PPI*, proton pump inhibitors.
Source: ASHP, 2018; Lexicomp, 2018; Micromedex Drugdex, 2018.

(Table 1). The therapy should be started within 24 h of the onset of an acute attack and continued until complete resolution. The usual duration of therapy is 5–10 days. Once the acute attack has resolved, the dose should be tapered down. Drug is discontinued after 2 days of complete resolution of symptoms. Aspirin is generally not recommended because in low doses it alters uric acid levels and increases the risk of gout attack. Cyclooxygenase-2 selective NSAIDs (e.g., celecoxib) are also effective and may be indicated in patients with a history of peptic ulcer disease or GI bleeding (Khanna et al., 2012b; Richette et al., 2017).

Colchicine can effectively reduce symptoms of an acute gout attack. It can be used if NSAIDs are contraindicated or fail to produce the desired response. According to the ACR guidelines, colchicine therapy must be initiated within 36 h of onset of an acute gout attack because of diminished success rates when delayed (Khanna et al., 2012b). Colchicine is orally administered at a loading dose of 1.2 mg followed by a maintenance dose of 0.6 mg every 1 h. The drug is discontinued if symptoms of acute attack resolve or

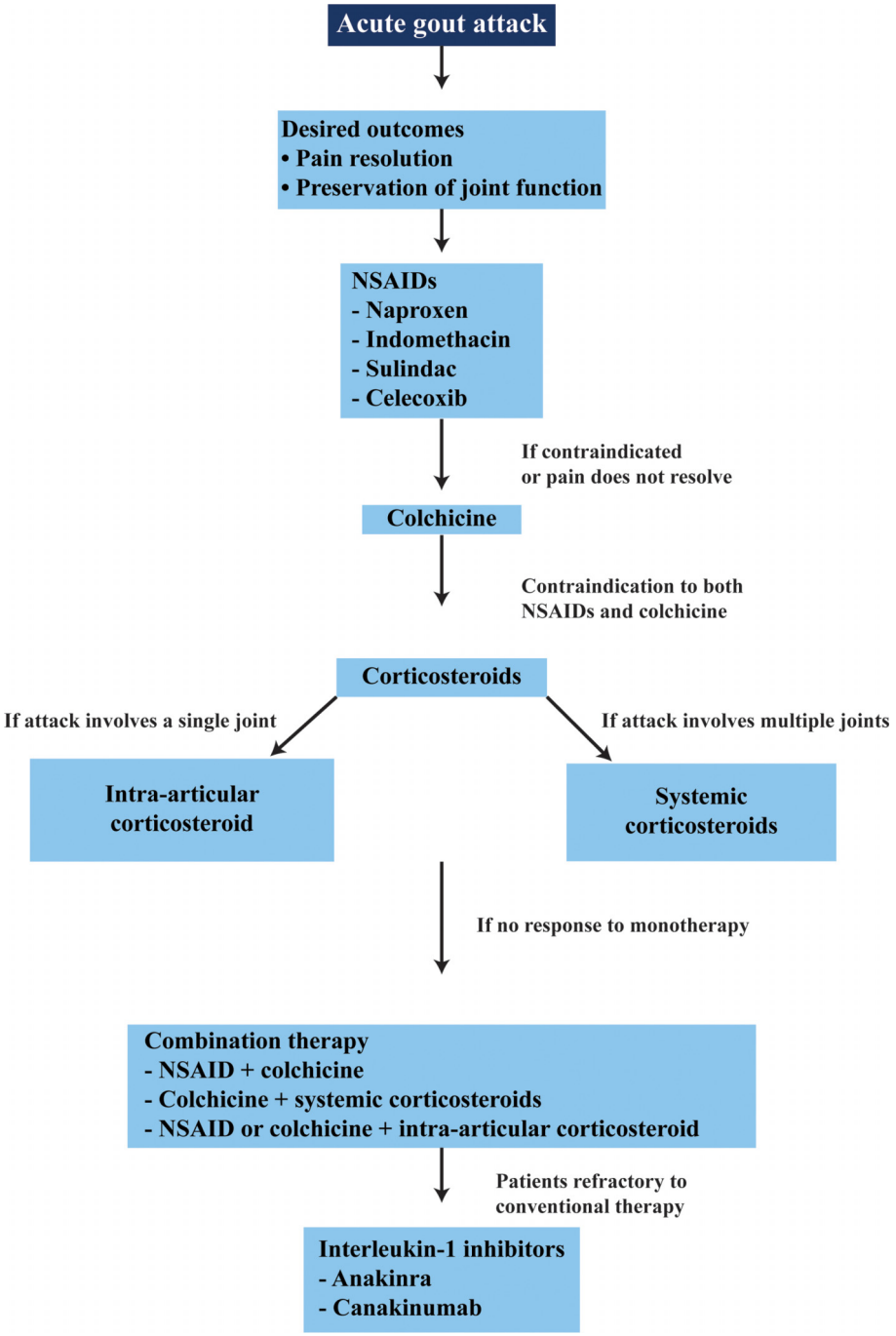

Figure 2 Algorithm for the treatment of acute gout.

GI adverse effects develop. Alternately, the ACR guidelines recommend oral colchicine at a loading dose of 1.2 mg followed by 0.6 mg every 12 h until the symptoms of an acute attack resolve. The dose of colchicine must be tailored in patients with hepatic or moderate renal impairment (Khanna et al., 2012b).

Corticosteroids are recommended in patients who are intolerant or do not respond to NSAIDs/colchicine therapy. The selection of corticosteroid treatment depends on the number and type of affected joints. Intra-articular therapy is recommended when one or two joints are affected, while systemic corticosteroid therapy is preferred in patients with multiple affected joints. For systemic corticosteroid therapy, oral prednisone or prednisolone at a daily dose of 0.5 mg/kg are used for 5–10 days. A full dose shall be prescribed initially (for 2–5 days) followed by down tapering of dose for the subsequent duration of therapy. Alternately, a single intramuscular injection of triamcinolone acetonide (60 mg) followed by oral prednisone or prednisolone therapy may be used (Khanna et al., 2012b).

Table 2 Recommended doses, dose adjustment and cautions of drugs used for the management of hyperuricemia

Drugs	*Adult dosage*	*Dose adjustments*	*Cautions*
Allopurinol	Mild gout: 200–300 mg oral once daily Moderately severe tophaceous gout: Oral 400–600 mg daily in divided doses Dose escalation in patients receiving allopurinol therapy for at least 1 month with serum urate ≥6 mg/dL: Increase by 100 mg daily every month until serum urate of ≤6 mg/dL is achieved	*Renal impairment and cancer patients:* Dose adjustment is necessary CrCl 10–20 mL/min: 200 mg orally daily CrCl 3–10 mL/min: Do not exceed 100 mg orally daily CrCl <3 mL/min: 100 mg orally at intervals Chronic kidney disease stage 4 or worse: Initial, 50 mg orally daily; titrate maintenance dose upward to target serum uric acid level every 2–5 weeks; may exceed 300 mg/day with adequate monitoring	Adjust dose based on target serum level
Febuxostat	40–80 mg oral once daily	*Cancer patients:* Dose adjustment is necessary *Renal impairment:* Limit dose to 40 mg once daily if CrCl is 15–29 mL/min	
Sulfinpyrazone	200–400 mg oral twice daily; increase dose gradually over a 1-week period titrating to desired urate blood levels to 400–800 mg/day	*Renal impairment*: Avoid in severe renal impairment	Avoid in acute gout attack
Probenecid	250 mg oral twice daily for 1 week followed by 500 mg twice daily, titrate dose every 4 weeks (maximum 2000 mg/day)		
Lesinurad	200 mg oral once daily in the morning with food and water (maximum 200 mg/day), give at the same time of the day with a xanthine oxidase inhibitor including allopurinol (at least 300 mg/day or 200 mg/day if CrCl is less than 60 mL/min) or febuxostat	*Renal impairment*: Avoid if CrCl is <30 mL/min *Hepatic impairment*: severe, do not use	
Pegloticase	8 mg intravenous infusion every 2 weeks	–	Infuse at slow rate

CrCl, creatinine clearance.
Source: ASHP 2018; Lexicomp 2018; Micromedex Drugdex, 2018.

Inadequate response to pharmacotherapy is defined as <20% improvement in pain score within 24 h of therapy or <50% improvement after 24 h of therapy (Khanna et al., 2012b). In patients with inadequate response to monotherapy, a combination therapy comprising any two drugs from the aforementioned classes (NSAIDs, colchicine, or corticosteroids), either in their full doses or one drug in its full dose and other at a lower dose, is recommended (Khanna et al., 2012b). Intravenous or intramuscular methyl prednisolone at a dose of 0.5–2 mg/kg may be considered in patients who cannot swallow oral corticosteroids (Khanna et al., 2012b). Patient refractory to the conventional therapy may be treated with interleukin-1 inhibitors such as anakinra and canakinumab (Khanna et al., 2012b).

Urate-Lowering Therapy

Urate-lowering therapy (ULT) is recommended to reduce serum uric acid level in individuals who experience two or more gout attacks per year. Additionally, patients having renal impairment (eGFR <60 mL/min), tophi, history of kidney stones, and elevated serum uric acid (>8 mg/dL) may be prescribed ULT (Hui et al., 2017; Richette et al., 2017). Appropriate ULT reduces the frequency of gout flares and recurrence and improves patient's quality of life (Richette et al., 2017). ULT comprises xanthine oxidase inhibitors (XOIs): allopurinol and febuxostat; and uricosuric agents: probenecid and sulfinpyrazone (Richette et al., 2017). They reduce uric acid level by different mechanisms (**Fig. 1**). Drugs doses and cautions of drugs used for the management of hyperuricemia are given in **Table 2**.

ULT is associated with acute gout flares due to dispersion or dissolution of urate crystals; therefore, preventive therapy is needed. For this purpose, colchicine or NSAID (e.g., naproxen) is recommended for a maximum duration of 3 (non-tophaceous gout) or 6 months (tophaceous gout). Low-dose corticosteroid (oral prednisolone or prednisone) may be considered as an alternate option (Hui et al., 2017; Khanna et al., 2012b).

ULT should be initiated at low doses and then titrated according to the desired serum uric acid level (<6 mg/dL) (Richette et al., 2017). Serum uric acid level should be monitored every 2–5 weeks during initial therapy when uric acid level is high. Once the desired serum uric acid level of <6 mg/dL or <5 mg/dL (in case of complicated gout) has been achieved, every 6 months monitoring is recommended.

Allopurinol is the recommended first-line therapy (**Fig. 3**), starting at a dose of 50–100 mg/day with an increment of 100 mg (50 mg in renal impairment) after every 4 weeks (maximum daily dose: 800–900 mg) till the desired serum uric acid level has been

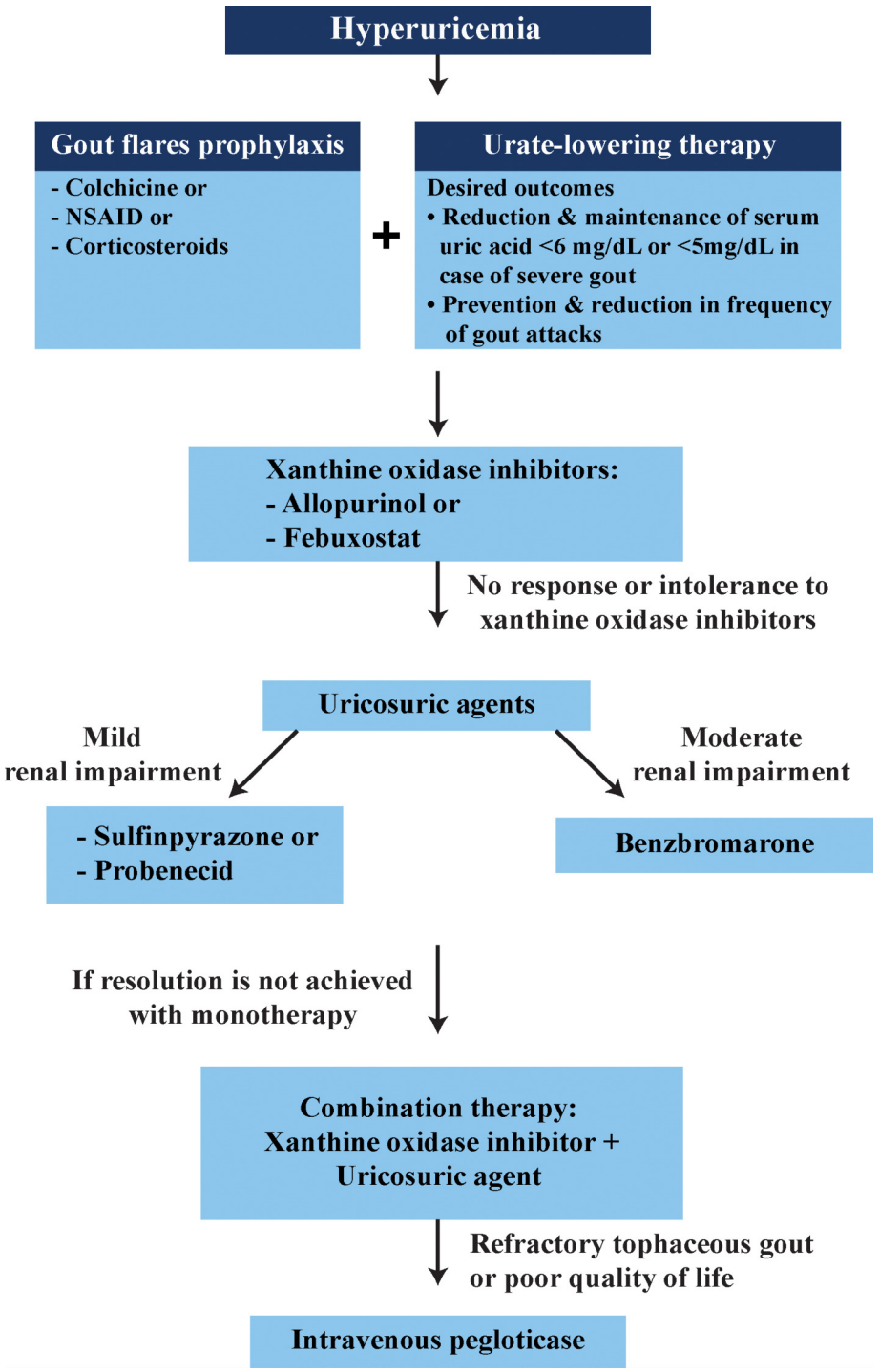

Figure 3 Algorithm for the management of hyperuricemia.

achieved (**Table 2**; Hui et al., 2017; Khanna et al., 2012a; Richette et al., 2017). Febuxostat is an alternate XOI, which is used at a dose of 80 mg/kg (may be titrated up to 120 mg/day after 4 weeks). Febuxostat is a preferred option in patients with mild to moderate renal impairment (Hui et al., 2017; Khanna et al., 2012a).

In case of inadequate response or intolerance to XOIs, uricosuric agents (probenecid and sulfinpyrazone) are recommended (**Fig. 3**). Sulfinpyrazone or probenecid might be used in patients with normal or mild renal impairment, whereas benzbromarone is suggested in patients with moderate renal impairment (Hui et al., 2017; Khanna et al., 2012a; Richette et al., 2017). However, they should be avoided in patients with history of kidney stones because they increase the risk of kidney stone

formation (Khanna et al., 2012a). Patients should be advised to increase fluid intake. Urine alkalinization with potassium citrate may also be considered in order to suppress reabsorption of uric acid (Khanna et al., 2012a). Combination therapy comprising a XOI and a uricosuric agent is recommended in patients who fail to respond to therapy with a single agent (Hui et al., 2017).

Lesinurad, a selective uric acid reabsorption inhibitor, may be used as an adjuvant with allopurinol or febuxostat. A combination of lesinurad and XOI is more efficacious with similar safety profile as compared with XOI alone (Dalbeth et al., 2017; Saag et al., 2017).

Refractory gout is characterized by severe tophaceous gout and poor quality of life with no response to maximal tolerated doses of a single or multiple drug therapy (Khanna et al., 2012a; Richette et al., 2017). In such situation, intravenous pegloticase in a dose of 8 mg every 2 weeks may be used. However, cost and higher rates of hypersensitivity reactions have greatly limited its use in practice (Shannon and Cole, 2012).

Several investigational drugs including canakinumab, rilonacept, and arhalofenate have been proven effective and safe in multiple clinical trials but none of them has been approved by the FDA for the treatment of gout.

Other Crystal-Induced Joint Disorders

Joint disorders may also be caused by intra-articular deposition of other crystals such as calcium pyrophosphate dihydrate (pseudogout), basic calcium phosphate, and calcium oxalate (Schumacher and Chen, 2018).

Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

The calcium pyrophosphate dihydrate crystals deposition (CPPD) disease formerly known as pseudogout is a joint disorder caused by the deposition of CPPD in joints, articular cartilage, and hyaline cartilage. It may be asymptomatic (diagnosed after radiography) or symptomatic causing episodic pain. CPPD disease commonly affects joints of knees, wrists, and hips, but other joints may also be affected (Rosenthal and Ryan, 2016). This disease is common among elderly and is rare among individuals below 55 years of age (Richette et al., 2009). It has been postulated that increasing age and genetic predisposition increase breakdown of adenosine triphosphate thus producing large amount of pyrophosphate which binds with calcium and forms calcium pyrophosphate crystals (Coiffier and Albert, 2015; Rosenthal and Ryan, 2016).

CPPD disease is often asymptomatic and is only diagnosed incidentally following a radiography. Some patients may experience pain involving single or multiple joints that mimics gout. Uncontrolled CPPD disease may lead to synovitis and degenerative arthritis. Rarely, the affected joint may get infected and results in high fever. CPPD disease can be accurately diagnosed by characterizing CPPD crystals in synovial aspirate under a light microscope. Culture of the synovial fluid should be performed to rule out the possibility of any infection (Schlee et al., 2018b).

In an acute attack of CPPD disease, NSAIDs are preferred due to satisfactory efficacy and safety profile. Colchicine may be used for prophylaxis of acute pain. Whereas, intra-articular triamcinolone (10–40 mg) may be considered in patients who are intolerant or do not respond to NSAIDs or colchicine (Rosenthal and Ryan, 2016; Schumacher and Chen, 2018).

Basic Calcium Phosphate Deposition Disease

Basic calcium phosphate deposition disease develops as a result of deposition of hydroxyapatite, apatite, or other calcium phosphate salts in joints, tendons, ligaments, hyaline cartilage, skeletal muscles, and subcutaneous tissue. Various diseases such as calcific periarthritis, systemic sclerosis, Paget's disease, and ankylosing spondylitis impair mineral hemostasis, which leads to calcification of basic calcium phosphate in soft tissues. The dispersion or dissolution of these calcified masses provokes an inflammatory response that manifests as pain. NSAIDs and intra-articular corticosteroids are the recommended treatment options (Ea and Liote, 2014; Schumacher and Chen, 2018).

Calcium Oxalate Deposition Disease

Oxalosis is a rare metabolic condition characterized by deposition of calcium oxalate crystals in visceral tissues, blood vessels, bones, and cartilage. Oxalosis may be congenital (primary) or acquired (secondary). In primary oxalosis, increased levels of oxalates develop as a result of polymorphism in metabolic enzymes. Whereas, secondary oxalosis occurs as a result of impaired renal function which leads to reduced excretion of oxalates (Lorenz et al., 2013; Schumacher and Chen, 2018).

Calcium oxalate deposition disease has similar manifestations as other crystal deposition diseases and presents as pain in the affected area. The crystals of calcium oxalate appear bipyramidal when viewed under a microscope. NSAIDs, colchicine, and intra-articular corticosteroid are used for the symptomatic treatment of calcium oxalate deposition disease. Liver transplant in patients with primary oxalosis and frequent dialysis in patients with secondary oxalosis can help reduce crystals deposits (Lorenz et al., 2013; Schumacher and Chen, 2018).

Role of Pharmacists

Pharmacotherapy is an essential component of patient care that necessitates the specialized skills and knowledge of pharmacist in health-care team. Pharmacists can contribute significantly toward improving the appropriate, safe, and effective use of drugs and overall health of the patients. Many studies have addressed the role of pharmacist in the management of gout. Most notable role includes patient education about the importance of pharmacological and nonpharmacological treatment, and monitoring of medication adherence. Studies have evaluated community pharmacist's role in emphasizing lifestyle modifications and diet such as managing weight, limiting meat and seafood intake, and minimizing alcohol consumption (Cassagnol and Saad, 2013; Counsell et al., 2018).

The studies have also evaluated pharmacist-led patient's education about their medications, including appropriate dosing, duration of therapy, adverse effects, contraindications, drug interactions, colchicine use, and gout flares at the first 6 months of urate-lowering therapy (Counsell et al., 2018). Ambulatory care pharmacists and automated calling technology represent potentially important and underutilized resources for improving health outcomes in gout patients (Coburn et al., 2016b). Moreover, ambulatory care pharmacists also assist in implementing guidelines through developing evidence-based algorithms and processes, educating providers and staff, and participating in population management (Hawes and Tong, 2015). An interactive and patient-centered approach can enhance gout educational interventions (Fields and Batterman, 2018). A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid levels in a high percentage of patients with recurrent gout in a primary care setting (Goldfien et al., 2014). Additionally, a simple ambulatory pharmacist-led intervention results in improvement of medication adherence and achievement of serum uric acid goal in gout patients using allopurinol (Mikuls et al., 2018). Pharmacist awareness of clinically significant interactions between colchicine and antibiotics that inhibit CYP3A4 can help ensure the efficacy of colchicine and minimize the risk of associated adverse events (Davis et al., 2013).

Pharmacists' Patient Care Process for Gout

Pharmacist as a member of the health-care team can optimize patients' medication therapy and contribute toward improving patients' health outcome. Pharmacists through effective communication with patients, their families, and other members of the health-care team collect, document, and recommend valuable information that promotes the appropriate, safe, and effective use of medicines and improve overall therapy outcome (ASHP, 2004; Shane and Abramowitz, 2015). The process of collecting, documenting, and recommending various aspects of patients' care has been improved and formalized following the development of Pharmacists' Patient Care Process by the Joint Commission of Pharmacy Practitioners (Gonyeau et al. 2018, JCPP, 2014). Pharmacists' patient-centered activities with special reference to gout are illustrated in **Fig. 4**.

Patient Education and Counseling

Patient education is of utmost importance in the management of gout. Patient education promotes therapy adherence and improves therapeutic outcome. Patients should be well-informed about the disease, its precipitating factors, and therapy. The patient needs to know about how to manage diet and acute attack and what to expect from pharmacological and nonpharmacological therapy. The patient must be involved in therapy selection process and all potential barriers to therapy adherence including doubts about the effectiveness of therapy, remission of gout symptomology, potential adverse effects, and cost of therapy should be addressed (Fields et al., 2017).

Patient must be informed about the curable nature of disease, its recurrence, role of hyperuricemia in disease progression, and the impact of lifestyle and dietary modifications. The need of lifestyle and dietary modifications must be stressed (Alvarez-Lario and Alonso-Valdivielso, 2014). Exercise should be encouraged in all patients because regular exercise reduces the incidence of gout flares. Overweight patients should be advised to lose weight; however, rapid weight loss should be avoided as it causes ketosis and increases uric acid level thus precipitating gout attack (Dessein et al., 2000). Diet comprising alcohol, seafood, red meat, sugar-sweetened beverages, and beer increases the risk of hyperuricemia; thus, they need to be avoided or taken in moderation. Intake of low-fat dairy products, such as coffee and fiber, must be encouraged as they reduce the risk of gout. Patient should be advised to drink water/fluid in sufficient amount in order to reduce kidney stone formation (Alvarez-Lario and Alonso-Valdivielso, 2014; Fields et al., 2017).

Adequate information about the benefits, potential harms, cost, and duration of pharmacotherapy should be provided to all patients. Patient must be educated about self-medication during an acute gout attack. Clear instruction about the dose, time, and duration of therapy must be communicated to each patient. The patient needs to understand the significance of ULT despite no symptoms of acute gout (Fields et al., 2017). Education about avoiding certain over-the-counter (OTC) medicines such as aspirin that may precipitate a gout attack is necessary. Regular monitoring of serum uric acid level must be encouraged in order to maintain the required serum uric acid level (Coburn et al., 2016a; Ramsubeik et al., 2018). Patient should be well-informed about the possible adverse effects of prescribed drugs and how to manage them (Aung et al., 2017; Fields et al., 2017).

Monitoring of Therapy Outcome

The primary outcome measure of therapy in acute gout is the resolution of pain and preservation of joint function. While, the outcome of ULT is assessed by measuring the reduction and maintenance of serum uric acid to the desired level, that is, <6 mg/dL in

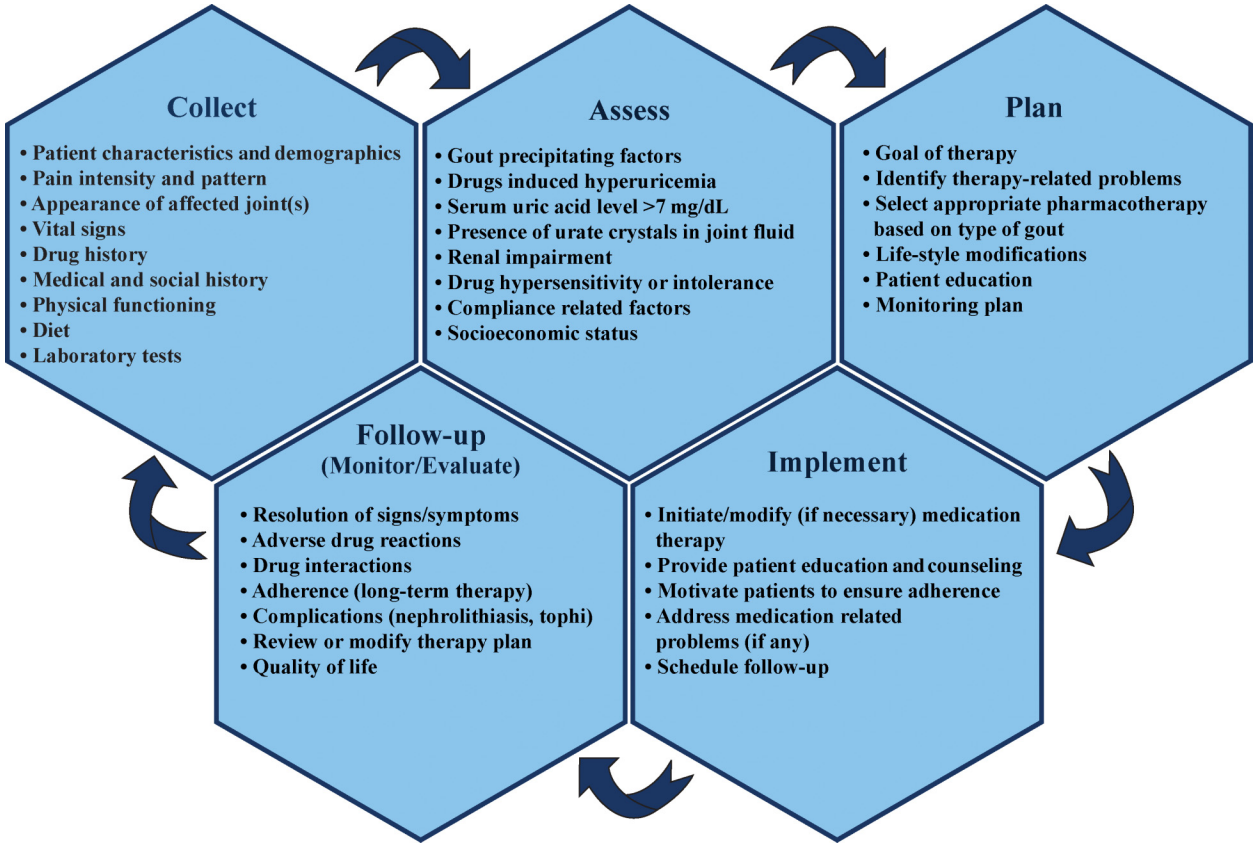

Figure 4 Pharmacists' patient care process for gout.

patients with noncomplicated gout and <5 mg/dL in patients with tophaceous gout (Khanna et al., 2012a). Regular monitoring of serum uric acid level is necessary in all patients. Serum uric acid tests should be performed every 2–5 weeks during initial phases of ULT (when the serum uric acid level is high) in order to titrate their dose to achieve the desired level. Once the desired serum uric acid level has been achieved, uric acid level should be assessed once every 6 months (Khanna et al., 2012a). Patients receiving ULT and prophylaxis therapy with colchicine or NSAIDs for gout flares should undergo laboratory tests including serum creatinine, blood urea nitrogen, and liver function tests in order to assess the status of renal or hepatic impairment and the need for dose adjustment (Perez-Ruiz et al., 2000). Patients with gout often have multiple comorbidities such as hypertension, diabetes, hyperlipidemia, and other cardiac diseases. Such patients should be regularly assessed, and appropriate therapy for these comorbidities should be selected considering their hyperuricemic effect, drug interactions, and adverse effects (Bardin and Richette, 2017).

Monitoring of Adverse Drug Reactions

Adverse drug reactions (ADRs) are inevitable consequences of pharmacotherapy of gout, thus monitoring of ADRs is necessary in all patients (Stamp, 2014). NSAID therapy may cause gastric bleeding, elevated blood pressure, and renal impairment; hence, they must be used with caution in patients predisposed to these conditions (Harirforoosh et al., 2013; Sostres et al., 2010). Corticosteroids are well-tolerated when used for a shorter duration of time, but their prolonged use may lead to hypothalamic pituitary adrenal axis suppression, hyperglycemia, osteoporosis, and impaired immunity. GI side effects such as vomiting and diarrhea are major limiting factors for colchicine therapy (Pelechas et al., 2019; Poetker and Reh, 2010). ULT precipitates gout flares and may cause other adverse effects, which can significantly affect patient's compliance (McHugh, 2018; Stamp, 2014). All ADRs should be monitored and timely managed. Patient should be educated regarding self-management of ADRs, their reporting, and situations when consultation with health-care professionals is needed. Moreover, many ADRs may be of minor nature that do not require any intervention. Patients need to be educated about the associated ADRs in order to improve patient satisfaction and compliance (Reach, 2011). **Table 3** enlists some of the common and serious ADRs associated with the drugs used for the management of gout.

Table 3 Adverse drug reactions associated with pharmacotherapy of gout

Drugs	*Cardiovascular*	*Dermatologic*	*Gastrointestinal*	*Renal*	*Hepatic*	*Neurologic*	*Respiratory*	*Others*
Naproxen	Edema, *fluid retention, vasculitis CHF, HTN, MI*	Pruritus, rash, *TEN, SJS*	Abdominal pain, constipation, heart burn, nausea, *GI hemorrhage, IBD*	*Acute renal failure, nephritis, nephrotic syndrome*	*Hepatitis, hepatotoxicity*	Dizziness, headache, *aseptic meningitis, stroke, seizure*	Dyspnea, *bronchospasm, pulmonary edema*	Ototoxicity, *hyperkalemia, agranulocytosis, anaphylaxis*
Sulindac	Edema, *MI*	Pruritus, rash, *erythema multiforms, SJS, TEN*	Abdominal pain, constipation, diarrhea, nausea and vomiting, *gastrointestinal ulceration, pancreatitis*	*Interstitial nephritis, nephrotic syndrome, papillary necrosis, renal failure*	*Cholestasis, hepatitis, hepatotoxicity, jaundice, liver failure*	Dizziness, headache, *stroke, seizure*	*Bronchospasm*	Tinnitus, *Agranulocytosis, neutropenia, thrombocytopenia, anaphylactoid reaction*
Indomethacin	*Dysrhythmia, thrombosis, CHF, HTN, MI*	*Erythroderma, SJS, TEN*	Abdominal pain, constipation, diarrhea, indigestion, nausea, *GI hemorrhage, GI ulceration, GI perforation*	Newborn renal dysfunction, *nephrotoxicity, renal failure*	Elevated liver enzymes, *hepatic necrosis, hepatitis, hepatotoxicity, jaundice, liver failure*	Dizziness, headache, vertigo, *stroke, seizure, ventricular hemorrhage*	*Persistent pulmonary hypertension of the newborn, pulmonary hemorrhage*	Hyponatremia, tinnitus, transitory neonatal hyperkalemia, *hearing loss, anemia, hemorrhage, neutropenia, anaphylaxis*
Celecoxib	HTN, *MI, TdP, ventricular hypertrophy*	*Erythema multiforms, SJS, TEN*	Diarrhea, nausea, *GI hemorrhage, GI perforation, GI ulceration*	*Acute renal failure, injury of kidney*	*Fulminant hepatitis, hepatotoxicity, rheumatoid arthritis, liver failure*	Headache, *stroke*	*Asthma, bronchospasm*	*Hyperkalemia, hemorrhage, thrombosis, anaphylactoid reaction*
Colchicine	–	–	Diarrhea, nausea, vomiting	–	–	–	–	*Myelosuppression*
Prednisolone	Fluid retention, HTN, *CHF*	Acne, ecchymosis, superinfection, *Kaposi's sarcoma*	Superinfection, *GI perforation, pancreatitis*	–	–	Headache, *pseudotumor cerebri, seizure*	*Pulmonary tuberculosis*	Hyperglycemia, muscle weakness, osteoporosis, cataract, glaucoma, superinfections, *diabetes mellitus with hyperosmolar coma, diabetic ketoacidosis, drug induced myopathy*
Triamcinolone	–	Injection site reaction	*GI perforation*	–	–	Headache, stroke, *infarction of spinal cord, seizure, paraplegia*	Pharyngitis, *perforation of nasal septum*	Cushing syndrome, influenza-like illness, *abnormal electrolytes, anaphylaxis, osteoporosis, cataract, glaucoma*
Anakinra	*Cardiorespiratory arrest*	Injection site reaction, *bacterial cellulitis, malignant melanoma*	–	–	–	–	*Bacterial pneumonia*	*Neutropenia, thrombocytopenia, anaphylaxis, infectious disease, breast cancer,*

(*Continued*)

Table 3 Adverse drug reactions associated with pharmacotherapy of gout (*cont.*)

Drugs	*Cardiovascular*	*Dermatologic*	*Gastrointestinal*	*Renal*	*Hepatic*	*Neurologic*	*Respiratory*	*Others*
Allopurinol	–	Maculopapular eruption, pruritus, *drug reaction with eosinophilia and systemic symptoms, rash, SJS, TEN*	–	*Renal failure*	*Granulomatous hepatitis, hepatic necrosis, hepatotoxicity*	–	–	*Agranulocytosis, aplastic anemia, eosinophilia, myelosuppression, thrombocytopenia, hypersensitivity reaction*
Febuxostat	*Myocardial infarction*	Rash, *drug reaction wit eosinophilia and systemic symptoms, SJS, TEN*	Nausea	–	*Hepatotoxicity*	*Stroke*	–	Arthralgia, *gout, myositis, rhabdomyolysis*
Probenecid	–	*SJS*	–	*Nephrotic syndrome*	*Hepatic necrosis*	–	–	*Aplastic anemia, leukopenia, neutropenia, thrombocytopenia, anaphylaxis*
Lesinurad	–	–	–	Elevated serum creatinine, *nephrolithiasis, renal failure*	–	Headache	–	Influenza
Pegloticase	Chest pain	–	Constipation, nausea, vomiting	–	–	–	Nasopharyngitis	Antibody development gout flare, *G6PD deficiency anemia, anaphylaxis, infusion reaction*

Note: Serious adverse effects are given in italics.

CHF, congestive heart failure; *G6PD*, glucose-6 phosphate dehydrogenase; *GI*, gastrointestinal; *HTN*, hypertension; *IBD*, inflammatory bowel disease; *MI*, myocardial infarction; *SJS*, Stevens-Johnson syndrome; *TdP*, torsades de pointes; *TEN*, toxic epidermal necrolysis.

Source: Lexicomp 2018; Micromedex Drugdex, 2018.

Monitoring of Drug Interactions

Patients with gout often have comorbidities and require concomitant administration of multiple drugs, which increases the probability of drug–drug interactions and its associated adverse outcomes (Stamp, 2014; Stamp and Chapman, 2013). NSAIDs decrease the antihypertensive effect of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers (Floor-Schreudering et al., 2015; Gualtierotti et al. 2013). They also increase the risk of bleeding when coadministered with anticoagulants and selective serotonin reuptake inhibitors (Choi et al., 2010; Masclee et al., 2014; Teklay et al., 2014). Colchicine is a substrate of CYP3A4 and P-glycoprotein; hence, caution is advised when it is used in combination with inhibitors or inducers of CYP3A4 and P-glycoprotein. Colchicine also interacts with statins leading to increased risk of rhabdomyolysis and myopathy (Davis et al., 2013; Kwon et al., 2017; Liuzzi et al., 2019; Terkeltaub et al., 2011). XOIs cause serious adverse effects when combined with azathioprine and mercaptopurine. They also increase the likelihood of bleeding with anticoagulants. Probenecid increases the plasma concentration of rifampin, lorazepam, and naproxen (Jordan and Gresser, 2018; Keith and Gilliland, 2007). **Table 4** enlists some important drug–drug interactions associated with pharmacotherapy of gout.

Table 4 Important drug–drug interactions

Interacting drugs	*Potential adverse outcome*	*Monitoring/management strategies*
Naproxen		
Amitriptyline; aspirin; betamethasone; budesonide; citalopram; clomipramine; clopidogrel; diclofenac; dexamethasone; duloxetine; enoxaparin; escitalopram; fluoxetine; gingko biloba; indomethacin; heparin; hydrocortisone; ibuprofen; ketorolac; nortriptyline; prednisolone; rivaroxaban; sulfasalazine; warfarin	Bleeding/gastrointestinal ulcer	Avoid combination; consider alternate therapy; monitor for PT, APTT, INR and signs of bleeding
Cyclosporine; tenofovir	Nephrotoxicity	Monitor electrolytes, RFTs and blood pressure; consider alternate therapy
Furosemide; hydrochlorothiazide; indapamide; spironolactone	Nephrotoxicity and reduced efficacy of diuretics	
Lithium	Lithium toxicity (diarrhea, tremors, abdominal pain, drowsiness)	Monitor for signs of lithium, digoxin or methotrexate toxicity
Digoxin	Digoxin toxicity (vomiting, diarrhea, abdominal pain, arrhythmias)	
Methotrexate	Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)	
Probenecid	Increased naproxen toxicity	Consider dose adjustment of naproxen if co-administered with probenecid and titrate to higher doses cautiously and in small increments
Bisoprolol; candesartan; captopril; carvedilol; lisinopril; losartan; propranolol; ramipril; valsartan	Renal dysfunction and/or increased blood pressure	Monitor antihypertensive efficacy, and RFTs, particularly in elderly patients, during treatment initiation, volume-depleted patients, or those with preexisting renal dysfunction
Indomethacin		
Amitriptyline; aspirin; betamethasone; budesonide; citalopram; clomipramine; clopidogrel; diclofenac; dexamethasone; duloxetine; enoxaparin; escitalopram; fluoxetine; gingko biloba; heparin; hydrocortisone; ibuprofen; ketorolac; naproxen; nortriptyline; prednisolone; rivaroxaban; sulfasalazine; warfarin	Bleeding/gastrointestinal ulcer	Avoid combination; consider alternate therapy; monitor for PT, APTT, INR and signs of bleeding
Cyclosporine; tenofovir	Nephrotoxicity	Monitor electrolytes, RFTs and blood pressure; consider alternate therapy
Furosemide; hydrochlorothiazide; indapamide; spironolactone	Nephrotoxicity and reduced efficacy of diuretics	
Lithium	Lithium toxicity (diarrhea, tremors, abdominal pain, drowsiness)	Monitor for signs of lithium, digoxin, methotrexate, gentamicin or amikacin toxicity
Digoxin	Digoxin toxicity (vomiting, diarrhea, abdominal pain, arrhythmias)	
Methotrexate	Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)	

(*Continued*)

Table 4 Important drug–drug interactions (*cont.*)

Interacting drugs	*Potential adverse outcome*	*Monitoring/management strategies*
Gentamicin (systemic); amikacin (systemic)	Gentamicin toxicity (renal dysfunction, ototoxicity)	
Probenecid	Increased indomethacin toxicity	Consider dose adjustment of indomethacin if co-administered with probenecid and titrate to higher doses cautiously and in small increments
Potassium (systemic)	Hyperkalemia	Discontinue potassium supplementation, decrease indomethacin dose, monitor serum potassium and ECG. Administration of intravenous sodium bicarbonate, glucose and insulin
Bisoprolol, candesartan; captopril; carvedilol; lisinopril; losartan; propranolol; ramipril; valsartan	Renal dysfunction and/or increased blood pressure	Monitor antihypertensive efficacy, and RFTs, particularly in elderly patients, during treatment initiation, volume-depleted patients, or those with preexisting renal dysfunction
Levofloxacin; ofloxacin	Seizures	Consider alternative therapy, particularly in patients predisposed to seizure activity
Diclofenac		
Amitriptyline; aspirin; betamethasone; budesonide; citalopram; clomipramine; clopidogrel; dexamethasone; duloxetine; enoxaparin; escitalopram; fluoxetine; gingko biloba; heparin; hydrocortisone; ibuprofen; indomethacin; ketorolac; naproxen; nortriptyline; prednisolone; rivaroxaban; sulfasalazine; warfarin	Bleeding/gastrointestinal ulcer	Avoid combination; consider alternate therapy; monitor for PT, APTT, INR and signs of bleeding
Cyclosporine; tenofovir	Nephrotoxicity	Monitor electrolytes, RFTs and blood pressure; consider alternate therapy
Furosemide; hydrochlorothiazide; indapamide; spironolactone	Nephrotoxicity and reduced efficacy of diuretics	
Lithium	Lithium toxicity (diarrhea, tremors, abdominal pain, drowsiness)	Monitor for signs of lithium, digoxin or methotrexate toxicity
Digoxin	Digoxin toxicity (vomiting, diarrhea, abdominal pain, arrhythmias)	
Methotrexate	Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)	
Ciprofloxacin	Increased ciprofloxacin plasma concentration	Monitoring for signs of ciprofloxacin-related adverse effects
Bisoprolol, candesartan; captopril; carvedilol; lisinopril; losartan; propranolol; ramipril; valsartan	Renal dysfunction and/or increased blood pressure	Monitor antihypertensive efficacy, and RFTs, particularly in elderly patients, during treatment initiation, volume-depleted patients, or those with preexisting renal dysfunction
Levofloxacin; ofloxacin	Seizures	Consider alternative therapy, particularly in patients predisposed to seizure activity
Miconazole; fluconazole; voriconazole	Increased diclofenac exposure	Do not exceed the lowest recommended diclofenac dose
Carbamazepine; phenobarbital; st john's wort; rifampin;	Reduced diclofenac exposure	Higher diclofenac dose may be required
Celecoxib		
Amitriptyline; aspirin; betamethasone; budesonide; citalopram; clomipramine; clopidogrel; dexamethasone; diclofenac; duloxetine; enoxaparin; escitalopram; fluoxetine; gingko biloba; heparin; hydrocortisone; ibuprofen; indomethacin; ketorolac; naproxen; nortriptyline; prednisolone; rivaroxaban; sulfasalazine; warfarin	Bleeding/gastrointestinal ulcer	Avoid combination; consider alternate therapy; monitor for PT, APTT, INR and signs of bleeding
Cyclosporine; tenofovir	Nephrotoxicity	Monitor electrolytes, RFTs and blood pressure; consider alternate therapy
Furosemide; hydrochlorothiazide; indapamide; spironolactone	Nephrotoxicity and reduced efficacy of diuretics	

Table 4 Important drug–drug interactions (*cont.*)

Interacting drugs	*Potential adverse outcome*	*Monitoring/management strategies*
Lithium	Lithium toxicity (diarrhea, tremors, abdominal pain, drowsiness)	Monitor for signs of lithium, digoxin or methotrexate toxicity
Digoxin	Digoxin toxicity (vomiting, diarrhea, abdominal pain, arrhythmias)	
Methotrexate	Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)	
Ciprofloxacin	Increased ciprofloxacin plasma concentration	Monitoring for signs of ciprofloxacin-related adverse effects
Bisoprolol, candesartan; captopril; carvedilol; lisinopril; losartan; propranolol; ramipril; valsartan	Renal dysfunction and/or increased blood pressure	Monitor antihypertensive efficacy, and RFTs, particularly in elderly patients, during treatment initiation, volume-depleted patients, or those with preexisting renal dysfunction
Levofloxacin; ofloxacin	Seizures	Consider alternative therapy, particularly in patients predisposed to seizure activity
Fluconazole; voriconazole	Increased celecoxib exposure	Do not exceed the lowest recommended celecoxib dose
Colchicine		
Clarithromycin; cyclosporine; diltiazem; erythromycin; fluconazole; indinavir; itraconazole; ketoconazole; lopinavir; quinidine; ritonavir; saquinavir; verapamil	Colchicine toxicity (diarrhea, abdominal pain, vomiting, seizures and hypotension)	Avoid combination
Atorvastatin; lovastatin; pravastatin; rosuvastatin; simvastatin	Rhabdomyolysis, myopathy	Use with caution. Monitor level of creatine kinase and sign/symptoms of rhabdomyolysis
Corticosteroids		
Rotavirus vaccine	Live vaccine induced infection	Avoid combination
Ciprofloxacin; levofloxacin; moxifloxacin; norfloxacin; ofloxacin;	Tendon rupture	Use with caution. Monitor for pain, inflammation and tendon rupture
Lopinavir; ritonavir	Cushing syndrome and reduced effectiveness of ritonavir/lopinavir	Monitor for signs of cushing syndrome
Aspirin; celecoxib; diclofenac; ibuprofen; indomethacin; ketorolac; mefenamic acid; naproxen	Gastrointestinal Bleeding	Monitor for PT, APTT, INR and signs of bleeding. Consider alternate therapy
Allopurinol		
Didanosine	Didanosine toxicity (diarrhea, vomiting, abdominal pain)	Avoid combination. Consider alternate therapy
Azathioprine	Azathioprine toxicity (vomiting, leukopenia, anemia)	Reduce the dose of azathioprine by 60%–75%. Monitor for signs of azathioprine toxicity
Mercaptopurine	Mercaptopurine toxicity (myelosuppression, vomiting)	Reduce the dose of azathioprine by 60%–75%. Monitor for signs of mercaptopurine toxicity
Warfarin	Bleeding	Monitor INR, PT, APTT and signs of bleeding
Captopril; enalapril	Hypersensitivity reactions	Monitor for signs of hypersensitivity reaction
Febuxostat		
Azathioprine	Azathioprine toxicity (vomiting, leukopenia, anemia)	Avoid combination. Consider alternate therapy
Mercaptopurine	Mercaptopurine toxicity (myelosuppression, vomiting)	Avoid combination. Consider alternate therapy
Probenecid		
Ketorolac	Ketorolac toxicity (gastric ulceration, edema, headache)	Avoid combination
Indomethacin	Indomethacin toxicity (gastric ulceration, bleeding and perforation)	Consider reducing the total daily dose of indomethacin. Monitor for signs of toxicity

(*Continued*)

Table 4 Important drug–drug interactions (*cont.*)

Interacting drugs	*Potential adverse outcome*	*Monitoring/management strategies*
Naproxen	Naproxen toxicity (diarrhea, drowsiness, headache and confusion)	Consider reducing the dose of Naproxen. Monitor for signs of toxicity
Methotrexate	Methotrexate toxicity (Leukopenia, thrombocytopenia, anemia, nephrotoxicity)	Avoid combination or monitor serum levels of methotrexate. Consider reducing the dose of methotrexate
Citalopram	QT interval prolongation	Limit the daily dose of citalopram to 20 mg. Monitor for changes in ECG and discontinue citalopram if QTc interval exceeds 500 ms.
Pegloticase	Anaphylaxis and infusion reactions	Avoid combination

APTT, activated prothrombin time; *ECG*, electrocardiogram; *INR*, international normalized ratio; *ms*, millisecond; *PT*, prothrombin time; *RFTs*, renal function tests.
Sources: ASHP, 2018; Lexicomp, 2018; Micromedex Drugdex, 2018.

Conclusions

Gout is a distressing life-long disease with a negative impact on patient's quality of life. It is often preceded by hyperuricemia and deposition of monosodium urate crystals in joints and soft tissues. The selection of appropriate pharmacotherapy relies on the presentation of disease, response to therapy, and patient's adherence. The specialized skills and knowledge of pharmacist for the development of an individualized care plan, provision of evidence-based therapy, and monitoring of adverse effects and drug interactions can improve the outcome of therapy and patient's quality of life.

Glossary

Hyperuricemia An abnormally increased level of uric acid (>7 mg/dL) in blood.
Monoarthritis Inflammation (arthritis) involving one joint at a time.
Nephrolithiasis Presence of calculi (crystalline stones) within the urinary system (kidneys and ureters).
Podagra Gout attack of foot especially affecting the big toe.
Polyarthritis Inflammation (arthritis) affecting more than one joint simultaneously.
Tophi A deposit of monosodium urate crystals that develop in and around joints, typically in patients with long-standing gout.
Urate-lowering therapy Drugs decreasing the serum uric acid level, such as xanthine oxidase inhibitors, uricosurics, and uricase.
Uricosuria Excessive amounts of uric acid in the urine.
Xanthine oxidase A form of xanthine oxidoreductase that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid.

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Further Reading

Guidelines

International

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Management of Rheumatology Disorders and the Pharmacist's Role: Osteoporosis

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Learning Objectives

Among other health-care professionals, pharmacists have been considered important contributors to osteoporosis risk assessment and prevention as well as monitoring of rationale, safe and adherent medication therapy.

The learning objectives of this chapter are as follows:

- to understand what is osteoporosis and what are the causes and risk factors of this disease and what risk scores to use for patient evaluation;
- to learn about osteoporosis symptoms and what are the consequences if this condition is not early diagnosed and treated;
- to know about what medicines are used for the treatment of osteoporosis;
- to understand the role of vitamin D and calcium supplements for osteoporosis;
- to learn about how pharmacist can contribute to the prevention and risk analysis of osteoporosis;
- to know about counseling aspects of medication use: administration details, adverse drug reactions, and drug–drug interactions;
- to understand the importance of medication adherence in osteoporosis treatment.

Take Home Messages

Osteoporosis is common; approximately one in two women and one in four men aged 50 and older will have fracture due to osteoporosis. Osteoporosis is asymptomatic until a fracture occurs, thus patients tend to underestimate the need for proper medication use.

There are several factors and diseases that can increase bone loss and the risk of developing osteoporosis, including age, sex, insufficient calcium, and vitamin D intake; low physical activity; increased alcohol consumption, low BMI; family history of fracture or osteoporosis; diabetes; several hormone-related conditions (hyperthyroidism, hyperparathyroidism, Cushing's disease); rheumatoid arthritis; malabsorption problems; long term use of high-dose glucocorticoids.

There are several risk-scores available online that can be used to assess the risk of a patient for developing osteoporosis.

The key elements for prevention of osteoporosis are sufficient exercise, vitamin D and calcium intake, and smoking cessation.

Bisphosphonates are the drugs of choice for treating osteoporosis to prevent fractures. Denosumab can be offered to patients who are intolerant of oral bisphosphonates or have trouble following the administration guidelines. Raloxifene, teriparatide, and strontium ranelate are less frequently used in certain patients and only if oral bisphosphonates are contraindicated and patients are closely monitored for potential adverse events.

Bisphosphonates should be taken after an overnight fast and an hour before the first food or drink of the day or any other oral medicinal products or supplementation (including calcium). The tablets must not be sucked or chewed. The patient should be sitting or standing in an upright position, while administration and the patient should not lie down for 1 h after taking bisphosphonates.

Patients should be instructed to discontinue the bisphosphonate and seek medical attention if they develop symptoms of esophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, or new, or worsening heartburn.

During the treatment, patients should be advised to report any thigh, hip, or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

All patients should be encouraged to maintain good oral hygiene, receive routine dental checkups, and report any oral symptoms such as dental mobility, pain, or swelling.

Although there is a need to stress the favorable benefit–risk ratio of osteoporosis medicines among patients who need pharmacological therapy, quoting relevant statistics to patients is not usually sufficient to allay their concerns and improve adherence. Each patient's reasons for nonadherence tend to be different and depend on individual beliefs or circumstances. Thus, strategies to improve adherence to medicines should be individualized accordingly. Understanding patients' preferences and incorporating them in clinical decision-making could lead to improved care.

Counseling by pharmacists on aspects regarding administration, effectiveness, and possible side-effects and highlighting the importance of long-term continuous use at the first dispense of osteoporosis medicine has been shown to effectively improve adherence to medicines.

Introduction to Condition

Osteoporosis is a very common condition. Bone is a living tissue that is in a constant state of regeneration. The body removes old bone (called bone resorption) and replaces it with new bone (bone formation). Osteoporosis becomes more common with age. It is more common in women than in men. About 22 million women and 5.5 million men in the European Union (Hernlund et al., 2013) and 9 million women and 2.8 million men in the United States (Cawthon, 2011) had osteoporosis in 2010.

Osteoporosis is silent because there are no symptoms. Breaking a bone is a serious complication of osteoporosis though, especially for older patients. Osteoporotic fractures are most likely to occur in the hip, spine, or wrist, but other bones can break too. In addition to causing permanent pain, osteoporosis causes some patients to lose height and often leads to a stooped or hunched posture. Osteoporosis is responsible for two million broken bones and $19 billion in related costs every year. By 2025, experts predict that osteoporosis will be responsible for approximately three million fractures and $25.3 billion in costs annually (National Osteoporosis Foundation website, 2018).

Osteoporosis can present as an independent disease, but there are numerous rheumatic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis/polymyositis, and vasculitis are characterized by osteoporosis and fragility fractures. Inflammatory cytokines, glucocorticoid treatment, immobilization, and reduced physical activity due to painful joints and muscle weakness are considered the main risk factors that cause low body mass density values in these diseases (Maruotti et al., 2014)

Osteoporosis in patients with rheumatic disease is of particular concern because bone loss may result from the disease process and from the medications used to control inflammation. Decreased bone mass, combined with an increased tendency of persons with musculoskeletal disease to fall, may also increase the risk of fractures.

Disease/Condition Information

Osteoporosis is characterized by reduced bone mineral density (BMD) and disruption of bone microarchitecture, resulting in increased bone fragility and increased fracture risk (Consensus development conference, 1993; Ström et al., 2008). Bone is a living tissue that is constantly being renewed (Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group, 1994). Under pathologic conditions, bone formation—resorption balance is disrupted. Continuous high osteoclast activity or low osteoblast activity leads to low bone mass (osteoporosis) (Zhong et al., 2014). Loss of bone mass per se and osteoporosis are usually asymptomatic until a fracture occurs (Silverman et al., 2011). The disease has clinical and public health importance only because of the fractures (Cummings and Melton, 2002), which cause pain, degrade people's quality of life, and are often disabling (Borgström et al., 2013). Clinically, osteoporosis is recognized by the occurrence of characteristic fractures after low-energy trauma; usually these are fractures of the hip, vertebrae, or distal forearm (Woolf and Pfleger, 2003).

Fracture incidence trends have been shown to differ in different parts of the world (Cooper et al., 2011). The potential drivers of negative changes to fracture rates are urbanization and a general aging of the population. Conversely, osteoporosis medication use, birth cohort effects such as maternal and offspring nutrition, an average increase in body mass index (BMI), and lifestyle interventions such as smoking cessation and fall prevention can result in a more positive trend (Ballane et al., 2014; Jürisson et al., 2015). Increasing and improving the consumption of osteoporosis medicines per a population has been shown to be one of the main factors that could positively influence fracture incidence trends (Alves et al., 2013; Støen et al., 2012).

Losing bone mass and quality is a normal part of the ageing process, but some people lose bone density at a higher than average rate and this can lead to the development of osteoporosis and fractures. Postmenopausal women are most affected by bone loss, due to changes in levels of reproductive hormones (Riggs, 2000; Sowers et al., 2006). Although men are less disposed to osteoporosis, they have been shown to be undertreated (Bor et al., 2015).

Osteoporosis develops slowly over several years. It is a chronic and progressive disease and is the most common metabolic bone disease. An understanding of bone metabolism and osteoporosis mechanisms is crucial in terms of effective disease prevention, diagnosis, and therapy. Osteoporosis diagnosis and fracture risk estimation are based mostly on bone densitometry (DXA) T-scores on BMD scale. T-score is the difference between a measured BMD and the average BMD in healthy young adults (Blake and Fogelman, 2007). Osteoporosis in postmenopausal women is defined as a T-score ≤2.5 SD (Kanis and Glüer, 2000); however, osteoporotic fractures might also occur among those at a moderate risk (Cefalu, 2004; Schuit et al., 2004; Siris et al., 2004). There are also several web-based osteoporosis risk tests and fracture risk calculators—tools to help doctors and health professionals estimate fracture risk.

Management of Condition

Treatment for osteoporosis is based on using medicines that strengthen bones. As a chronic and progressive bone disease, long-term treatment is needed to control bone metabolic disruption, and patients need to adhere to treatment if it is to be effective and cost-effective (McCombs et al., 2004; Rietbrock et al., 2009).

The efficacy of osteoporosis drugs ultimately depends on whether they reduce the risk of fractures (Diez-Perez et al., 2012). The medicines used to ameliorate osteoporosis are the bisphosphonates (ATC group M05BA), peptides of the parathyroid hormone family (ATC group H05AA), selective estrogen-receptor modulators (SERMs) (ATC group G03XC), and other drugs that affect bone structure and mineralization (strontium ranelate and denosumab) (ATC group M05BX) (Kanis et al., 2013).

The drugs used against osteoporosis have all been shown to reduce the risk of vertebral fractures, some have also been shown to reduce the risk of nonvertebral fractures and those of the hip (Body et al., 2010; Delmas, 2002). To date, no single agent has been shown to be significantly superior in preventing fractures (MacLean et al., 2008; Sanderson et al., 2016). The safety profile of the existing osteoporosis medicines has also been shown as favorable (Lewiecki, 2011).

The bisphosphonates group is the first-line osteoporosis treatment option in most countries, and the most used agents are orally administered alendronic acid, ibandronic acid, and risedronic acid and parenterally administered zolendronic acid. Bisphosphonates combination preparations consist of bisphosphonates with added calcium, colecalciferol, or both.

Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate, a naturally occurring compound in which 2 phosphate groups are linked by esterification. Bisphosphonates have a very high affinity for bone mineral because they bind to hydroxyapatite crystals. Accordingly, bisphosphonate skeletal retention depends on availability of hydroxyapatite binding sites. Bisphosphonates are preferentially incorporated into sites of active bone remodeling, as commonly occurs in conditions characterized by accelerated skeletal turnover (Drake et al., 2008).

All bisphosphonates are associated with beneficial effects on reducing osteoporosis-induced fractures relative to placebo, with hazard ratios varying from 0.41 to 0.92, depending on treatment and fracture site. For vertebral fractures and percentage change in BMD, the treatment effects are also statistically significant. Pairwise comparisons between bisphosphonates indicate that no bisphosphonates is statistically significantly more effective than any other bisphosphonates for fracture outcomes (Davis et al., 2016).

Denosumab is a fully human monoclonal IgG2 antibody that specifically targets nuclear factor kappa B ligand (RANKL) that has been identified to be associated with osteoclast driven bone resorption and subsequent bone loss (von Keyserlingk et al., 2011). Denosumab is recommended for use in women who have known osteoporosis by the Committee of the American College of Physicians as a drug of choice beside the bisphosphonates (Qaseem et al., 2017) or it may also be restricted to patients for whom oral bisphosphonates are unsuitable due to contraindication, intolerance, or inability to comply with the special administration instructions due to cost-effectiveness or budget impact issues (Denosumab for the prevention of osteoporotic fractures in postmenopausal women, SMC advice on denosumab (Prolia), 2010).

SERMs are nonsteroidal agents that bind to the estrogen receptor and act as estrogen agonists or antagonists. Raloxifene is the most used SERM that is widely available for the prevention and treatment of postmenopausal osteoporosis. Raloxifene is recommended only as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of bisphosphonates or have a contraindication to or are intolerant (Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, NICE Guidance, 2008).

The intermittent administration of parathyroid hormones (PTHs) (e.g., with daily subcutaneous injections) results in an increase in the number and activity of osteoblasts, leading to an increase in bone mass and in an improvement in skeletal architecture at both cancellous and cortical skeletal sites. The 1-34 N terminal fragment (teriparatide) of PTH is therefore used for the management of osteoporosis. It has been shown to reduce significantly the risk of vertebral and nonvertebral fractures (Kanis et al., 2013). Similar to SERMs, teriparatide is recommended for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to take bisphosphonates or have a contraindication to or are intolerant them (Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, NICE Guidance, 2008).

Strontium ranelate is an orally administered drug that may dissociate bone formation and bone resorption by allowing continued production of bone while decreasing bone resorption. In clinical trials, strontium ranelate (2 g/d) has been shown to reduce the relative risk of new vertebral and nonvertebral fractures (Reginster et al., 2005). But its use is restricted in Europe because of its increased risk of serious heart problems to treatment of patients with severe osteoporosis and contraindicated for patients with

a current or past history of ischemic heart disease, peripheral arterial disease, or cerebrovascular disease, or with uncontrolled hypertension (Recommendation to restrict the use of Protelos/Osseor (strontium ranelate), European Medicines Agency, 2013), and it is not authorized in the Unites States.

A new agent that is currently being developed for osteoporosis treatment is romosozumab. It is a monoclonal antibody that binds to and inhibits sclerostin, increases bone formation, and decreases bone resorption. It has shown promising results compared to alendronate in reducing clinical fractures (Saag et al., 2017), but its potential place in clinical practice is yet to be determined in the future.

Regardless of the active ingredient, all the trials that ascertained the efficacy of an osteoporosis medicine to ameliorate the risk of vertebral fractures lasted mostly at least three years, and patients' medicine intake was monitored to assure sufficient adherence (Black et al., 2007; Chesnut et al., 2004; Cummings et al., 2009; Ettinger et al., 1999; Harris et al., 1999; Karpf et al., 1997; Meunier et al., 2004). These trials indicate that the optimal treatment duration using osteoporosis medicines is at least three years and sufficient adherence is necessary to obtain the results hoped for. Although there are some studies that have shown self-reported improvement in patients' quality of life after only 1 year of treatment with bisphosphonates (Kamatari et al., 2007).

The maximum required duration of treatment with bisphosphonates has recently been the subject of debate. Some authors recommend a drug holiday to prevent side effects from long-term use after 5–10 years of bisphosphonate treatment. Because bisphosphonates accumulate in bones and continue to provide some residual antifracture risk reduction, it does not pose a risk. The duration of treatment and length of the holiday should be based on individual fracture risk. Patients at a mild risk might stop treatment after 5 years and remain on holiday as long as their bone mineral density is stable and no fractures occur; higher risk patients should be treated for 10 years and have a holiday of no more than a year or 2 (Watts and Diab, 2010). Other research has shown that long-term bisphosphonate use does not influence bone material properties, but is associated with adverse effects (Hassler et al., 2015).

Monitoring the efficacy of antiosteoporotic drugs in a real-life setting is part of successful osteoporosis management, as it can help identify poor-adherent nonresponder patients (Bruyère and Reginster, 2014).

Role of Pharmacist in Health-care Team

A pharmacist is often the most accessible health-care specialist in many health-care settings and plays a key role as a drug expert. The pharmacist's role has shifted over the years with the focus on compounding during the early days, then focusing on drug dispensing in the end of the last century and to patient-centered pharmaceutical care nowadays (Hepler and Strand, 1990; Jones et al., 2005). There are a lot of interventions that can be carried out in a pharmacy that help improve patient's quality of care (patient counseling, education, medication management, etc.). The potential role for pharmacists in osteoporosis management is the improved identification of high-risk patients and high-quality patient counseling, which has been shown to increase central DXA testing and calcium and vitamin D intake among individuals at high risk for osteoporosis (Elias et al., 2011).

The main goal of counseling in a pharmacy is to make patients more knowledgeable about their disease and their medicines to improve their adherence to medicines. As osteoporosis consists of chronic and progressive metabolic bone failure that requires long-term treatment, the pharmacy provided counseling on aspects regarding administration, the benefits and risks of the medicine, and the long-term duration of osteoporosis treatment are very important (Heilmann et al., 2013).

Risk Factors

To alleviate the public and private burden of osteoporosis-related fractures, risk assessments and a reduction in individuals' risk of fractures are critical (Cauley, 2013). Key steps highlighted to tackle osteoporosis are awareness raising campaigns; preventive lifestyle strategies; evidence-based guidelines; fracture care; postfracture rehabilitation, and prevention of falls and available economic data (Compston, 2004).

The most important risk factors for postmenopausal osteoporosis that put patients in risk for osteoporosis-related fractures are as follows:

- Low bone mineral density
- Advancing age
- Personal history of fractures
- Maternal history of fractures
- Low body weight
- Low body mass index
- Use of certain medications (oral glucocorticoids, antiepileptics, aromatase inhibitors, excessive thyroid hormone)
- Estrogen deficiency (early menopause)
- Current smoking
- Certain medical conditions (inflammatory bowel disease, eating disorders that lead to malabsorption, lymphoma, leukemia, multiple myeloma, systemic mastocytosis)
- History of falls

One possibility to assess patients' risk factors is to use a web-based risk-score, such as the International Osteoporosis Foundation one-minute osteoporosis risk test (IOF One-minute osteoporosis risk test, 2018). Patients in risk of developing osteoporosis need extra attention in the pharmacy and should be counseled on the risks of osteoporosis (Levine, 2007).

Prevention/screening

The majority of women 60 years of age or older who attended a community pharmacy osteoporosis screening were at moderate or high risk for osteoporosis (Johnson et al., 2008). For patients who have been identified as being in the risk group for developing osteoporosis, the following recommendations on their lifestyle changes could be given:

Exercise—Regular physical activity and exercise is recognized as one of the most effective lifestyle strategies to maximize peak bone mass during growth and prevent bone loss during ageing. In frail and very elderly adults, resistance training and balance exercises in combination reduce falls and risk factors (Ebeling et al., 2013). As the physical exercise of choice, Nordic walking could be recommended for the elderly patients (Bieler et al., 2017);

Calcium—Most systematic reviews of scientific evidence favor supplementation of calcium plus vitamin D to reduce fracture risk. Dietary calcium is the preferred source of calcium, and calcium supplements should be limited to 500–600 mg/day;

Vitamin D—Vitamin D adequacy is important for bone and muscle function. Maintaining the recommended (Endocrine Society and the International Osteoporosis Foundation) serum level of 25(OH)D on the level of 75 nmol/L requires at least 1500–2000 IU (37.5–50 μg) per day of supplemental vitamin D. For the treatment of severe vitamin D deficiency, doses ≤ 10 000 IU (250 μg) per day have shown to be safe;

Smoking cessation—Cigarette smoking is an independent risk factor for osteoporosis and increases the risk of fractures (Kanis et al., 2005). Thus, patients in risk of osteoporosis should be counseled on cessation of smoking.

Education and counseling programs in pharmacies have shown to provide a significant increase in patients' daily calcium intake and duration of weekly exercise (Kalkım and Dağhan, 2017; Wong et al., 2004). An interdisciplinary, multifaceted intervention based on building knowledge has also been shown to improve the uptake of vitamin D and calcium in in long-term care facilities (Kennedy et al., 2015).

Patient satisfaction with the pharmacist interaction in identifying risk patients and with their role in improving awareness has been shown to be high among patients, and a large proportion of patients are highly motivated to follow the instructions by the pharmacist on their calcium intake, exercise, and/or consulting with their doctor (Law and Shapiro, 2005). A pharmacist-led intervention has proved efficacious in primary care clinics regarding the proportion of patients with the diagnosis of osteoporosis without contraindications to antiosteoporosis medicines who were prescribed an antiosteoporotic medicine (Tan et al., 2014). These data suggest pharmacists can play an important role in screening for osteoporosis patients and providing preventive counseling to high-risk patients.

Diagnosis

Pharmacists can provide osteoporosis screenings using questionnaires to detect high fracture risk patients and offer education. Sometimes peripheral devices for osteoporosis screening can be used, but for official diagnosis and treatment needs assessment DXA is required (MacLaughlin and Raehl, 2008).

BMD measurements, when used in conjunction with a fracture risk assessment tool (FRAT), help in determining the need for treatment. The Fracture Risk Assessment Tool (FRAX) is one such tool that helps clinicians determine a patient's risk for osteoporosis-related fracture (FRAX, 2018). The process can be time-consuming and may contribute to lower rates of screening in the primary care setting. Simpler instruments, such as the Osteoporosis Self-Assessment Screening Tool (OST), which relies on age and weight, have been developed to try and decrease the need for patient risk-factor data collection (Williams et al., 2017).

The FRAT and FRAX tools may also be used regardless of whether BMD information is available or not. They are helpful for areas of the country where BMD testing with DXA is not readily available (e.g., rural towns) (MacLaughlin, 2010).

Administration

Oral bisphosphonates are administered once a week (e.g., alendronate, risedronate) or once a month (e.g., ibandronate).

Bisphosphonates should be taken after an overnight fast (at least 6 h) and 1 h before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of water (approx. 200 mL) while the patient is sitting or standing in an upright position.

- Patients should not lie down for 1 h after taking bisphosphonates;
- Water is the only drink that should be taken with bisphosphonates;
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration

Patients should be instructed that if they miss a dose of the bisphosphonate, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day (Bonviva SmPC, 2018; Fosavance SmPC, 2018).

The recommended dose of zoledronic acid is a single intravenous infusion administered once a year in hospital or other healthcare facility (Aclasta SmPC, 2018).

Denosumab is administered as a single subcutaneous injection once every 6 months into the thigh, abdomen, or upper arm (Prolia SmPC, 2018).

The absorption of strontium ranelate is reduced by food, milk, and derivative products and therefore should be administered in-between meals. Given also the slow absorption of strontium ranelate should be taken at bedtime, preferably at least 2 h after eating (Protelos SmPC, 2018).

Adverse Drug Reactions and Their Management

Upper gastrointestinal adverse reactions Bisphosphonates can cause local irritation of the upper gastrointestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when bisphosphonates are given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal disease, gastritis, duodenitis, ulcers, or with a recent history of major gastrointestinal disease. Esophageal reactions (sometimes severe and requiring hospitalization), such as esophagitis, esophageal ulcers, and esophageal erosions, rarely followed by esophageal stricture, have been reported in patients receiving bisphosphonates. Therefore, patients should be instructed to discontinue the bisphosphonate and seek medical attention if they develop symptoms of esophageal irritation such as dysphagia, pain on swallowing, or retrosternal pain or new or worsening heartburn. The risk of severe esophageal adverse reactions appears to be greater in patients who do not administer bisphosphonates as they should, thus counseling on the correct administration is vital (Bonviva SmPC, 2018; Fosavance SmPC, 2018).

- Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate and denosumab therapy, primarily in patients receiving long-term treatment for osteoporosis. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, before presenting with a completed femoral fracture. During treatment, patients should be advised to report any thigh, hip, or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture (Aclasta SmPC, 2018; Bonviva SmPC, 2018; Fosavance SmPC, 2018; Prolia SmPC, 2018).

- Musculoskeletal pain

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In postmarketing experience, these symptoms have rarely been severe and/or incapacitating. The time to onset of symptoms varied from 1 day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment (Aclasta SmPC, 2018; Bonviva SmPC, 2018; Fosavance SmPC, 2018).

- Osteonecrosis of the jaw

Osteonecrosis of the jaw, generally associated with tooth extraction and/or a local infection, has been reported in patients with cancer who are receiving treatment regimens, including intravenously or orally administered bisphosphonates and denosumab. Many of these patients were also receiving chemotherapy and corticosteroids.

During osteoporotic treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling (Aclasta SmPC, 2018; Bonviva SmPC, 2018; Fosavance SmPC, 2018; Prolia SmPC, 2018).

- Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates and denosumab, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates or denosumab who present with ear symptoms such as pain or discharge or chronic ear infections (Aclasta SmPC, 2018; Bonviva SmPC, 2018; Fosavance SmPC, 2018; Prolia SmPC, 2018).

- Skin infections

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalization. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis (Prolia SmPC, 2018).

- Skin reactions

Life-threatening cutaneous reactions (Stevens-Johnson (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)) have been reported with the use of strontium ranelate. Patients should be advised of the signs and symptoms and monitored closely for skin reactions (Protelos SmPC, 2018).

- Cardiac ischaemic events

In pooled randomized placebo-controlled studies of postmenopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in patients treated with strontium ranelate. Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration. During treatment, these cardiovascular risks should be monitored on a regular basis generally every 6–12 months. Treatment should be stopped if the patient develops ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or if hypertension is uncontrolled (Protelos SmPC, 2018).

- Venous thromboembolism

Raloxifene is associated with an increased risk for venous thromboembolic events that is similar to the reported risk associated with current use of hormone replacement therapy (Raloxifene hydrochloride SmPC, 2018).

- Orthostatic hypotension

Teriparatide might episodes of transient orthostatic hypotension. Typically, an event begins within 4 h of dosing and spontaneously resolves within a few minutes to a few hours. When transient orthostatic hypotension occurs, it happens within the first several doses. Patients should be placed in a reclining position. Treatment does not have to be discontinued (Teriparatide SmPC, 2018).

Drug–Drug Interactions

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of the bisphosphonates and strontium ranelate. Therefore, patients must wait at least 1–2 h after taking bisphosphonates before taking food/drink or any other oral medicinal product (Bonviva SmPC, 2018; Fosavance SmPC, 2018; Protelos SmPC, 2018).

Since Nonsteroidal Antiinflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with oral bisphosphonates.

No other clinically important interaction with osteoporotic medicines has been described.

Improving Adherence

Osteoporosis consists of chronic and progressive metabolic bone failure that requires long-term treatment. Previous research has shown that even a small decrease in the medication possession ratio (MPR) increases the risk of a hip fractures, and the relative risk reduction of a hip fracture can be up to 60% per persistent patients compared to nonpersistent ones (Jürisson et al., 2015; Rabenda et al., 2008). These results emphasize the importance of adherence to treatment to achieve optimal antifracture efficacy (Rabenda et al., 2009). The number of patients to receive treatment within a year after an osteoporosis-related fracture has been shown to be less than 20% (Elliot-Gibson et al., 2004), indicating there is a significant gap between the need for osteoporosis treatment and the actual prescribing of medicines (Haaland et al., 2009). About half of the patients who do receive treatment adhere to it sufficiently, and only 30%–35% persist with the treatment for at least a year (Clowes et al., 2004; Cramer et al., 2007; Laius et al., 2017). Although once weekly or monthly, rather than daily administered medicines are associated with improved adherence, uptake is still suboptimal (Cramer et al., 2006). The number of fractures prevented and the QALY gain obtained at real-world adherence levels are only 38% and 41%, respectively, of those expected with full adherence (Hiligsmann et al., 2010).

Improvement in adherence to osteoporosis medicines is imperative, as it would effectively prevent more fractures (Caro et al., 2004) and help save health-care resources from being spent on the treatment of bone fragility fractures (Sabaté, 2003). There are several factors that have been shown to affect patients' medication adherence, but most important seem to be the doctor–patient relationship, patient awareness about the medicine and the disease, and also the copayment of medicines (Cutler and Everett, 2010; Vermeire et al., 2001). The efficacy and safety of medicines are important determinants of patient preferences, and informed patient decision-making can have a beneficial impact on adherence to treatment of osteoporosis (Gold, 2011). Although there is a need to stress the favorable benefit–risk ratio of osteoporosis medicines among patients who need pharmacological therapy, quoting relevant statistics to patients is not usually sufficient to allay their concerns and improve adherence (Khosla et al., 2017). Each patient's reasons for nonadherence tend to be different and depend on individual beliefs or circumstances. Thus, strategies to improve adherence to medicines should be individualized accordingly (Elaine et al., 2008). Understanding patients' preferences and incorporating them in clinical decision-making could lead to improved care (Hiligsmann et al., 2015).

One of the interventions that has been shown to be effective in improving adherence is a proactive intervention by pharmacists. The intervention consisted of the pharmacy provided structured counseling on aspects regarding administration, effectiveness, and possible side-effects at the first dispense of osteoporosis medicine. The importance of continuous use was highlighted (Stuurman-Bieze et al., 2014).

In another study, pharmaceutical care intervention participants reported significantly higher medication adherence at 6 and 12 months compared with the control group. The intervention consisted of an explanation on osteoporosis, risk factors, lifestyle modifications, goals of osteoporosis therapy, side effects, and the importance of medication adherence. Verbal counseling was reinforced with an osteoporosis booklet (Lai et al., 2011).

Although patients should be warned of common adverse effects of medications and counseled on how to recognize them and how to react, but there is also a risk that such information might be misunderstood, leading to unjustifiable fear of adverse effects. As a result, the patient may refuse to take any medication (Lai et al., 2012). Thus, the pharmacist should take extra care in explaining the benefits and risks of osteoporosis medicines in a balanced manner. Side effects of medicines have been shown to be the critical element for therapy discontinuation (Bajger, 2018; Sewerynek et al., 2013). The patients who have a greater belief in the benefits of medication are more likely to initiate therapy, while those who reported a greater distrust of medications were less likely to do so (Barrett-Connor et al., 2012). Thus, recognition and management of side effects should have a distinct place in counseling.

Community pharmacies offer a good platform for monitoring and improving therapy adherence and for providing medication therapy management. If community pharmacies have the ability to monitor long-term dispensing data, it helps to identify non-adherent patients and approach them for intervention (van Boven et al., 2014).

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Management of Rheumatoid Arthritis and the Pharmacist's Role

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Learning Objectives

On completion of this chapter, the reader will know about:

1. Causes and risk factors for developing rheumatoid arthritis (RA).
2. Clinical presentations of RA.
3. Treatment goals and therapeutic plans for RA patients.
4. Pharmacological and nonpharmacological treatment offered to RA patients.
5. Pharmacist's role in managing RA.
6. Monitoring of drugs used for RA.

7. Important drug–drug interactions with antirheumatic drug therapy.
8. Pharmaceutical dosage forms of different antirheumatic drugs.

Take Home Messages

- RA is an autoimmune and chronic inflammatory disease of the joints that affects 1.3 million Americans and as much as 1% of the worldwide population.
- Genetic variations and exposure to external environmental factors are the main risk factors for RA.
- The American College of Rheumatology/European League Against Rheumatism has developed criteria for RA classification.
- Different diagnostic tests such as rheumatoid factor, C-reactive protein, erythrocyte sedimentation rate, X-rays, ultrasound, and magnetic resonance imaging are used for RA diagnosis.
- Drug treatment for RA comprises of nonsteroidal anti-inflammatory drugs, disease modifying antirheumatic agents, biologics, and corticosteroids.
- Close monitoring of antirheumatic drug therapy is recommended to prevent or minimize adverse effects such as gastrointestinal bleeding, risk of fractures, osteoporosis, hypertension, weight gain, and hepatotoxicity.
- Nondrug treatment for RA includes weight reduction, proper rest, and occupational therapy.
- Adherence to drug therapy can be significantly improved by patient counseling provided by pharmacists.

Introduction to Rheumatoid Arthritis

Rheumatic disorder, also known as rheumatism, is a cluster of a minimum of 200 different diseases that affect joints and/or connective tissues (Altorok et al., 2016). Rheumatoid arthritis (RA) is an autoimmune disorder that causes systemic inflammation by targeting the joints of the wrist and/or feet, making them painful, warm, and swollen. The term RA is of Greek origin, which means "inflamed and watery joints." It was first distinguished from rheumatic fever and gout in the mid-nineteenth century by Garrod (Paget et al., 2002). The deleterious effects of RA are not restricted to joints or connective tissues, but the heart, eyes, and lungs may also be affected (Alenghat, 2016; Prete et al., 2011). Patients may face joint degradation and premature death as a result of RA-induced systemic inflammation. A significant reduction in the health-related quality of life in RA patients has been observed because of fatigue, loss of bodily functions, and pain.

Epidemiology—Burden of Disease

Rheumatoid arthritis, shares a substantial burden not only for the individual, but society at large. It is estimated that between 1% and 2% of the world's population is affected by RA. It was estimated in 2015 that nearly 24.5 million people were suffering from RA worldwide (Vos et al., 2016). Rheumatoid arthritis diagnosis peaks between the ages of 20 and 40 years, but it can occur in any age group. It can be a debilitating condition, with approximately 50% of patients unable to continue their fulltime employment after 10 years post-onset. The prevalence of RA differs between sexes; it has been reported that in RA is slightly more common among women than men (3:1) (van Vollenhoven, 2009).

Regional variations in the prevalence of RA have also been reported; the rate of incidence was highest in Chippewa (6.8%) and Pima North American Indigenous Peoples (5.3%) and lowest in China and Japan (0.2%–0.3%) (Silman and Pearson, 2002). Nearly a 50% increase in premature deaths have been seen in RA patients (after adjusting for comorbid conditions), which causes a 3–10-year reduction in life expectancy (Myasoedova et al., 2010). There are also some suggestions that RA is a "new" disease, being reported only since the industrial revolution in Europe. It appears to be milder in less developed countries, raising the possibility of some new environmental agent that may be more common in industrialized nations (Kalla and Tikly, 2003).

Etiology

The exact cause of RA is unknown; however, it is a multifactorial disease associated with genetic and environmental factors. RA causes abnormal regulation of the immune system, with tissue damage and inflammation of the joints as the major outcomes (McInnes and Schett, 2017). The risk of RA is three to five times higher in patients with a positive family history of the disease indicating a genetic link. The expression of the disease is dependent on genetic predisposition and exposure to some undetermined environmental chemicals. Genetics is the major risk factor in 40%–65% of RA seropositive cases. Different genes known or suspected to affect the immune system have been studied as risk factors for RA. Human leukocyte antigen (HLA) genes, for example the HLA-DRB1 gene, are regarded as the key risk factor for RA. As a result of variations in HLA-DRB1, the body is unable to differentiate between the proteins produced by the host and intruders such as bacteria and viruses (Doherty et al., 2018). More recently, certain genetic variants of PTPN22 and other genes have been identified as a risk factor for RA (van der Helm-van Mil et al., 2007).

Table 1 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA

Assessment criteria	*Score*
(1) At least 1 joint with definite inflammation of synovial membrane (clinical synovitis) (2) Synovitis not better described by any other abnormality This is a score-based algorithm and if the score of a patient is ≥6 (10 is the maximum score) after adding A–D categories then this patient is need to be classified as having definite rheumatoid arthritis[a]	
A. Joint involvement[b]	
1 large joint (elbows, knees, shoulders, ankles, and hips)	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints)[c]	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint, e.g., temporomandibular, acromioclavicular, sternoclavicular)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or normal ESR	1
D. Duration of symptoms (depending upon the report of patient)	
<6 wks	0
≥6 wks	1

CRP, C-reactive protein; *anti-CCP*, anticitrullinated protein antibody; *ESR*, erythrocyte sedimentation rate; *RF*, rheumatoid factor; wks, weeks.

[a]Those patients whose score is less than 6 they can be reexamined as they may be able to meet RA standard criteria over time.

[b]First carpometacarpal joints, first metatarsophalangeal joints, and distal interphalangeal joints are not included.

[c]Small joints include proximal interphalangeal joints, metacarpophalangeal joints, 2nd–5th metatarsophalangeal joints, wrists and thumb interphalangeal joints.

Source: Aletaha, D., Neogi, T., Silman, A.J., et al., 2010. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annal. Rheum. Dis. 69, 1580–1588.

Diagnosis

There is no single set of globally confirmed criteria to diagnose RA. Patients often experience inflammation of joints, tenderness, and morning joint stiffness with abnormally elevated values of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). There are a number of potential differential diagnoses that should be considered, such as osteoarthritis, septic arthritis (bacterial or viral), psoriatic arthritis, reactive arthritis, and autoimmune diseases including connective tissue disorder (Majithia and Geraci, 2007). The classification criteria of the American College of Rheumatology and European League Against Rheumatism for RA is presented in **Table 1**.

Various tests are used in the diagnosis and management of RA including X-rays, ultrasonography, rheumatoid factor (RF), anticyclic citrullinated peptide (Anti-CCP), complete blood count (CBC), white blood cell count (WBC), and magnetic resonance imaging (MRI).

Rheumatoid factor is positive in nearly 75% of patients with RA, although it is not etiologically linked to RA. High RF titers show a worst prognosis, as patients with higher RF levels are likely to have more severe disease and more intense treatment will be required. Anti-CCP detection is one of the most advance marker used to diagnose RA. It is found in 70% of RA patients and regarded as an important player in the progression of RA. It has sensitivity similar to rheumatoid factor (39%–94%) but has more specificity (81%–100%). Usually, these are detectable in the earlier phase of RA (Heidari et al., 2009). In order to determine the level of inflammation, ESR and C-reactive protein (CRP) are also advised but these levels may be normal in approximately 40% of RA patients so these readings need to be interpreted cautiously if done alone but when used in conjunction with other tests mentioned above are helpful in confirming diagnosis of RA.

Clinical Presentation—Signs and Symptoms

Some common signs and symptoms of RA are as follows:

- Warm, tender, and inflamed joints
- Weight loss

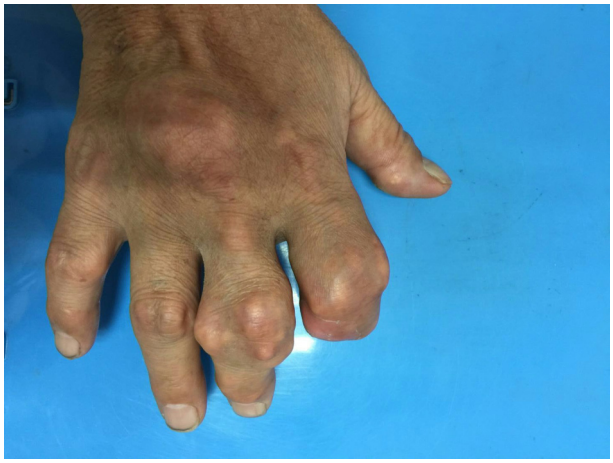

Figure 1 Patient with rheumatoid arthritis showing affected hand.

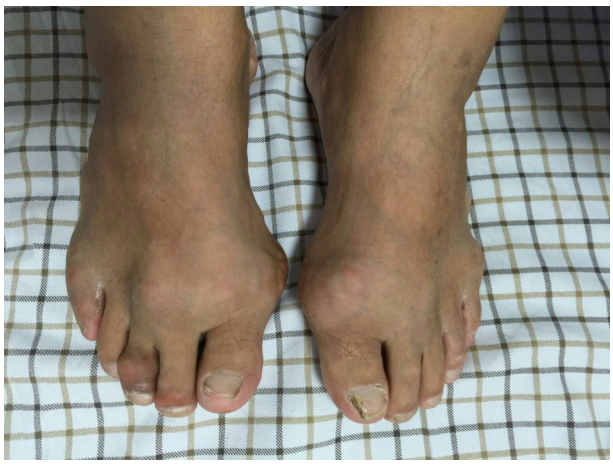

Figure 2 Patient with rheumatoid arthritis showing affected feet.

- Fever
- Fatigue
- Morning joint stiffness generally exceeding 30 min, which may persist for the whole day.

In the initial phase of RA, small joints of the hands and feet are affected as shown in **Figs. 1 and 2**. As the disease progresses, many other joints become affected, including ankles, knees, elbows, wrists, shoulders, and hips. It is important to note that the signs and symptoms of RA are not restricted to joints, but many nonjoint structures such as skin, lungs, heart, kidneys, nervous tissues, and bone marrow are also affected in up to 40% of RA patients (Shlotzhauer, 2014). Extra-articular features, such as rheumatoid nodules over the extensor surfaces of tendons or vasculitic skin involvement, may be seen but is less common.

Management of Rheumatoid Arthritis

If appropriate management of RA is not initiated early on in the disease diagnosis, it can lead to various short- and long-term complications such as joint destruction, deformity, osteoporosis, cardiac diseases, depression, and early death (Kiely and Nikiphorou, 2018; Nurmohamed, 2009; Wang, 2015). Treatments are targeted at reversing inflammation. The reduction in further damage or progression of the disease and improvement in physical function are possible if inflammation is reduced (Smolen et al., 2007). Therefore, a multifaceted and strategic approach is required to treat RA including pharmacologic and nonpharmacologic therapies (Smolen et al., 2016b).

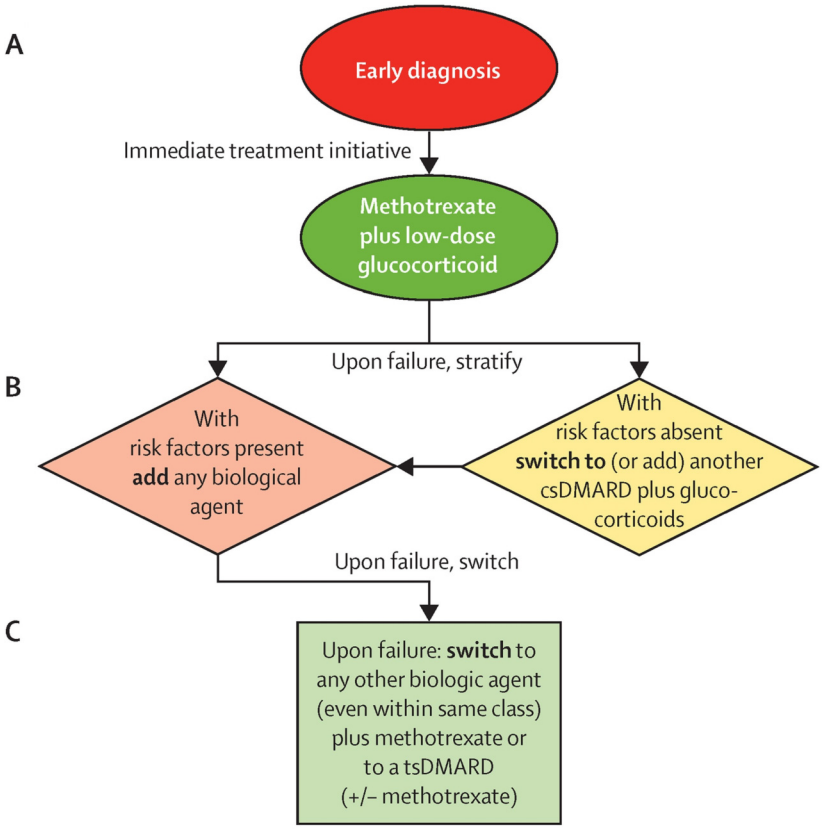

Figure 3 Therapeutic approaches to rheumatoid arthritis.

Pharmacological Management

Fortunately, the development and availability of newer drugs such as biologicals to treat RA in the last few years have significantly improved therapeutic outcomes including quality of life (Davies and Hyrich, 2018). The specific components of the immune system, such as T cells, antigen presenting cells (APCs), cytokines, and B cells, are all potential targets for drugs. The major therapeutic classes of drugs that are currently used in RA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) (Kiely and Nikiphorou, 2018). As per European League against Rheumatism (EULAR) recommendations, the treatment of RA should be initiated with a combination of methotrexate (conventional synthetic DMARD) with a low-dose glucocorticoid (Smolen et al., 2016a). **Fig. 3** shows an algorithm and different therapeutic approaches used for the treatment of RA.

NSAIDs and Analgesics

These agents are primarily used on a temporary basis to treat an acute flare up of RA because they possess mild to moderate analgesic as well as anti-inflammatory properties. However, they do not have any role in slowing the progression of RA (Crofford, 2013b). Therefore, these drugs are usually given in combination with other drugs such as DMARDs and corticosteroids (Gøtzsche, 1989). Acetaminophen is the most commonly prescribed analgesic drug because of its limited side effects.

The selection of NSAIDs for a specific patient is based on efficacy, patient risk factors, potential toxicities related to concomitant drugs, and cost. Acetaminophen should be prescribed in older patients or patients with renal or hepatic diseases (Crofford, 2013a). The COX-2 inhibitors, or coxibs, such as celecoxib and meloxicam, are also effective and possess fewer gastrointestinal side effects than the older medicines.

NSAIDs work best when given in low doses to RA patients with mild inflammation, but higher doses are required in other forms of arthritis, such as inflammatory arthritis. The effectiveness of NSAIDs should be determined over a 4-week period and if the patient is unable to tolerate the medication or does not get any significant benefit, then another type of NSAID should be tried.

Corticosteroids

Corticosteroids are not only able to restrict the inflammatory cascade but can also suppress the functions of the immune system (i.e., they are immunomodulatory agents) (Coutinho and Chapman, 2011). Different corticosteroids, such as prednisone and methyl

prednisolone, are used for short periods in RA patients to limit disease progression and acute flare ups (Haraoui et al., 2015). The clinical effectiveness of the therapy increases if corticosteroids are given as adjuvant therapy to DMARDs. Therefore, monotherapy with DMARDs is not as effective as combination therapy with corticosteroids in suppressing the progression of RA (Landewé et al., 2002).

These agents can be administered orally (prednisone 5–10 mg daily) or parenterally (methyl prednisolone 40 or 80 mg/mL) with the lowest possible dose to minimize side effects. It is difficult to discontinue the therapy once started even with the low dose due to the risk of withdrawal effects. So, clinicians do not stop corticosteroids therapy suddenly but taper off gradually over a period of weeks (Goekoop-Ruiterman et al., 2005).

Facial flushing is a common side effect that most patients develop after the first few days of parenteral (intermuscular or intra-articular) corticosteroid therapy (Berthelot et al., 2013). Other side effects with chronic use of corticosteroids include Cushingoid appearance, gastrointestinal bleeding, risk of fractures, osteoporosis, hypertension, weight gain, diabetes mellitus (DM), peptic ulcer disease (PUD), cataracts, and infections (Courtney and Doherty, 2005).

Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs (DMARDs) reduce the progression of active RA disease by improving radiographic outcomes (Kumar et al., 2009). The improvement with DMARDs is slower and may take weeks to months, which contrasts with the rapid effect of NSAIDs and corticosteroids. The use of DMARDs as an early treatment option is usually preferred because they provide numerous beneficial effects including a reduction in mortality rates (Yeganeh et al., 2018). DMARDs are classified as either biologic or nonbiologic. The most frequently used nonbiologics are methotrexate (MTX), leflunomide, hydroxychloroquine (HCQ), and sulfasalazine (SSZ) (Soriano et al., 2014). The common side effects associated with nonbiologics are nausea, vomiting, diarrhea bone marrow suppression, abdominal pain, and hepatitis.

Biologic DMARDs, such as infliximab, rituximab, abatacept, tocilizumab, and anakinra, are used in RA patients when non-biologic DMARDs fail to produce desired therapeutic goals.

Biologic Disease-Modifying Antirheumatic Drugs

Biologic DMARDs (bDMARDs) are newer and the most effective therapeutic agents for treating RA; however, they are costly (Keystone et al., 2012; Singh et al., 2016). The use of different bDMARDs in RA depends on efficacy, dose, cost, side effects, route of administration, and clinical practice guidelines. These agents are very selective in their mode of action and are involved in (1) interference with cytokine function or production, (2) inhibition of "second signal" required for T-cell activation, and (3) depletion of B-cells or inhibiting factors that active B-cells (rituximab and belimumab). According to the guidelines given by the American College of Rheumatology (ACR), nonbiologic DMARDs (monotherapy) should be considered as the first choice of treatment for early low, moderate, or severe forms of RA because of their lower cost and higher safety. However, if a patient does not respond to traditional DMARDs, then a combination of different nonbiologic DMARDs or a tissue necrosis factor (TNF) inhibitor, with or without methotrexate, can be recommended (Bongartz et al., 2006; Singh et al., 2016).

There is a standard nomenclature in practice for these bDMARDs; for example, if a drug's name ends with "inib" it is small kinase inhibitor and if it ends with "cept," "mab," "zumab," or "mumab," it is a receptor, chimeric monoclonal antibody, humanized monoclonal antibody, or fully human monoclonal antibody, respectively.

Anti-TNF bDMARDs

Tissue necrosis factor (TNF) is found in abundant quantity in the synovial fluid and serum of patients suffering from RA and plays an integral role in the disease pathogenesis by causing systemic inflammation. The efficacy of anti-TNF bDMARDs can be reduced due to the production of autoantibodies against them. All anti-TNF bDMARDs show promising results when given in combination with methotrexate (Breedveld et al., 2006; Edwards et al., 2004; Keystone et al., 2004, 2008, 2009; Klareskog et al., 2004; Maini et al., 1999, 2004). Examples of anti-TNF bDMARDs are infliximab, etanercept, adalimumab, certolizumab, and golimumab.

The most common side effects associated with anti-TNF DMARDs are diarrhea, abdominal pain, vomiting, headache, itching, bleeding, reactions at the injection site, bruising, and respiratory tract infections. Patients with tuberculosis (TB) should be treated first with anti-TB drugs before starting therapy with bMARDs to avoid the risk of reactivating latent TB (Bongartz et al., 2006; Thalayasingam and Isaacs, 2011).

These agents are contraindicated in conditions of active infection, heart failure and in patients with a history of demyelination. Caution should be exercised in patients with previous malignancy and pregnancy (Verstappen et al., 2011).

Anti-B Cell Therapy

B cells, which are part of the immune system, increase the severity of RA when activated. Rituximab is the only approved anti-B cell therapy. It removes nearly all the peripheral B cells after binding with them (CD20). It stimulates the complement system and antibodies to cause cellular toxicity. It is approved by the US Food and Drug Administration (FDA) and is the preferred therapeutic approach for treating RA in patients who have had a poor response to anti-TNFs or methotrexate. The effectiveness of combination therapy with rituximab and methotrexate has been highlighted in different randomized clinical trials in patients who have inadequate response to methotrexate alone or methotrexate plus anti-TNFs (Cohen et al., 2006; Edwards et al., 2004; Lopez-Olivo et al., 2015).

Table 2 Summary of clinical monitoring of antirheumatic drug therapy

Drug	*Toxicities requiring monitoring*	*Symptoms to inquire about*
NSAIDs and salicylates	Renal impairment, GIT ulcer and bleeding	Hematochezia, melena, dyspepsia, nausea/vomiting, weakness, dizziness, abdominal pain, edema, weight gain, and SOB
Corticosteroids	Hyperglycemia, hypertension, and osteoporosis[a]	Blood pressure if available, polydipsia, polyuria, edema, SOB, visual changes, weight gain, headaches, and bone pain
Azathioprine	Hepatotoxicity, myelosuppression, and lymphoproliferative disorders	Symptoms of myelosuppression (fatigue, bleeding or bruising, infection), jaundice
Hydroxychloroquine	Macular injury, diarrhea, and rash	Visual changes (reduction in night or peripheral vision), rash, diarrhea
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, fibrosis, stomatitis, and rash	Symptoms of myelosuppression, SOB, nausea/vomiting, lymph node swelling, jaundice, coughing, mouth sores, and diarrhea
Leflunomide	Hepatitis, GIT distress, and alopecia	Gastritis, nausea/vomiting, diarrhea, hair loss, and jaundice
Sulfasalazine	Melosuppression, rash	Symptoms of myelosuppression, photosensitivity, rash, and nausea/vomiting
Etanercept, Adalimumab, and Anakinra	Local injection-site reactions, infection	Symptoms of infection
Infliximab, Rituximab, and Abatacept	Post infusion reactions, Immune reactions, and infection	Symptoms of infection

GIT, Gastrointestinal tract; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SOB*, shortness of breath.

[a]Osteoporosis usually does not occur at the beginning of the treatment; however, patients should take precautionary measures to avoid bone loss.

Source: American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum. 39, 723–731.

Rituximab is administered parentally at a dose of 1 g over 2 weeks, in addition to premedication with methylprednisolone (100 mg) and an antihistamine to prevent the risk of infusion-related side effects.

T-lymphocyte Co-Stimulation Blocker

Abatacept is the only approved T-cell activation inhibitor. It binds to CD80/CD86 receptors and prevents the interaction between T-cells and antigen presenting cells (APCs). Thus, T-cells are unable to become active, and the inflammatory cascade produced by T-cells is blocked. Patients who do not clinically benefit from TNF inhibitors can benefit from abatacept (Genovese et al., 2005; Maxwell and Singh, 2010; Rubbert-Roth and Finckh, 2009).

Abatacept can be given via intravenous (IV) and subcutaneous (SC) routes, but the dose is based on the body weight of patients when given as an IV preparation. For example, 500 mg is given if the patient's weight is less than 60 kg, 750 mg is given to patients whose weight is in between 60 and 100 kg, and patients who are over 100 kg receive 1000 mg. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks subsequently.

Abatacept causes nasopharyngitis, dizziness, cough, headache, nausea, back pain, dyspepsia, and urinary tract infections (UTIs). However, despite these side effects, it is well tolerated by RA patients (Schiff et al., 2008). The summary of major clinical monitoring parameters of anti-rheumatic drug therapy is indicated in **Table 2**.

Interleukin Inhibitors

Interleukins such as interleukin-1 (IL-1) and interleukin-6 (IL-6) are inflammatory mediators that cause joint destruction in RA patients by driving inflammation and multiplication of synovial cells. Tocilizumab (an IL-6 inhibitor) and anakinra (an IL-1 inhibitor) are the only approved drugs in this class to treat RA (Cohen et al., 2002; Smolen et al., 2008). Headache, arthralgia, upper respiratory tract infection, and nasopharyngitis are most frequent side effects with the use of interleukin inhibitors.

Protein Kinase Inhibitors

Janus kinase (JAK) is a type of tyrosine kinase that helps in signaling cytokines and factors important for the growth of the immune system and hematopoiesis. Tofacitinib is the only FDA-approved bDMARD that can be taken orally at a dose of 10 mg/day in moderate to severe RA patients who have had an inadequate response or are intolerant to methotrexate (Lee et al., 2014; van Vollenhoven et al., 2012). The side effects of Tofacitinib are headache, nasopharyngitis, upper respiratory tract infection, diarrhea, and elevated cholesterol levels.

Nonpharmacological Management

The management of RA is not limited to drugs, but nonpharmacological interventions also play a vital role. These interventions include physical activity, appropriate rest, weight reduction, occupational therapy, and surgery (Vlieland and van den Ende, 2011).

Physical Activity

Many of the RA patients are not physically active because of disease complications, including cachexia (accelerated loss of muscles). Thus, quality of life is reduced. Hence, the comprehensive management of RA also includes physical activity that helps in regaining the muscle strength to do daily activities (de Jong and Vlieland, 2005). Numerous studies advocate the advantages of exercise in RA patients without affecting their joints (Metsios et al., 2007; Plasqui, 2008; Veldhuijzen van Zanten et al., 2015). Patients should be encouraged to perform aerobic and moderate exercise as a part of their therapy (Cooney et al., 2011; Stenström and Minor, 2003). Effectiveness of physiotherapy and exercise (aerobic, joint flexibility, and muscle strength) in RA improves fitness, enhances psychological status, reduces pain and fatigue, and has a positive effect on functional capacity, without exacerbating RA or accelerating joint damage.

Occupational Therapy

Occupational therapy (OT) helps RA patients by providing them with the necessary training and counseling about joint protection to overcome disease associated barriers. It further offers assistive devices, such as walkers, canes and splints, to encourage patients to maintain or improve their mobility (Steultjens et al., 2002). There is good evidence that psychological interventions (e.g., relaxation, stress management, and cognitive coping skills) have a beneficial impact on pain and functional ability, and that stress reduction techniques and cognitive behavioral therapy could improve some aspects of psychological status.

Weight Reduction and Surgery

The stress of inflamed joints reduces with the reduction in weight in RA patients. However, healthy weight reduction strategies could be used under the supervision of a qualified health-care professional to get maximum clinical benefits (Sparks et al., 2017). Surgeries such as synovectomy and joint replacement are only done in patients suffering from the severe forms of RA (Ali and Khalid, 2016).

Dosage Forms

Antirheumatic drugs are available in different dosage forms with different strengths. Detailed information about dosage forms, strength, and route of administration is shown in **Table 3**.

Dose Tapering

The sustained remission in RA is possible by using conventional and DMARD therapy. Dose tapering has become a thought-provoking concept in patients who have controlled RA completely by antirheumatic drug therapy because of higher risk of adverse effects that outweigh the benefits. A tailored approach is needed in patients to provide the optimal management of RA (Schett et al., 2016). However, this process demands great caution as the disease may flare up at any time. Thus, continuous monitoring is recommended to resume DMARD therapy if required (O'Mahony et al., 2010). There are no approved criteria to deescalate or withdraw antirheumatic drugs in RA patients. Gradual dose tapering over a period of 6 months is recommended by the American College of Rheumatology.

Role of the Pharmacist in the Management of Rheumatoid Arthritis

To manage RA, pharmacists are engaged primarily in compounding, screening of diseases, improving patient safety, counseling, and encouraging adherence to drug therapy. A community pharmacist is the only health-care professional who could be accessed easily by RA patients to refill their prescriptions and to get answers to some of their medical queries.

In hospital settings, pharmacists are involved in dispensing drugs, discharge counseling, medication reconciliation, and providing suggestions or treatment options for RA patients during ward rounds with physicians.

Role in Medication Management

A pharmacist can have a significant role in medication management for RA patients, including (Carissa Flick, 2013):

- Designing drug-use policies
- Developing pharmaceutical care services for RA patients
- Providing drug information
- Developing treatment guidelines and protocols for managing RA
- Monitoring patients and reporting side effects

Role in Pharmaceutical Care Services

The role of pharmacists in providing pharmaceutical services to RA patients is (Carissa Flick, 2013) as follows:

- Establishing a trusting relationship with patients
- Obtaining the history of patients

Table 3 Information about selected antirheumatic preparations

Generic	*Brand*	*Dosage form and strength*	*Route of administration*
NSAIDs			
Aspirin/acetylsalicylic acid	Easprin	Regular, enteric-coated, buffered 81, 165, 325, 500, 650, 800 mg tablets; 81, 650, and 800 mg timed- or extended-release tablets	Oral
		120, 200, 300, 600 mg suppositories	Rectal
Celecoxib	Celebrex	100, 200 mg capsules	Oral
Diclofenac	Cataflam, Voltaren	50 mg tablets; 25, 50, and 75 mg delayed-release tablets; 100 mg extended-release tablets	Oral
Diflunisal	Dolobid	250, 500 mg tablets	Oral
Fenoprofen	Nalfon	200, 300 mg capsules; 600 mg tablets	Oral
Flurbiprofen	Ansaid	50, 100 mg tablets	
Ibuprofen	Motrin	100, 200, 400, 600, 800 mg tablets; 50, 100 mg chewable tablets; 200 mg capsules; 100 mg/2.5 mL suspension, 100 mg/5 mL suspension	Oral
Indomethacin	Indocin	25, 50 mg capsules; 75 mg sustained-release capsules; 25 mg/5 mL suspension	Oral
		50 mg suppositories	Rectal
Meloxicam	Mobic	7.5, 15 mg tablets; 7.5 mg/5 mL suspension	Oral
Nabumetone	Relafen	500, 750 mg tablets	Oral
Piroxicam	Feldene	10, 20 mg capsules	Oral
Naproxen	Naprosyn	200, 220, 250, 375, 500 mg tablets; 375, 550 mg controlled-release tablets; 375, 500 mg delayed-release tablets; 125 mg/5 mL suspension	Oral
DMARDs			
Abatacept	Orencia	250 mg/vial lyophilized, for reconstitution for IV injection	Parenteral (IV)
Adalimumab	Humira	40 mg/0.8 mL for SC injection	Parenteral (SC)
Anakinra	Kineret	100 mg solution for SC injection	Parenteral (SC)
Auranofin	Ridaura	3 mg capsules	Oral
Etanercept	Enbrel	50 mg/mL, 25 mg powder for SC injection	Parenteral (SC)
Hydroxychloroquine	Plaquenil	200 mg tablets	Oral
Infliximab	Remicade	100 mg powder for IV infusion	Parenteral (IV)
Leflunomide	Arava	10, 20, 100 mg tablets	Oral
Methotrexate	Rheumatrex	2.5 mg tablet dose packs, 5, 7.5, 10, 15 mg tablets	Oral
Penicillamine	Cuprimine, Depen	125, 250 mg capsules; 250 mg tablets	Oral
Rituximab	Rituxan	10 mg/mL for IV infusion	Parenteral (IV)
Sulfasalazine	Azulfidine	500 mg tablets; 500 mg delayed-release tablets	Oral
Corticosteroids			
Methylprednisolone	Medrol	2, 4, 8, 16, 24, 32 mg tablets	Oral
Prednisone	Meticorten	1, 2.5, 5, 10, 20, 50 mg tablets; 1, 5 mg/mL solution and syrup	Oral

IV, Intravenous; *SC*, subcutaneous.

Source: Daniel, E., Furst, R., W. U., 2007. Basic and Clinical Pharmacology, McGraw-Hill Education, New York.

- Dispensing drugs
- Monitoring RA patients to determine the effects of medication
- Identifying and preventing or resolving medication-related issues
- Patient education

RA Medication Assessment Tool

Pharmacists can make a substantial contribution by developing medication assessment tools when working with a RA team to improve the standards of care provided. Medication assessment tool helps ensure that doctors comply with guidelines for prescribing drugs (Whitman et al., 2018). Such tools are of great importance to determine issues related to pharmaceutical care and gaps in the official guidelines. This can only be done through efforts of a multidisciplinary team that includes pharmacists. RA medication assessment tool (RhMAT) is one example where the pharmacist can collaborate with other health-care professionals to help and improve the pharmaceutical care of RA patients (Grech et al., 2015). There are 11 sections with 54 criteria for RhMAT. The 11 sections are as follows:

1. Diagnosis of RA
2. Use of analgesics and nonsteroidal anti-inflammatory drugs

3. Use of methotrexate
4. Use of sulfasalazine
5. Use of hydroxychloroquine
6. Use of leflunomide
7. Use of sodium aurothiomalate parenteral preparation
8. General screening for biological therapies
9. Use of biological therapies
10. Use of glucocorticoids
11. Handling remission cases

Clinicians can select any response from four choices starting from not applicable (N/A), adherence (yes), nonadherence (no), and inadequate data to select any criterion. This tool is very useful for pharmacists to rationalize the pharmacotherapy offered to RA patients by identifying gaps in treatment strategies, thereby improving the quality of life of RA patients (Grech et al., 2015).

Role in Decision Making

Pharmacists play an important role in the decision-making process to start DMARD therapy to treat RA patients. The monitoring of drug therapy becomes crucial before and during therapy if patients do not have any prior information. There is a need for baseline information about complete blood count, liver enzymes, and serum creatinine before starting RA treatment (Francart, 2013).

Community pharmacists provide a free service called Medicine Use Review (MUR) for RA patients in the United Kingdom, where patients can discuss any concerns they have about their medication. The purpose behind a MUR is to improve patient adherence and understanding of their medications. Where clinically appropriate pharmacists may suggest a few changes in drug therapy to get the optimal benefit from the medication, which may be discussed with the patient's GP.

Role in Patient Counseling

There is a need to design customized counseling guidelines for RA patients so pharmacists can provide rational and risk-free delivery of medication. Pharmacists working in different health-care settings can provide education and counseling to enable RA patients to comply with their dosage regimen appropriately. Different interventions based on counseling and education, including oral and written information for patients with diabetes, AIDS, asthma, and cardiac diseases, have shown a positive impact on their health (Mitchell et al., 2011; Penn et al., 2011; Saini et al., 2011; van Geffen et al., 2011). Designing similar interventions for RA patients has the potential to improve their quality of life.

The most important purpose of patient counseling is to enhance patient's compliance with drug therapy. Medication adherence is often a critical challenge in patients suffering from chronic diseases such as RA. More than half (55%) of the patients with osteoporosis stop taking medication after the first year, and similarly low medication adherence (as low as 38%) has also been detected in RA patients. Different factors that affect medication adherence are age, marital status, patient beliefs, socioeconomic status, and presence of comorbidities (Chua et al., 2018; Suh et al., 2018).

Pharmacists are the integral part of a multidisciplinary team (MDT) that comprises physicians, nurses, and pharmacists to treat RA. The major fears of patients about drug therapy are related to safety, cost, and indication for use. By using motivational messages during counseling to RA patients about the adverse effects of antirheumatic medication, how to take the drugs, dietary modifications, and justification for their use can improve adherence to their pharmacotherapy regimen (Kreps et al., 2011).

Pharmacists are expert in interpretation and analysis of the literature. By using this skill, they can arrange face-to-face educational sessions with RA patients to improve the understanding of the patient's drug therapy. Different studies have highlighted that health-care professionals are unable to provide detailed information about the side effects of drugs (Auyeung et al., 2011; Saini et al., 2011; Schmitt et al., 2011). Pharmacist can fill this gap by focusing more on providing side effects related information to RA patients.

Role in the Interprofessional Team

Pharmacists are the most neglected and under-used member of the health-care professional team despite their accessibility (Giberson et al., 2011). Most patients assume that the role of pharmacists is restricted to dispensing medication, but pharmacists also provide direct patient care related services in different hospital settings. A teamwork approach adopted by all health-care professionals to optimize the health benefits is already in use (Florentinus et al., 2006). There is a need for active collaboration among all members of a well-defined health-care team to treat and manage RA. Pharmacists through their education have the skills and abilities to prevent and solve drug-related problems that RA patients encounter. The partnership of the pharmaceutical care practitioner with all stakeholders will maximize the benefits of RA patients (Dupotey and De Oliveira, 2009; Dupotey Varela et al., 2011).

Different multidisciplinary and interprofessional models of care have shown positive outcomes in the management of numerous chronic disease such as diabetes, psychiatric disorders, infectious, and cardiac diseases (Archer et al., 2012; Holland et al., 2005; Sherer et al., 2002; Stellefson et al., 2013). The management of RA is difficult as it targets more than one system, affects different age

Table 4 Important drug–drug interactions of antirheumatic drugs.

Antirheumatic drug	*Interacting drug*	*Manifestations*	*Level of severity*
Glucocorticoids (GC)	Warfarin	↑ INR	Severe
	Fluoroquinolones	Tendon rupture	Moderate
	Azole antifungals	↑ GC adverse effects	Moderate
Methotrexate (MTX)	Co-trimoxazole	MTX toxicity	Severe
	PPIs	MTX toxicity	Severe
	Hepatotoxic drugs	Hepatotoxicity	Severe
	Nephrotoxic drugs	Nephrotoxicity	Severe
Leflunomide (LEF)	Warfarin	↑ INR	Severe
	Cholestyramine,	↓ Efficacy of LEF	Severe
Azathioprine (AZA)	Allopurinol	AZA toxicity	Severe
	Warfarin	↓ INR	Severe
Ciclosporin	CYP3A4 inhibitors	↑ Ciclosporin toxicity	Moderate to very severe
	Statins	Statin toxicity	very severe
Cyclophosphamide	Allopurinol	Myelosuppression	Moderate

csDMARDs, Conventional synthetic DMARDs such as methotrexate and hydroxychloroquine; *DMARD*, disease-modifying antirheumatic drug; *INR*, international normalized ratio; ↑, increases; ↓, decreases; *tsDMARDs*, targeted synthetic DMARD such as adalimumab and abatecept.

(A) Early treatment phase. (B) Treatment approach if methotrexate (plus glucocorticoid) does not achieve the treatment target. (C) Treatment approach after a first biologic has failed.

Moderate level: Significant changes in pharmacokinetic parameters (C-max increased by 25%–99%, C-max reduced by 20%–49%, AUC increased by 25%–199%, AUC reduced by 25%–59%).

Severe level: Excessive changes in pharmacokinetic parameters (above the ranges given for moderate interactions) requiring one/both drug dosage adjustment in most patients to prevent adverse events or toxicity.

Very severe level: Excessive changes in pharmacokinetic parameters associated with adverse events, toxicity and hospitalization and/or death or considered as contraindication.

Source: Adapted with permission from Lancet: Hromadkova, L., Soukup, T., Vlcek, J., 2012. Important drug interactions in patients with rheumatic disorders: interactions of glucocorticoids, immunosuppressants and antimalarial drugs. Drugs Today, 48, 545; Smolen, J.S., Aletaha, D., Mcinnes, I.B., 2016. Rheumatoid arthritis. Lancet, 388, 2023–2038.

groups, and requires specialized education for drug administration. The presence of an interprofessional team, including a pharmacist, is an ideal way to cope with such problems because pharmacists are expert in medication therapy management. This type of pharmacist-based care is already in practice in different rheumatology clinics in many countries (Dennis et al., 2008; Rowley et al., 2007; Wilbur and Kur, 2015). For example, in the United Kingdom, pharmacists work in collaboration with consultant rheumatologists and in the capacity as independent prescribers. They are involved in medication reviews, to screen for contra-indications, to agree a clinical management plan (CMP) with the patient and the clinic consultant, and to optimize currently prescribed treatment. A number of follow-up appointments are offered to new patients at which pharmacists evaluate the effectiveness of any pharmaceutical intervention and either add new medicines or dose titrate existing medicines according to the CMP (Thomas, 2005).

Important Drug–Drug Interactions

The chronic nature of RA with multiple drugs of different combinations used to prevent the progression of disease most RA patients are older adults with comorbidities, so these factors amplify the risk of adverse effects and drug–drug interactions. It is better to avoid or manage such interactions by providing appropriate awareness. The most common drug–drug interactions are highlighted in **Table 4**.

Role of Primary and Secondary Care

Early diagnosis and treatment of RA can help in achieving optimal therapeutic outcomes. A large set of studies advocate the commencement of antirheumatic drug therapy within 3 months of disease onset (Hochberg, 1999; Quinn et al., 2001). There is a need to provide sufficient resources to meet this timely delivery of DMARDs in primary and secondary care. Primary care is usually offered by a general physician (GP) or family physician, and secondary care is provided in referral cases because of disease complications. It is possible to manage RA patients in primary care effectively by a MDT approach. Different hospitals have established a primary care-based rheumatology service to prevent unnecessary referral of RA patients. This not only improves patient care but also reduces wasted time (Critchley and Ball, 2007). Continuous educational programs for GPs can further help in managing RA in primary and secondary care (Wise and Isaacs, 2005).

Conclusion

The major therapeutic target in RA is the reversal of inflammation because it is the apex of all the clinical events. Thus, a multifaceted and strategic approach is required to treat RA, including nonpharmacologic (physical activity, appropriate rest, weight reduction,

and occupational therapy) and pharmacologic therapies (nonsteroidal anti-inflammatories (NSAIDs), analgesics, corticosteroids, biologics, and nonbiologic DMARDs). In managing RA, pharmacists are working in a community or hospital setting involved in dispensing of drugs, screening of diseases, improving patient safety, counseling, and ensuring adherence to drug therapy.

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Management of Eye and Ear Disorders and the Pharmacist's Role: Glaucoma

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Glaucoma

Glaucoma is the leading cause of irreversible *preventable* blindness around the world and second to cataracts for causing blindness around the world (World Health Organization, 2012). The World Health Organization has estimated that in 2010 glaucoma accounted for 8% of global blindness and 2% of visual impairment (World Health Organization, 2012). Glaucoma refers to a group of conditions that are defined as "progressive optic neuropathy with characteristic structural damage to the optic nerve and characteristic visual field defects" (Gupta and Weinreb, 1997). Although raised intraocular pressure (IOP) is recognized as an important risk factor, it is not a defining characteristic of glaucoma (Gupta and Weinreb, 1997). Hence, patients may have a raised IOP without having glaucoma, known as ocular hypertension, or may have glaucoma without having a raised IOP, known as "normal-pressure" glaucoma (Tezel et al., 1996).

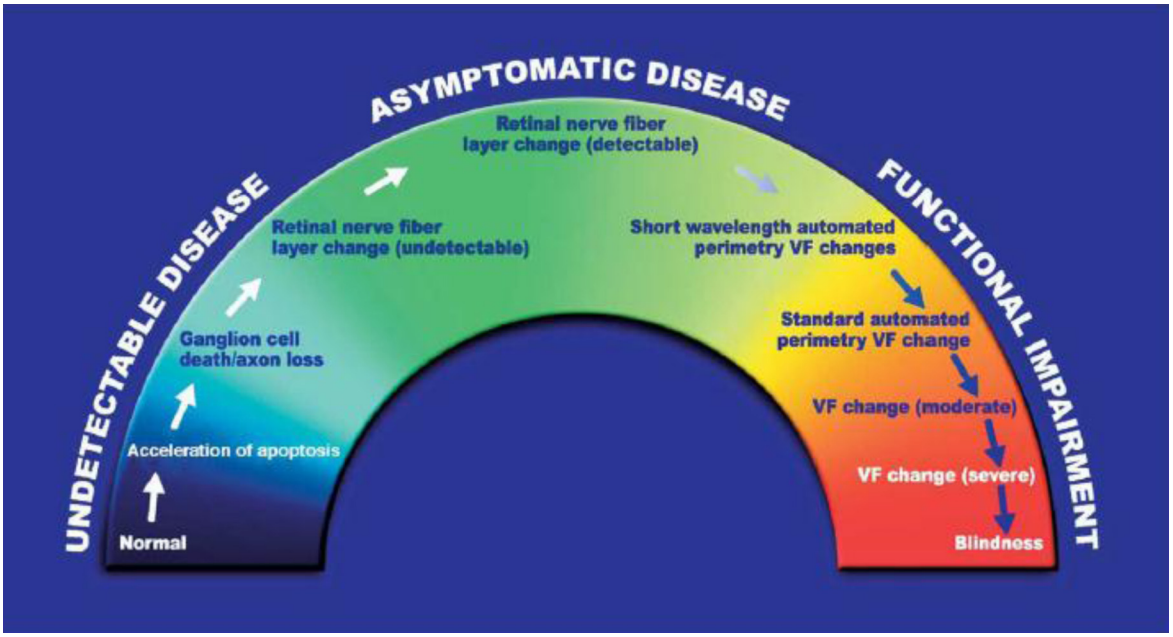

Figure 1 The glaucoma continuum. *Source: Reproduced from Weinreb, R.N., Friedman, D.S., Fechtner, R.D., et al. Risk assessment in the management of patients with ocular hypertension. Am. J. Ophthalmol. 138 (3) (2004) 458–467 (Weinreb et al., 2004).*

Structural damage associated with glaucoma is detected by examining the optic disk and surrounding retinal nerve fiber layer, whereas functional loss is detected by automated visual field testing. Initial structural damage to the optic nerve and retina are asymptomatic and often undetectable with current diagnostics (Weinreb et al., 2004). Glaucoma is considered a continuum (**Fig. 1**) where undetectable disease progresses to asymptomatic disease with optic nerve and visual field (VF) changes, then progresses on to visual impairment and eventually the risk of blindness. Visual impairment from glaucoma is usually observed as "tunnel vision" from preferential loss of mid-peripheral vision (Taylor et al., 2008). Once functional visual impairment from glaucoma is present, the disease is already at an advanced stage on the continuum with more than 30% of retinal ganglion cell axons damaged or dead (Broadway, 2012). Screening and treatment of patients in the asymptomatic disease state is important to arrest, delay, or limit progression of early optic nerve damage to significant visual impairment.

The glaucomas are classified in part on the anatomical configuration of the drainage pathways at the iridocorneal angle (King et al., 2013). Normally, aqueous humor is produced by the ciliary body and leaves the anterior chamber via the trabecular meshwork and Schlemm's canal (conventional outflow) or via the ciliary muscle, through the sclera and into the orbit (uveoscleral or unconventional outflow) (**Fig. 2**A) (Grehn and Stamper, 2009a). Normally, 90% of the aqueous is drained through the trabecular outflow, the remaining 10% through the uveosclearal outflow route (Olver and Cassidy, 2005). In open angle glaucoma, the aqueous outflow via the trabecular meshwork is generally restricted, increasing IOP (**Fig. 2**B) (King et al., 2013). Primary open angle glaucoma (POAG) is the most common type of glaucoma and has been estimated to account for 70% of cases (King et al., 2013).

In primary angle-closure glaucoma (PACG), the iridocorneal angle is narrow (between the iris and cornea). When these structures are close together, even intermittent contact may affect trabecular function, later adhesions may form between them; drainage of the aqueous is affected (**Fig. 2**C) (King et al., 2013). This obstruction of draining pathways by the iris increases IOP and results in glaucoma.

Glaucoma can also be classified as "primary" (no identifiable cause) or secondary. Secondary glaucomas can result from comorbidities such as uveitis, rubeosis associated with ocular ischemia from vascular occlusion or diabetes, exfoliation syndrome, or after ophthalmic surgery (e.g., retinal detachment surgery) (King et al., 2013).

Epidemiology

In 2013, the total number of people (aged 40–80 years) estimated to have glaucoma globally was 64.3 million (3.5% of the population) (Tham et al., 2014). Based on the United Nations' classification of macro-geographic continental regions (Asia, Africa, Europe, North America, Latin America and the Caribbean, and Oceania), Asia had over 60% of the world's glaucoma cases: 53% of global POAG persons and 77% of global PACG sufferers. Africa had the second highest number of glaucoma cases with 8.3 million (13% of the world's total glaucoma cases).

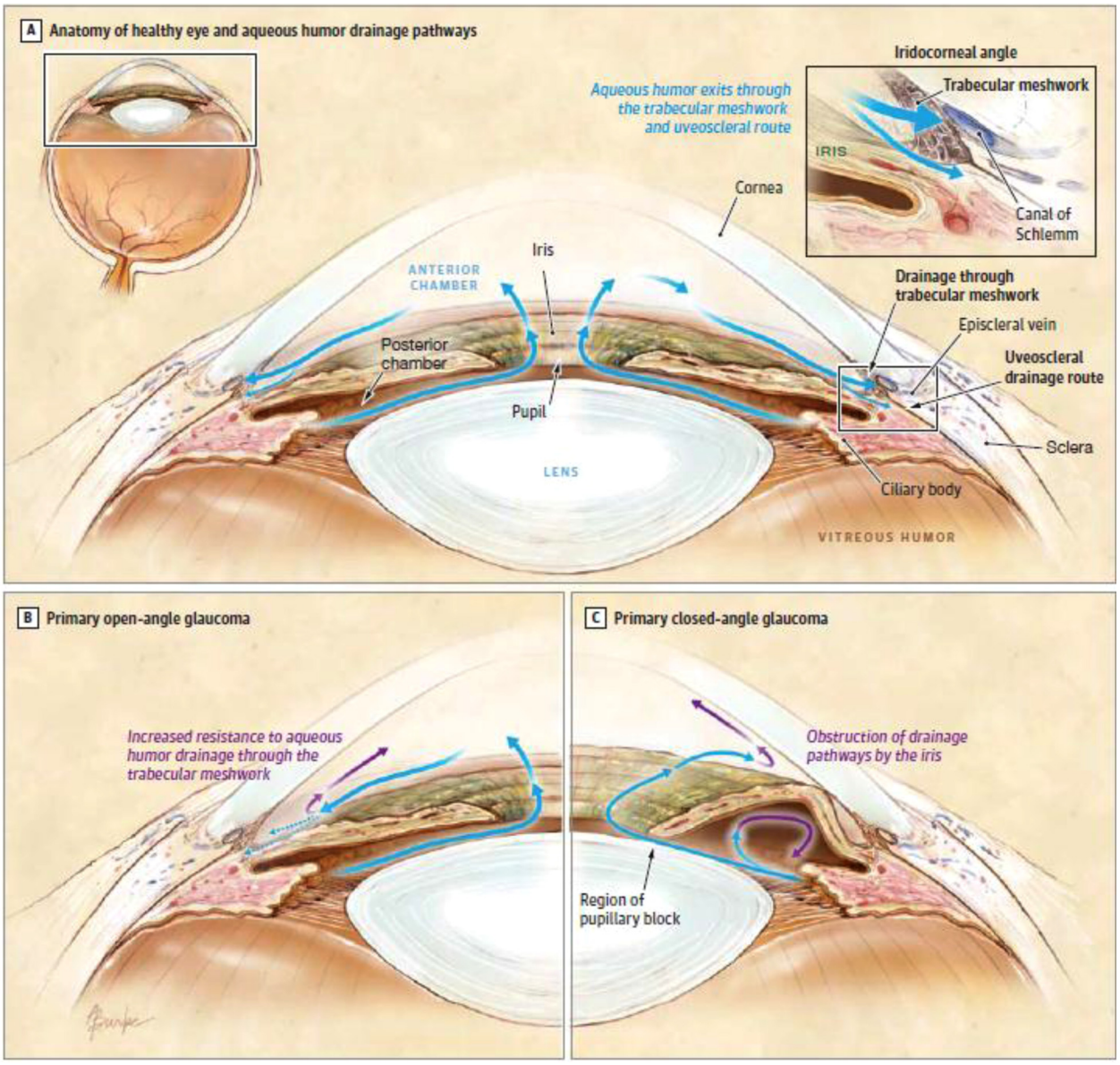

Figure 2 Aqueous humor drainage pathways. *Source: Reproduced from Weinreb, R.N., Aung, T., Medeiros, F.A. The pathophysiology and treatment of glaucoma: a review. JAMA 311 (18) (2014) 1901–1911. (Weinreb et al., 2014).*

By 2020, the number of people (aged 40–80 years) with glaucoma worldwide has been predicted to increase by 18.3% to 76 million and to 111.8 million by 2040. Many of these increases are attributable to Asian and African communities.

Pathophysiology

While the pathophysiology of glaucoma is not well understood, there is a strong association between IOP levels and retinal ganglion cell death (Weinreb et al., 2014). IOP can cause mechanical stress on the posterior structures of the eye, notably the lamina cribrosa and adjacent tissues (**Fig. 3**) (Quigley et al., 1981), provoking structural damage at the lamina, the weakest site in the wall of the pressurized eye, where retinal ganglion cell axons exit. Hence, increased IOP may compress, deform, and remodel the lamina cribrosa, thereby damaging retinal ganglion cell axons. By possibly disrupting axonal transport, IOP may interrupt retrograde delivery of essential trophic factors to retinal ganglion cells from their brain target regions (Fechtner and Weinreb, 1994).

Neurodegenerative changes associated with glaucomatous optic neuropathy also occur in individuals with IOP within the normal range. This may be caused or exacerbated by low cerebrospinal fluid pressure in the optic nerve subarachnoid space. This

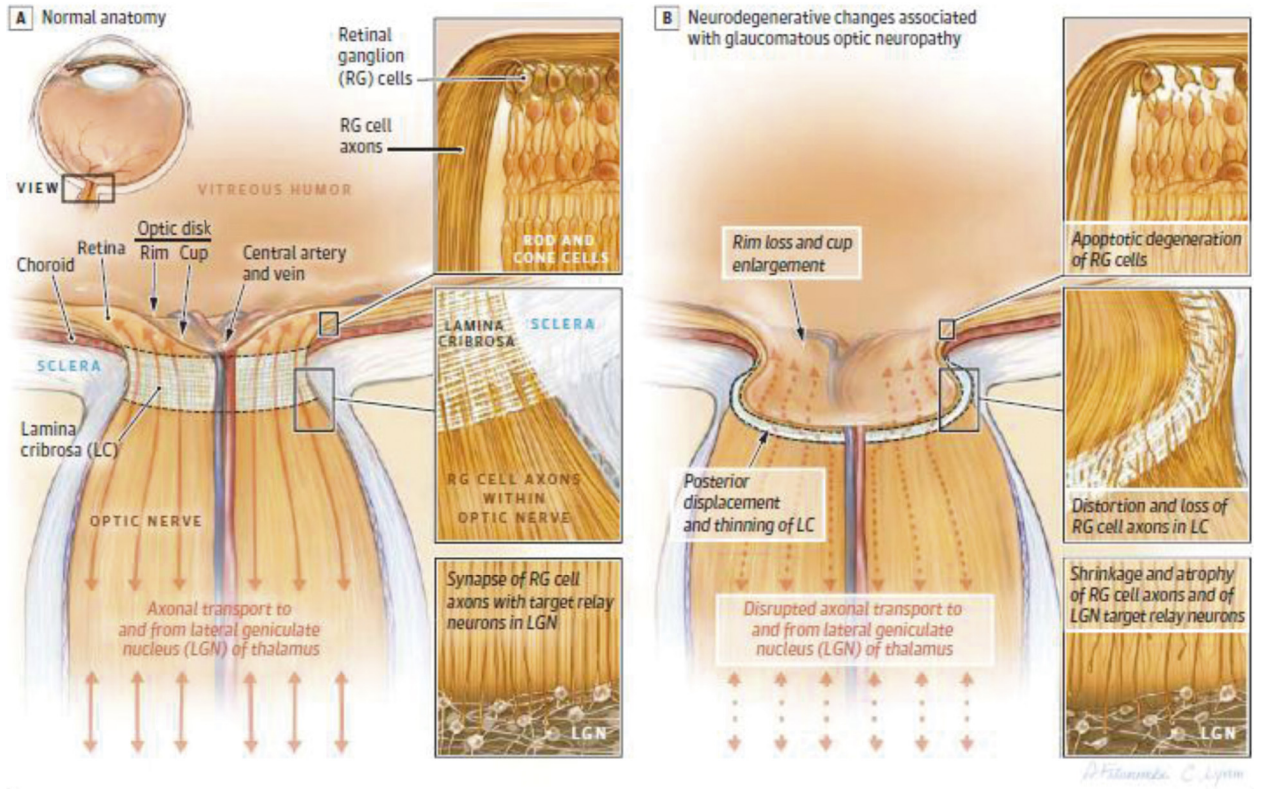

Figure 3 Normal anatomy and neurodegenerative changes associated with glaucomatous optic neuropathy *Source: Reproduced from Weinreb, R.N., Aung, T., Medeiros, F.A. The pathophysiology and treatment of glaucoma: a review. JAMA 311 (18) (2014) 1901–1911. (Weinreb et al., 2014).*

results in an abnormally large pressure gradient across the lamina (Wang et al., 2012). Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress may also contribute to glaucoma (Weinreb et al., 2014).

Risk Factors for Glaucoma

Risk factors for glaucoma are identified through a comprehensive patient history and a full ocular examination by suitably trained health-care providers. For the purposes of this chapter, only risk factors that can be identified with a patient history will be presented. Ocular signs identified by a full ocular examination will be discussed under "Diagnosis" as they identify definite or highly likely glaucoma.

Age

Advancing age is a major risk factor for glaucoma. In the Melbourne Visual Impairment Project, participants aged 50 years and older were more likely to have glaucoma (odds ratio range: 2.6–17.6) than those aged 40–49 (Weih et al., 2001a). In particular, those aged 80 years and older were 17 times more likely to have glaucoma than participants aged less than 50 years (Weih et al., 2001a).

Family History

A family history for glaucoma is another major risk factor for glaucoma. It has been estimated that individuals with first-degree relatives diagnosed with glaucoma have ten times the risk of developing glaucoma compared with the general population, adjusting for age and other risk factors (Mitchell et al., 2002; Tielsch et al., 1994; Weih et al., 2001b; Wolfs et al., 1998). A criticism of most of these studies is that they rely on self-reported family history of glaucoma rather than clinical examination of relatives, which may result in recall bias. However, Wolfs et al. confirmed a positive family history by examining first-degree relatives and also showed this association (Wolfs et al., 1998).

Ethnic Origin

People of African descent were reported to have four times the risk of developing glaucoma compared with Caucasians, adjusting for age (Tielsch et al., 1991). Optic nerve glaucoma damage is reported at least a decade earlier in people of African descent rather than Caucasian ancestry (Leske et al., 1994; Mason et al., 1989).

Prevalence of PACG has been reported to be highest among those of Chinese, Mongolian, Vietnamese, Pakistani, or Inuit descent, with rates in these populations reported to be over three times that of other ethnic groups (Bourne et al., 2001; Stein et al., 2011).

Diabetes Mellitus

A recent meta-analysis of 47 studies showed that the pooled relative risk of having POAG in patients with diabetes mellitus compared with those without diabetes was 1.48 (95% CI, 1.29–1.71) (Zhao et al., 2015). In this meta-analysis, the risk of POAG increased by 5% for each year since diabetes mellitus was diagnosed (Zhao et al., 2015). Hence, both the presence of diabetes and its duration appear to be associated with a significantly increased risk of glaucoma.

Myopia

Pooled relative risk from four studies of POAG among participants with myopia compared with nonmyopic studies was estimated to be 1.88 (95% CI, 1.53–2.31) (Burr et al., 2007). More recently, the Los Angeles Latino Eye Study also showed an independent relationship between longer axial length (axial myopia) and OAG (Kuzin et al., 2010). Perhaps individuals with axial myopia have weaker scleral support at the optic nerve head, placing them at greater risk of glaucomatous damage (Kuzin et al., 2010).

Smoking

A systematic review and meta-analysis of six studies found that people that smoked cigarettes had an odds ratio of 1.37 (95% CI, 1.00–1.87) for having glaucoma compared with nonsmokers (Bonovas et al., 2004). Past smokers had no increased risk (OR = 1.03, 95% CI, 0.77–1.38) (Bonovas et al., 2004).

Other Factors—Long-term Steroid Users, Migraine and Peripheral Vasospasm, Hypertension

Several factors have been associated with glaucoma, but the strength of those associations has not been established. From a pharmaceutical perspective, corticosteroids are the main cause of drug-induced glaucoma, which is a secondary glaucoma (Adis International, 2004). Steroids administered via multiple routes (oral, inhaled, topical ophthalmic, and topical skin) may increase IOP (Kersey and Broadway, 2006). Case–control and retrospective data of prolonged nasal and inhaled corticosteroid appear to be associated with developing glaucoma (Kersey and Broadway, 2006); however, the cumulative dosage that poses a risk has not been ascertained (Leone et al., 2003).

Migraine and peripheral vasospasm (Raynaud's) are risk factors for glaucomatous optic nerve damage (Budenz et al., 2006; Mitchell et al., 1996). These conditions may decrease autoregulation of optic nerve head blood flow causing an increased risk of optic nerve damage (Park et al., 2014).

Systemic arterial hypertension and its treatment appear to be significant risk factors for glaucoma. Although numerous studies have presented conflicting data, this may stem from the extent potential confounders were or were not adjusted for (Bonomi et al., 2000; Leske et al., 1995; Quigley et al., 2001; Tielsch et al., 1995). For instance, Newman Casey et al. (2011) found that when adjusting for diabetes and hyperlipidemia, patients with systemic arterial hypertension had a 17% increased risk of developing OAG (95% CI, 13–22%) (Newman-Casey et al., 2011). Systemic arterial hypertension may increase glaucoma due to increased perfusion of the ciliary body, resulting in increased aqueous production and higher IOP (Bulpitt et al., 1975), decreased perfusion to the optic disk from damaged and sclerotic arterioles (Wolf et al., 1993), or treatment of systemic arterial hypertension with antihypertensives causing systemic hypotension and a reduction in perfusion of the optic nerve (Graham and Drance, 1999).

Angle Closure Glaucoma

The American Academy of Ophthalmology (2016) states that risk factors for developing angle closure glaucoma are family history of angle closure (AC); advancing age; female gender; Chinese, Vietnamese, Pakistani, or Inuit descent; hyperopia; short axial length; and shallow anterior chamber (American Academy of Ophthalmology, 2016). However, there is limited quantification of the risk (**Table 1**).

Diagnosis

Glaucoma can present in many ways, rarely as a medical emergency. A diagnosis of glaucoma is made based on the presenting history, a search for relevant risk factors, and an ocular examination to assess the structure and function of the eye. A comprehensive clinical examination usually includes slit lamp examination, tonometry, fundus and optic nerve head examination, gonioscopy, and corneal thickness measurement. Additional investigations may also be conducted to document the extent of structural damage to the optic nerve head and the retinal nerve fiber layer, using optic nerve and retinal nerve fiber layer analysis and/or disk photography, computer-assisted visual field (VF) analysis. Optic disk structural review is particularly important, as commonly a loss in disk neuroretinal rim and/or retinal nerve fiber loss is detected prior to VF loss.

Open Angle Glaucoma

Open angle glaucoma is generally symptomless in its early stages. It is not until significant neuronal damage has occurred that characteristic visual loss is observed. Ocular examination for open angle glaucoma should include an assessment of the (1) pupil, (2)

Table 1 Summary of risk factors from patient history for glaucoma

Risk	*Risk factor from patient history*[a]
Extremely high	IOP > 21 mmHg
(≥12×)	Age >80 years
High	Age > 50 years
(≥3×)	Family history
	Ethnic origin:
	• African (POAG)
	• Chinese, Vietnamese, Pakistani or Inuit descent (PACG)
Moderate	Diabetes
(≥1.5×)	Myopia (POAG)
Lower	Smoking
(>1×)	Steroid use[b]
	Migraine[b]
	Eye injury[b]
	High blood pressure[b]

IOP, Intraocular pressure; *POAG*, primary open angle glaucoma; *PACG*, primary angle-closure glaucoma.
[a]No statistic has been provided for this risk factor.
[b]The presence of ocular signs indicating possible glaucoma immediately raises risk.
Adapted from the National Health and Medical Research Council Guidelines for the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma (NHMRC, 2010).

anterior segment, (3) IOP, (4) central corneal thickness (CCT), (5) gonioscopy (to evaluate the anterior chamber angle to exclude AC or other causes), (6) optic nerve head and retinal nerve fiber layer evaluation, and (7) VF sensitivities.

Angle Closure

AC can present in either primary or secondary forms, in acute or chronic situations. Patients may also present with acute attacks superimposed on a chronic condition. When optic disk damage occurs, the eye is deemed to have progressed from primary angle closure (PAC) to PACG (American Academy of Ophthalmology, 2016).

Chronic PACG presents similarly to POAG. However, acute angle closure crisis (AACC) is associated with significant and distressing symptoms, and if left untreated, may cause permanent vision loss or blindness (American Academy of Ophthalmology, 2016). Symptoms of AACC include blurred vision, colored rings around lights, pain, frontal headache, palpitations and abdominal pain, and nausea and vomiting (American Academy of Ophthalmology, 2016). Although some cases of acute angle-closure crisis may be self-limited, any patient experiencing symptoms like these should be referred immediately.

Examination of Eye Structure

Glaucoma describes a group of eye diseases in which there is progressive damage to the optic nerve. This is characterized by specific structural abnormalities of optic nerve head and associated patterns of VF loss (Burr et al., 2004). Examination of the optic nerve head is conducted by assessing the optic disk and the retinal nerve fiber layer. Changes that occur in glaucoma include increasing excavation of the optic nerve head (also referred to as cupping), progressive loss of neuroretinal rim, and possibly optic disk margin hemorrhages.

Optic Disk

Retinal ganglion cell axons exit the eye through the posterior scleral foramen, which forms a truncated cone with a narrower neck internally and a broader base externally (Varma and Spaeth, 1993). The narrow internal neck of this cone is clinically visualized as the optic disk (Fig. 4) (Schacknow and Samples, 2010). The optic disk may be examined using a direct ophthalmoscope, with the patient's pupils dilated and the room darkened. A cup to disk ratio of approximately 0.3 is seen in a healthy optic nerve head (Fig. 4). However, an increased cup to disk ratio may indicate glaucoma. Direct ophthalmoscopy displays a magnified view of the optic disk with an appreciation of depth only possible with clues and experience. Indirect ophthalmoscopy performed on a slit lamp offers a magnified stereoscopic view of the optic disk and retinal nerve fiber layer, usually best with a dilated pupil.

A wide variety of digital and non-digital cameras are available to provide color images of the optic disk. Photography has an advantage over ophthalmoscopy as it provides a permanent baseline image of the optic disk that serves as a baseline for future comparisons.

Retinal Nerve Fiber Layer

The retinal nerve fiber layer can be highlighted or quantified in various ways. In nerve fiber photography enhanced with red-free illumination, the fiber bundles are seen as silver striations, radiating from the superior and inferior poles of the optic disk. In early

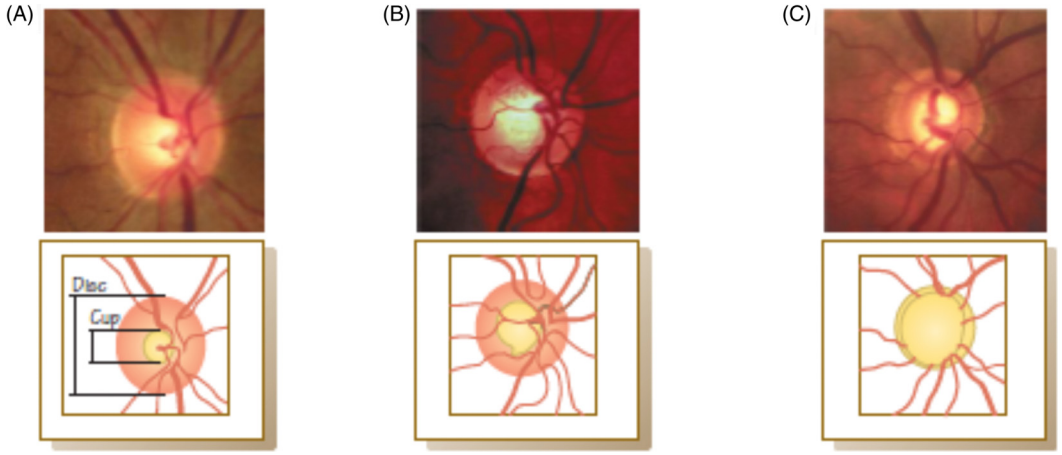

Figure 4 Normal and cupped optic nerve heads. (A) Normal disc (cup-disc ratio 0.3), (B) glaucoma: focal notch and (C) glaucoma: diffuse cup enlargement (cup-disc ratio 0.8) *Source: Reproduced from Olver, J., Cassidy, L., Jutley, G., Crawley, L., 2014. Ophthalmology at a Glance, second ed. Wiley Blackwell, Oxford, UK.*

glaucoma, estimation of structural abnormalities from serial nerve fiber layer photographs may be more sensitive than assessment of the optic nerve head itself (NHMRC, 2010).

Other methods include scanning laser ophthalmoscopy (Heidelberg Retinal Tomography), optical coherence tomography, and scanning laser polarimetry (GDx). Scanning laser ophthalmoscopy can provide objective, quantitative measures of the optic disk topography (Miglior et al., 2003), optical coherence tomography measures the thickness of the retinal nerve fiber layer before the axons reach the optic nerve head (high-resolution, cross-sectional, in vivo imaging of the human retina in a fashion analogous to B-scan ultrasonography, using near infrared (840 nm) light instead of sound) (Johnson et al., 2007), while scanning laser polarimetry provides an objective, quantitative measure of the retinal nerve fiber layer thickness by using the retardation of a reflected 780 nm polarized laser light source. No single test (or group of tests) appears to be more accurate than any other for diagnosing glaucoma (Burr et al., 2007).

Assessment of the Anterior Chamber

Assessment of the anterior chamber is essential to identify the risk of AC (supplemented by gonioscopy) and to identify other causes of glaucoma. These include sectoral iris atophy, glaukomflecken, posterior synechiae, and peripheral anterior synechiae. Signs of secondary glaucoma can also be identified such as uveitis, pigment dispersion (iris transillumination and pigment deposits on the corneal endothelium), exfoliation syndrome, and iris rubeosis (neovascular causes). In addition, on follow-up, signs of corneal epithelial toxicity, conjunctival hyperemia, and papillae can indicate adverse drug reactions (NHMRC, 2010). Gonioscopy allows observation of the angle of the anterior chamber including the angle anatomy and detection of appositional or synechial closure. It also determines the extent of any peripheral anterior synechiae (NHMRC, 2010). Gonioscopy of both eyes should be included in any glaucoma examination.

Examination of Eye Function

Optic nerve damage in glaucoma is characterized by specific structural abnormalities of the nerve fiber layer, optic nerve head, and patterns of VF loss (Burr et al., 2004). Glaucoma tends to produce localized areas of VF loss, while other conditions (e.g., cataracts) produce diffuse VF loss. Repeated and consistent VF measurements are required to diagnose glaucoma. As there are concerns about the reliability of VF testing, which is a subjective psychophysical test, a consistent examination approach that can be repeated over time is important.

Visual Field Testing

Standard automated perimetry (SAP) is the reference standard in VF examination of glaucomatous patients (NHMRC, 2010). It estimates the threshold sensitivity within the VF: target locations remain constant while the brightness is modified to determine sensitivity thresholds. SAP quantifies the reliability of a test and compares measured thresholds with an age-matched normal database. Examination of the visual fields in glaucoma is usually limited to the central 24–30° since almost all clinically relevant defects fall within this area (NHMRC, 2010). This test takes around 5–18 min to complete for both eyes, although newer software algorithms just released promise to reduce this by 50% (Burr et al., 2007).

Frequency doubling technology perimetry (FDT) is offered in a portable, relatively inexpensive instrument designed for fast and effective screening for VF loss. FDT is simpler to administer, reasonably tolerated by most patients, not greatly affected by refractive error and cataract, has high test-retest reproducibility, offers rapid screening tests, and has full threshold programs (NHMRC, 2010). In screening mode, it usually takes less than a minute to conduct in patients with a normal VF.

Oculokinetic perimetry (OKP) with the Damato chart is simple and inexpensive. Twenty numbers are located on a flat, white card within the central 30° of VF (Burr et al., 2007). The subject refixates from number to number, sequentially reporting whether the central 1.5-mm black spot remains visible or disappears. There is a 40-cm hinged arm that maintains the test distance and occludes the non-tested eye. Any points missed, other than the physiological blind spot area, are confirmed, before considered truly missed (Burr et al., 2004). It also has potential as a screening tool.

Intraocular Pressure Measurement

Glaucoma can be present in eyes with normal or raised IOP. However, IOP measurement remains core to diagnosis and management of glaucoma: it is the major modifiable risk factor for development and progression of glaucoma. With a "usual range" in most communities between 10 and 20 mm Hg, IOP is a continuous variable, with fluctuations.

Several instruments measure IOP, having either contact or no contact with the cornea. Applanation tonometry (e.g. Goldmann Applanation Tonometry, GAT) infers the IOP from the force required to flatten a constant area of the cornea (NHMRC, 2010). Noncontact tonometry uses rapid air pulses (air puffs) to flatten the cornea. IOP is estimated by detecting the force of the air jet at the instant of flattening (NHMRC, 2010).

Timing of Intraocular Pressure Measurements

As IOP varies throughout the day and night, IOP should be measured at different times (NHMRC, 2010). From 690 diurnal curves, a large proportion displayed an increased IOP in the morning with most peaks observed before noon (David et al., 1992). The usual diurnal variation is 3–6 mmHg (NHMRC, 2010). Although there is a decrease in aqueous production at night by about 50–60%, this does not account for the diurnal variation in IOP observed (Grehn and Stamper, 2009b). IOP measurements can also be affected by alcohol and marijuana (decrease IOP), rapid fluid intake (increases IOP), and posture (horizontal or head down position increases IOP) (NHMRC, 2010).

Central Corneal Thickness

The Goldmann Applanation Tonometer assumes an average CCT of 520 μm. A meta-analysis of values reported in the literature indicates that "normal" individuals have a significant variation in CCT (535 ± 31 μm) (Burr et al., 2007). This influences the accuracy of this IOP measurement. In thinner corneas, tonometers will read lower-than-true IOP values, while thicker corneas produce falsely high IOP values. There is no valid correction formula applicable to all individuals across the spectrum of measured IOP. A general approach is to correct by 1–3 mmHg per 40 μm deviation from 525 μm (NHMRC, 2010).

In contact tonometry, there is direct physical contact between the measuring instrument and the surface of the eye (Whitacre et al., 1993), raising concerns about transmissible disease. All equipment should undergo chemical disinfection after use to reduce the risk of cross infection (Whitacre et al., 1993). Salvi et al. (2005) recommend using disposable prisms for Goldmann and Perkins tonometry, or disposable covers for the Tono-Pen tip (Salvi et al., 2005). Disposable prism tonometry is potentially a reliable alternative to Goldmann Applanation Tonometry (Salvi et al., 2005).

In applanation tonometry, a specially calibrated disinfected probe attached to a slit lamp biomicroscope is used to flatten the central cornea by a fixed amount. As the probe makes contact with the cornea, a topical anesthetic eye drop is instilled. A yellow fluorescein dye is used in conjunction with a cobalt blue filter to highlight the circumference of flattened (applanated) cornea with a clearly defined end point. Insufficient fluorescein in the tear film falsely lowers readings, while excessive fluorescein falsely raises readings. Falsely elevated readings may also result from globe pressure from the eyelids (e.g., blepharospasm), digital pressure if the lids have to be held apart, obesity, a patient straining to reach the head/chin rest, patient breath holding, neck-constricting clothing, hair lying across cornea, or lens-corneal apposition (NHMRC, 2010).

Air puff (noncontact) tonometry is noncontact using a rapid air pulse to applanate the cornea. Applanation is detected via an electro-optical system. IOP is estimated by detecting the force of the air jet at the moment of applanation. Noncontact tonometry has the advantage of not requiring topical or general anesthesia and may be useful for patients uncooperative during applanation tonometry, or patients with corneal disease in whom contact tonometer cannot be accurately performed (NHMRC, 2010). Despite this, the puff of air may frighten some young children and make it difficult to get an accurate IOP reading (Lambert et al., 2013).

Rebound tonometry has shown to be useful in young children as it is better tolerated than noncontact tonometry (Lambert et al., 2013). Rebound tonometry uses a light probe that is propelled by an electrical-pulse generator that creates a magnetic field. After the probe strikes the cornea, it rebounds back into the instrument, causing a voltage change that is detected by a solenoid inside the tonometer. The IOP is calculated by the length of time the probe comes in contact with the cornea and the time it takes to rebound back into the tonometer. Due to its design, rebound tonometer is potentially less intimidating to young children (Lambert et al., 2013). In an observational study of 180 children, aged 6 months to 15 years, rebound tonometry successfully measured IOP in 89% of children compared with only 72% with noncontact tonometry (Kageyama et al., 2011). Also, as rebound tonometry is easy to perform with a handheld instrument, it has been used successfully by parents to monitor the IOP of their children in their homes, known as home tonometry (Flemmons et al., 2011).

Table 2 Intraocular pressure targets for primary open angle glaucoma

POAG stage	*Risk status*	*↓ IOP*	*Specified level*
Suspect	Low		No treatment
	Moderate	20%	
	High	20%	≤24 mmHg
Early	Unspecified		≤19 mmHg
Established	Moderate	20%	≤16 mmHg
	High	30%	Close to episcleral venous pressure
Advanced	Unspecified	30-50%	≤14 mmHg

Adapted from the National Health and Medical Research Council Guidelines for the Screening, Prognosis, Diagnosis, Management, and Prevention of Glaucoma (NHMRC, 2010).

Target Intraocular Pressure

A target IOP should be nominated at diagnosis, depending upon the glaucoma severity, presenting IOP, familial, and other risk factors. Usual recommendations suggest at least 25% reduction from baseline at diagnosis (Heijl et al., 2002; Leskea et al., 2004) with further 20% reductions if further progression occurs (Canadian Glaucoma Study Group, 2006). A lower IOP is set when glaucoma is more severe (Dally et al., 2003; Ederer et al., 2000). Target IOPs for POAG are outlined in **Table 2** and based on a 5-year prediction risk of POAG categorized as low (<5%), moderate (5–15%), and high (>15%). In normal tension glaucoma, a 30% IOP reduction or a target close to the episcleral venous pressure (8–11 mmHg) is recommended (NHMRC, 2010). Although IOP control is useful in PACG, these cases generally require an iridotomy using either a thermal (e.g., Argon) or neodymium yttrium-aluminum-garnet (Nd:YAG) laser (American Academy of Ophthalmology, 2016).

Treatment

Early treatment is recommended to reduce the number of patients with glaucoma who develop visual disability. The progression of visual defects from acute or poorly controlled glaucoma may lead to rapid damage with permanent loss of vision. This can have devastating consequences. Medication is generally the first management choice for most patients with glaucoma, even in patients with AAC as they are prepared for laser therapy or surgery. Medications to treat glaucoma aim to reduce IOP by enhancing aqueous outflow and/or by reducing aqueous production.

Glaucoma management often starts with topical eye drops. Hyperosmotic medications, such as intravenous mannitol or oral glycerol 50%, may be used to lower IOP in emergency situations. When initiating glaucoma medications, many factors should be considered including IOP-lowering potency, additive effects, interaction with concomitant systemic medications and disease states, side effects, and ease of administration (NHMRC, 2010). Persistence with and adherence to medication regimens is vital in the management of any chronic disease. In situations where patients are unable to administer eye drops safely or effectively, or where reduction in IOP is less than desired, oral acetazolamide or laser or surgical interventions may be required (NHMRC, 2010).

Initial treatment may start with one medication (monotherapy), traditionally in one eye only (monocular trial) (NHMRC, 2010). A monocular trail allows clinicians to use the untreated eye as a "control" to account for diurnal variations in IOP and monitor the efficacy of the medication. However, this is no longer recommended as each eye may respond to the medication differently and asymmetric spontaneous fluctuations in IOP have been reported (Realini et al., 2004). Instead, it is now recommended that the efficacy of the medication be assessed by comparing multiple measurements in the treated eye(s) (Realini et al., 2004).

Patients are generally followed up 3 to 6 weeks after initiation of a new medication. This is because medications such as prostaglandin analogs having a maximum IOP-lowering effect after 3 to 5 weeks (European Glaucoma Society, 2014). However, if a patient's IOP is not controlled by a single medication then either another medication is added or switched for the initial medication. The initial medication could be continued if its partial effect was beneficial, but otherwise should be ceased. If the initial medication is being switched, a washout period is generally required followed by a trial of the new medication. Wash out periods are necessary as medications may still have an effect on IOP even after they have been ceased (NHMRC, 2010). Effects of various topical medications on IOP and their washout periods are shown in **Table 3**.

Five main classes of medication are used in glaucoma: (1) prostaglandin analogs (PGA), (2) β-blockers (BB), (3) carbonic anhydrase inhibitors (CAIs), (4) α_2-agonists (AAs), and (5) cholinergics. PGAs and BBs are considered first choice/line agents due to their efficacy, once daily dose frequency and favorable side-effect profile (NHMRC, 2010). Topical CAIs and AAs are considered second choice/line agents. Many of these agents are also available commercially as combination therapy with BBs as well as one fixed combination of a CAI and AA to improve convenience and thereby to enhance adherence (NHMRC, 2010). Third choice/line agents include cholinergics and a systemic CAI. However, their unfavorable side-effect profile poses challenge and has resulted in them being used less commonly, with surgical or laser interventions preferred (NHMRC, 2010).

Table 3 Effect of topical medications on intraocular pressure

Drug	*Peak IOP*[a,b]	*Trough IOP*[a]	*Dose frequency*	*Washout period*[c]
Prostaglandin analogs				
Bimatoprost	−33%	−28%	Once a day	4–6 weeks
Latanoprost	−31%	−28%	Once a day	4–6 weeks
Travoprost	−31%	−29%	Once a day	4–6 weeks
Tafluprost	−30%	−26%	Once a day	4–6 weeks
β-Blockers				
Betaxolol	−23%	−20%	2 times a day	2–5 weeks
Timolol	−27%	−26%	1 to 2 times a day	2–5 weeks
Carbonic anhydrase inhibitors				
Brinzolamide	−17%	−17%	2 to 3 times a day	1 week
Dorzolamide	−22%	−17%	2 to 3 times a day	1 week
α_2-Agonists				
Brimonidine	−25%	−18%	2 to 3 times a day	1–3 weeks

[a]Data are based on a meta-analysis of 28 randomized clinical trials (van der Valk et al., 2005).
[b]Data for tafluprost based on (Konstas et al., 2013).
[c]National Health and Medical Research Council Guidelines for the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma (NHMRC, 2010).

Systemic Effects of Topical Ophthalmic Medications

Despite the relative safety of topical ophthalmic medications, they should all be considered as potentially potent systemically. Pharmacokinetics make topical ophthalmic medications more similar to intravenous than to oral administration as they may be absorbed by the highly vascular nasal mucosa, avoiding first-pass hepatic metabolism (Diggory and Franks, 1996; Korte et al., 2002). One drop of timolol 0.5% in each eye has similar effects to a 10 mg oral dose, used to treat hypertension or angina (Diggory and Franks, 1996). Combined use of topical and systemic β-blockers have been linked with adverse respiratory and cardiovascular events, as well as reduced topical ocular hypotensive efficacy (Schuman, 2000). Clinicians may not be aware of these systemic effects as many of them go unreported by patients or misdiagnosed (Goldberg et al., 2008). This is further complicated as many patients do not consider eye drops as "real" medications when asked about their drug history (Goldberg et al., 2008).

Prostaglandin Analogs

PGAs (bimatoprost, latanoprost, travoprost, and tafluprost) are considered first choice/line medications, and their use has increased over BBs as they are more effective at lowering IOP, have fewer systemic side effects, and also only require once a day administration (European Glaucoma Society, 2014). Their primary mechanism of action is to increase uveoscleral outflow, reducing IOP by up to 33% (van der Valk et al., 2005). Their effect is seen within 2–4 h of administration, with a peak effect at 8–12 h, and a maximum effect at 3–5 weeks (European Glaucoma Society, 2014). Evening administration of prostaglandin analogs has been shown to provide a better circadian IOP profile when measuring IOP over 24 h (Alm and Stjernschantz, 1995; Konstas et al., 2002; Konstas et al., 1999). A meta-analysis by Stewart et al. (2010) also showed that PGAs had the greatest effect on reducing IOP fluctuations compared with other topical agents (Stewart et al., 2010).

About 10% of patients do not respond to PGAs, with less than 10 or 15% reduction in IOP from baseline (Ikeda et al., 2006; Rossetti et al., 2006). As the PGAs are structurally different from one another, it may be appropriate to try a different prostaglandin analog if response has been poor to one (Bartlett and Jaanus, 2008; Rossi, 2018). Switching may be preferred as it keeps administration to once a day. As bimatoprost has provoked the greatest hyperemia, it is often prescribed after other prostaglandin analogs have been trialled (Bartlett and Jaanus, 2008; Honrubia et al., 2009). Prior exposure to another PGA may reduce the hyperemic effects of bimatoprost (Bartlett and Jaanus, 2008). When switching between PGAs, patients need to be sure to cease the first one, as the concomitant use of 2 PGAs diminishes their IOP lowering effect (Rossi, 2018).

The most common side effect of PGAs is conjunctival hyperemia. However, this side effect often diminishes over a few months. Eyelash growth and increased pigmentation of the iris and periorbital tissue have also been reported (Bartlett and Jaanus, 2008). This pigmentary change of the iris is irreversible and particularly noticeable in hazel-colored irides; it occurs over months of treatment. The change in pigmentary change of the iris or periorbital tissue can become quite noticeable when patients are treated monocularly. The increased eyelash growth may be popular with some patients and bimatoprost is now also marketed to promote eyelash growth under the brand name Latisse® (Allergan Inc., Irvine, CA) (Jones, 2011). Other side effects are displayed in **Table 4**.

Table 4 Contraindication, precautions, side effects, and interactions of common topical ophthalmic medications for glaucoma

Class	*Contraindications*	*Precautions*	*Ocular side effects*	*Systemic side effects*	*Interactions*
Prostaglandin Analogs	Active intraocular inflammation (uveitis) Active herpetic keratitis	Intraocular inflammation (iritis, uveitis) Aphakia, pseudophakia, torn posterior capsule, known risk factors for macular edema	Blurred vision Burning Stinging Conjunctival hyperemia Foreign-body sensation Itching Increased pigmentation of the iris/ periorbital skin Longer-darker, and thicker lashes Reversible macular edema Reactivation of herpetic infection Iritis/uveitis	Unlikely, but possible.	NSAIDs (eye drops)— reduce efficacy of prostaglandin analogs
β-Blockers	Reversible airways disease, e.g. asthma. Betaxolol, may be safer, used with care. Brady arrhythmia Heart block	Diabetes Hyperthyroidism Cardiac Failure COPD—betaxolol preferred Depression Elderly — May cause falls Children— May cause bradycardia, bronchospasm and mask warning symptoms of hypoglycemia	Burning Stinging Photophobia Itching Tearing Decreased corneal sensitivity Hyperaemia Punctate keratitis Diplopia	Bronchospasm Hypotension Bradycardia Heart block Mask hypoglycemia Adversely affects lipid profile Impotence Fatigue Depression Reduced exercise tolerance Syncope Confusion Alopecia	Systemic beta blockers—potential additive effects Catecholaminedepleting medications Medications that reduce BP, cardiac contractility and conduction— potential additive effects Verapamil— only use under specialist supervision
α_2 Agonists	Monoamine oxidase inhibitors therapy Children younger than two years—use with caution in children younger than seven years	Severe cardiovascular disease Depression	Ocular allergic reaction Burning Stinging Blurring Foreign-body sensation Itching Hyperaemia Lid retraction Conjunctival blanching Photophobia Mydriasis (Apraclonidine)	Central nervous system depression Oral dryness Headache Fatigue Drowsiness Bradycardia Systemic hypotension Hypothermia Apnoea Taste disturbance Syncope	CNS depressant: Alcohol Barbiturates Opiates Sedatives Anesthetics Tricyclic antidepressants Hypotensive agents—potential additive effect
Carbonic Anhydrase Inhibitors (topical)	Corneal grafts, endothelial dystrophy. Allergy to sulfonamides.	Severe hepatic/renal impairment	Burning Stinging Itching Punctate epithelial keratopathy Blepharoconjunctivitis Corneal endothelial cell-decompensation	Bitter taste Headache Nausea Fatigue Dry mouth Dizziness Anaphylaxis	None reported, but potential exists for similar interactions as for systemic carbonic anhydrase inhibitors

Adapted from the NHMRC Guidelines for the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma (NHMRC, 2010) Hyperosmotics

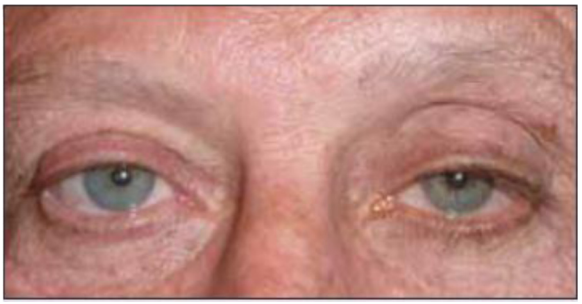

Figure 5 Prostaglandin-associated periorbitopathy in the left eye. *Source: Reproduced from Berke, S.J., A previously underrecognized but important side effect. Adv. Ocular Care (2011) 23–24 (Berke, 2011).*

Another previously under-recognized but important side effect is prostaglandin-associated periorbitopathy (PAP) (Berke, 2011; Shah et al., 2013). PAP had previously been referred to as Deep Superior Sulcus Syndrome or Deepening of Upper Eyelid Sulcus, but PAP appears to encompass all of the eyelid and orbital changes. PAP can include upper lid ptosis, deepening of the upper lid sulcus, involution of dermatochalasis, periorbital fat atrophy, mild enophthalmos, inferior scleral exposure, increased prominence of lid vessels, and tight eyelids (Berke, 2011). Aside from the cosmetic effects, PAP makes it difficult to perform applanation tonometry, surgery in the superior fornix, laser suture lysis, bleb needling, or argon/selective laser trabeculoplasty (Berke, 2011) (**Fig. 5**).

Due to prostaglandins' mechanism of action, they should be used cautiously in patients with intraocular inflammation. This includes a history of uveitis: they are relatively contraindicated in the presence of active intraocular inflammation (NHMRC, 2010). In addition, these medications should be used cautiously in patients with a history of herpetic keratitis, as it may reactivate the infection. They are contraindicated if herpetic keratitis is active (NHMRC, 2010), and in patients with aphakia, pseudophakia, or history of ruptured posterior capsule during cataract surgery, which are known risk factors for macular edema (NHMRC, 2010). Pharmacologically, nonsteroid anti-inflammatory drugs (NSAIDs) used topically with PGAs may reduce their IOP lowering effect (NHMRC, 2010).

β-Blockers

The BBs (timolol and betaxolol) are also first choice/line medications. These medications reduce aqueous humor production and can be potent ocular hypotensives (van der Valk et al., 2005). Timolol is a nonselective β-blockers, while betaxolol is β_1 selective. Side effects may include eye irritation, burning, tearing, and foreign body sensation. However, these effects are unusual and mostly short term. Longer term side effects include dry eye and tachyphylaxis, as some patients demonstrate less IOP lowering effects after years of use (Bartlett and Jaanus, 2008). Switching between BBs or different formulations does not overcome tachyphylaxis; if this occurs, a new medication class is usually required.

Systemic side effects of topical BBs are potentially serious. They may cause cardiovascular, respiratory, and/or nervous system effects. Even the β_1 selective/cardioselective betaxolol should be used with caution in patients with known respiratory dysfunction (Goldberg and Goldberg, 1995). Contraindications to topical BBs include sinus bradycardia, second- or third-degree heart block, cardiogenic shock, uncompensated overt cardiac failure, bronchial asthma, or chronic obstructive pulmonary disease. Owing to potential drug interactions, clinicians should be cautious when coprescribing topical β-blockers with adrenergic psychotropic, catecholamine-depleting, calcium channel blockers, or digitalis. Combined use of systemic with topical BBs should be minimized as this combination has been linked with adverse respiratory and cardiovascular events, as well as reduced topical ocular hypotensive efficacy (Schuman, 2000). Other contraindications, precautions, side effects, and interactions are displayed in **Table 4**.

Topical BBs are prescribed either once or twice a day. Once daily dosing may provide adequate therapeutic effect for most patients and will minimize their risk of side effects. Topical BBs once or twice a day reduce IOP by 20–25% (Soll, 1980). If once a day dosing is used, it is optimal to instil in the morning, because BBs reduce the production of aqueous humor and 50% more aqueous humor is produced in waking hours (Grehn and Stamper, 2009b).

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) suppress aqueous humor production and are considered second or third choice/line medications. Topical CAIs include brinzolamide and dorzolamide. Oral CAIs include acetazolamide. Topical CAIs are not as effective as PGAs/BBs and require administration 2–3 times a day. It is not uncommon for these medications to cause surface discomfort and a bitter metallic taste, more commonly with dorzolamide than brinzolamide (Bartlett and Jaanus, 2008).

Topical CAIs have been reported to contribute to corneal edema and may precipitate corneal decompensation in patients with pre-existing endothelial compromise (e.g., Fuchs' endothelial dystrophy) (Bartlett and Jaanus, 2008). Hence, they are often avoided

in patients with corneal grafts or endothelial dystrophy (NHMRC, 2010). Other contraindications, precautions, side-effects and interactions are displayed in **Table 4**.

Oral CAIs (acetazolamide) are generally limited to the management of AAC or in cases where other medications have been proven to be inadequate or contraindicated and as a temporizing measure while awaiting surgery. Despite its effectiveness in these scenarios, up to 50% of patients treated with acetazolamide do not tolerate it (Bartlett and Jaanus, 2008). Topical and oral CAIs act synergistically; there is little advantage to using both together except as a low-dose systemic supplement to topical instillation.

CAIs are also sulfonamide related and should not be used in patients with a history of severe sulfonamide allergy/reactions. Severe reactions to sulfonamides include aplastic anemia, Stevens-Johnson syndrome, and fulminant hepatic necrosis. As such, CAIs should be discontinued if any signs or symptoms of these reactions occur (Bartlett and Jaanus, 2008).

α_2-Agonists

The α_2-agonists (AAs) suppress aqueous humor production and facilitate uveoscleral outflow. They are considered second choice/line medications. Although two AAs are available (apraclonidine, brimonidine) on the market, brimonidine is mainly used in the longer term. Apraclonidine is not used long term as about a third of patients only have a modest treatment effect (3–5 mmHg) lasting for only 3–6 months (Bartlett and Jaanus, 2008). Hence, apraclonidine is most commonly used as a pretreatment medication to prevent spikes in IOP after glaucoma laser procedures (Bartlett and Jaanus, 2008).

A major concern with brimonidine is that a significant percentage of patients developed a delayed hypersensitivity reaction to the 0.2% formulation. As a result, the concentration was been reduced to 0.15 and 0.1% in newer formulations (using a different preservative) (Bartlett and Jaanus, 2008). These lower concentrations appear to reduce the incidence of delayed hypersensitivity reactions while also preserving similar IOP lowering effects (Bartlett and Jaanus, 2008).

Due to their mode of action, these medications may also cause a variety of systemic side-effects. In particular, brimonidine has also been shown to cause dry mouth and nose, fatigue, headache, drowsiness, dizziness, central nervous system depression, palpitations, and hypotension (Rossi, 2018). Patients should be warned especially about possible drowsiness or dizziness, as people generally do not associate these problems with their eye drops (Rossi, 2018). These medications are also not used in infants or young children owing to increased risks of lethargy, respiratory arrest, and somnolence. Other contraindications, precautions, side-effects, and interactions are displayed in **Table 4**.

Cholinergic Agonists

The cholinergic agonists decrease IOP by improving aqueous outflow through the trabecular meshwork through the contraction of the ciliary muscle. As they also stimulate the iris sphincter, they cause miosis. Although pilocarpine has been used widely to treat glaucoma in the past, its use has been superseded by the other topical ophthalmic medications discussed (NHMRC, 2010). Particular challenges with pilocarpine include an optimal administration frequency of 3–4 times a day and miosis-induced reduction in retinal illuminance that diminishes a patient's functional ability and negatively impact visual field testing (Bartlett and Jaanus, 2008). In addition, chronic use may result in the loss of the ability to dilate the pupil, making any subsequent cataract surgery more difficult (Bartlett and Jaanus, 2008).

Currently, this medication is primarily used in the management of AAC, once the pressure has been reduced to around 30 mmHg (Bartlett and Jaanus, 2008). Pilocarpine may be beneficial in these instances as pupillary miosis and mechanical deformation of the scleral spur decrease appositional iris-trabecular closure, allow aqueous access to the meshwork for drainage, decrease IOP, and stretch the iris, which facilitates laser peripheral iridotomy (Bartlett and Jaanus, 2008). However, if the AACC lasts for more than 1–2 h or if the IOP is greater than 50 mmHg then the iris sphincter muscle may be ischemic and unlikely to respond to pilocarpine. Another indication that pilocarpine may be useful is in the treatment of pigmentary glaucoma, as moving the iris away from the lens zonules might be beneficial (Bartlett and Jaanus, 2008).

Hyperosmotics are used in the treatment of AACC to lower IOP quickly, reduce pain, and to clear corneal edema. However, this is primarily to prepare the patient for laser iridotomy and possible laser iridoplasty. Hyperosmotics cause increased blood serum osmolarity, which pulls water from tissues into the bloodstream. By increasing the osmotic gradient between plasma and the eye, vitreal dehydration occurs, which results in reduced ocular volume and lowering the IOP. The results are relatively rapid (15 min to 2 h) and short in duration (6–8 h).

Hyperosmotics used include intravenous mannitol and oral glycerol 50%. Although mannitol has been recommended to be given as 1–2 g/kg iv over 30–45 min, most authors preferred the lower 1–1.5 g/kg dose due its safer side effect profile (Hill, 1964; Singh, 2005). Both of these drugs can cause electrolyte disturbances and should be used with caution in frail or elderly people (Schacknow and Samples, 2010). They are contraindicated in patients with kidney failure or who are on dialysis (Schacknow and Samples, 2010). The induced fluid shifts may cause congestive heart failure from expansion of blood volume (Schacknow and Samples, 2010). Due to their mode of action, other contraindications include acute pulmonary edema, anuria, severe dehydration, active intracranial bleeding (Bartlett and Jaanus, 2008). Patients with acutely high intraocular pressures may be nauseated. Imbibing oral glycerol 50% over ice helps palatability (Schacknow and Samples, 2010). Oral glycerol should be ingested over about 30 min, taking several sips at a time (Schacknow and Samples, 2010).

Laser Therapy and Surgery

The primary purpose of laser therapy and surgery is to reduce IOP when medications prove ineffective and/or intolerable. Outcome measures include a lowered IOP, reduction of antiglaucoma medication usage, maintenance of visual acuity, and minimization of VF loss (NHMRC, 2010). For the purposes of this chapter, laser therapy and surgery will not be discussed in depth.

Laser therapy includes iridotomy, iridoplasty, trabculoplasty, and cyclodestructive procedures. Laser iridotomy is used to treat AC by creating a hole in the iris in order to break pupil block. It is most frequently undertaken by Nd:YAG laser iridotomy (NHMRC, 2010). Laser iridoplasty is used in AC following iridotomy when the angle remains appositionally closed or occludable (NHMRC, 2010). Contraction burns are applied to the peripheral iris to pull it away from the trabecular meshwork. Laser trabculoplasty is used in OAG and uses a laser focussed on the trabecular meshwork to increase aqueous outflow (NHMRC, 2010). Cyclodestructive procedures can also be used for OAG by using a laser to damage the ciliary body, reducing aqueous humor production (NHMRC, 2010). However, as the effects of cyclodestruction are unpredictable, and visual loss is possible, it is usually reserved for uncontrollable IOPs in eyes with poor vision already.

Surgery for glaucoma typically includes trabeculectomy, iridectomy, and glaucoma drainage devices. A trabeculectomy includes surgically creating a drainage channel between the anterior chamber and subconjunctival space. Standard trabeculectomy 5-year survival is reported to be 80% (Dally et al., 2003). Trabeculectomy may be undertaken as a primary procedure, or when laser and medical therapies do not successfully lower IOP. Since excessive scarring in the operative area will lead to failure of filtering surgery, antifibrotic medications such as 5-fluorouracil and/or mitomycin C are often applied locally to retard healing. A serious drawback with antimetabolites is that some of the complications associated with filtering blebs are increased, such as a higher rate of bleb leaks and late-onset infections (Ederer et al., 2000; Dally et al., 2003).

An iridectomy is the surgical removal of part of the iris. This procedure is most frequently performed in the treatment of AC glaucoma but has been largely superseded by Nd:YAG laser iridotomy (NHMRC, 2010). Iridectomy is most commonly used as part of a trabeculectomy to prevent iris occlusion of the channel. It can also be performed when corneal clarity or lack of equipment precludes a laser iridotomy (NHMRC, 2010).

Glaucoma drainage devices (implants and shunts) are generally employed in secondary glaucomas or where trabeculectomy has failed (Minckler et al., 2006). Tube shunts work by allowing aqueous to flow along a plastic tube and delivered onto a plate surface, which creates a conduit and reservoir that cannot be obliterated by local fibrosis to reduce IOP. Although a 5-year IOP control success rate is between 50% and 100% (Molteno et al., 2001), a meta-analysis suggests approximately 10% failure rate per year for the first 3 years (Hong et al., 2005).

Recently, a number of so-called minimally invasive glaucoma surgeries (MIGS) have become available, including the iStent (Glaukos Corp. Laguna Hills, CA), Hydrus Microstent (Ivantis, Irvine, CA, USA), Trabectome (NeoMedix, Tustin, USA), the Xen Implant (Aliso Viejo, CA, USA), and the InnFocus Microshunt (InnFocus, Miami, FL, USA) (Nardi et al., 2015). Which devices work best for which patients, with or without simultaneous cataract surgery, is being determined by a series of clinical trials.

The Role of the Pharmacist

Like other chronic diseases, pharmacists have an important role to improve glaucoma management outcomes. In particular, they can assist patients to obtain optimal effects from their medications and to minimize the risk of adverse effects by addressing adherence, instillation techniques, timing, and choice of medications. Also, as pharmacists are one of the most accessible health-care professionals in many communities, they can impact public health strongly by improving screening rates for glaucoma in high-risk patients.

Ensuring Optimal Effect of Medications, Adherence, and Persistence

Adherence and persistence are major problems in glaucoma as it is asymptomatic and consequences are not immediately apparent when a medication is missed (European Glaucoma Society, 2014). Nonadherence in patients with glaucoma is reported to range from 24% to 59% (Gurwitz et al., 1993; Patel and Spaeth, 1995; Rotchford and Murphy, 1998). Adherence is reduced by increased frequency of instillations, increased side effects (especially those unexpected or alarming), and increased cost (NHMRC, 2010). Individualized strategies should be used to overcome specific issues identified that align with the patient's life style. Strategies to minimize side effects will be discussed later.

Due the asymptomatic nature of glaucoma, patient education about the disease process may aid adherence by highlighting the risk of VF loss that may results from nonadherence. Informed participation in treatment decisions has also been shown to improve adherence and treatment outcomes (Osterberg and Blaschke, 2005). Self-management strategies that engage patients in their own care have been shown to improve treatment outcomes compared with the traditionally "paternalistic" care offered by health-care professionals (Nys, 2008). To assist patients to manage their glaucoma and other health issues, pharmacies can provide a medicines profile, listing all the patient's prescriptions, over-the-counter and complementary medicines. These profiles can also be used as an effective communication tool when the patients see other health professionals. Patient-centered approaches appear to offer the most effective long-term strategies for glaucoma management.

For patients who have difficulty adhering to their medications, often despite best intentions and understanding of their disease(s), simplifying the medication regimen may help greatly. A once-daily medication can improve adherence compared with more frequent administrations. This can be facilitated by the use of combination eye drops instead of separate agents used sequentially (Stewart et al., 2004). Once daily medications such as PGAs and BBs could be used morning or evening, depending on the individual patient's preference and likelihood to remember.

Adherence may fail from physical obstacles such as tremors (e.g., Parkinson's) or poor hand/arm/finger control or power (e.g., arthritis). Physical barrier nonadherence is known as dyscompliance (NHMRC, 2010). Medication aids may help and may be purchased from local pharmacies, patient support associations, or some technology outlets. Ophthalmic medication manufacturers also have devices that are designed for their specific eye drop bottles to assist patients experiencing these issues. Local glaucoma associations may also be a valuable resource for patients to access assistive technologies. In Australia, Glaucoma Australia (www.glaucoma.org.au; 1800 500 880), is able to assist patients without cost.

Administration Timing of Medications

Administration timing is also important when patients are on multiple ophthalmic medications. On average, the total tear film volume is around 7 μL, and the rate of tear film turnover is approximately 15% (±1 μL) per minute but can double after application of a topical eye drop (each eye drop may have a volume of 30–50 μL) (European Glaucoma Society, 2014). Although the conjunctival cul-de-sac tear film compartment can expand, it cannot accommodate the whole volume of an eye drop; less than 5% enters the eye (European Glaucoma Society, 2014). The remaining medication will either run down the cheek, be absorbed through the conjunctival tissues, or be drained to the nose via the nasolacrimal duct. Once an eye drop is instilled into the conjunctival sac, spontaneous tear flow will wash it out completely within 5 min (European Glaucoma Society, 2014). If multiple eye drops are used in succession, for optimal efficacy, they should be separated by at least 5 min. When two ophthalmic medications are instilled only 30 s apart, almost 50% of the first drug will be washed out (European Glaucoma Society, 2014).

Ophthalmic medication formulation affects their recommended administration. Eye drop solutions should be applied first, followed by any eye drop suspensions (cloudy liquids, e.g., brinzolamide), followed in turn by any eye gels or ointments. Applying medications in this order allows the medications in solution to be absorbed through the cornea and sclera, preventing possible hindrance by insoluble or oily substances present in suspensions, gels, and ointments. Ophthalmic suspension requires to be shaken before use. If patients do not shake the bottle, they may instil only vehicle to the eye, rather than the active ingredient (European Glaucoma Society, 2014).

Minimizing and Addressing Side Effects

Administration technique for ophthalmic topical medications is important to maximize efficacy, to minimize risk of eye infection and systemic side effects. Patients should be advised to wash their hands before instillation and to ensure that the tip of the eye dropper or tube does not touch the eye, eyelid, or lashes to prevent infections. Many ophthalmic products should be discarded after 28–30 days after opening, unless stated otherwise (Rossi, 2018). Hospitals may have their own discard policy due to the increased risk of infection.

Pharmacokinetics make topical ophthalmic medications mimic intravenous rather than oral administration—they avoid first-pass hepatic metabolism via transconjunctival absorption and transnasal mucosal absorption (Diggory and Franks, 1996; Korte et al., 2002). See comments on timolol above The "double DOT" procedure is recommended as it reduces systemic absorption by 70% (Goldberg et al., 2008). The "double DOT" includes (1) Don't Open the eyelids Technique (DOT) and (2) Digital Occlusion of the Tear duct (DOT) for 1 to 2 min (Goldberg et al., 2008). Keeping the eyes closed and applying digital pressure over the lacrimal sac for 1–2 min after drop administration will significantly reduce systemic absorption of most agents. Two medications from the same class should not be coprescribed as this can increase the risk of side effects with no beneficial effects on IOP (Goldberg et al., 2008) (**Fig. 6**).

Preservative Toxicity and Effects on the Eye

Preservatives are used in ophthalmic medications to inhibit or destroy micro-organism growth and to maintain sterility. However, preservatives can also provoke local reactions or lead to preservative toxicity, especially when used frequently and in the longer term. Chronic use of antiglaucoma eye drops can cause eye burning and stinging, dry eyes, and reflex tearing (Baudouin, 2008). The majority of multidose eye drops contain benzalkonium chloride, a quaternary ammonium-based preservative. Adverse effects from preservatives may be diminished if benzalkonium chloride is substituted with a less toxic preservative or a nonpreserved drop is used. In particular, Purite (Alphagan P; Allergan Optical, Irvine, CA, USA), polyquaternium-1 (PolyQuad in Travatan; Alcon Laboratories, Inc, Fort Worth, TX, USA), and sofZia (Travatan Z; Alcon Laboratories, Inc, Fort Worth, TX, USA) are alternative ophthalmic preservatives designed to eliminate the toxic side effects of benzalkonium chloride (Yee, 2007). Tafluprost, bimatoprost, and timolol are available in preservative-free, single-dose units. Particularly if a patient is using four or more drops a day, products with less toxic preservatives or preservative-free should be considered (Rossi, 2018).

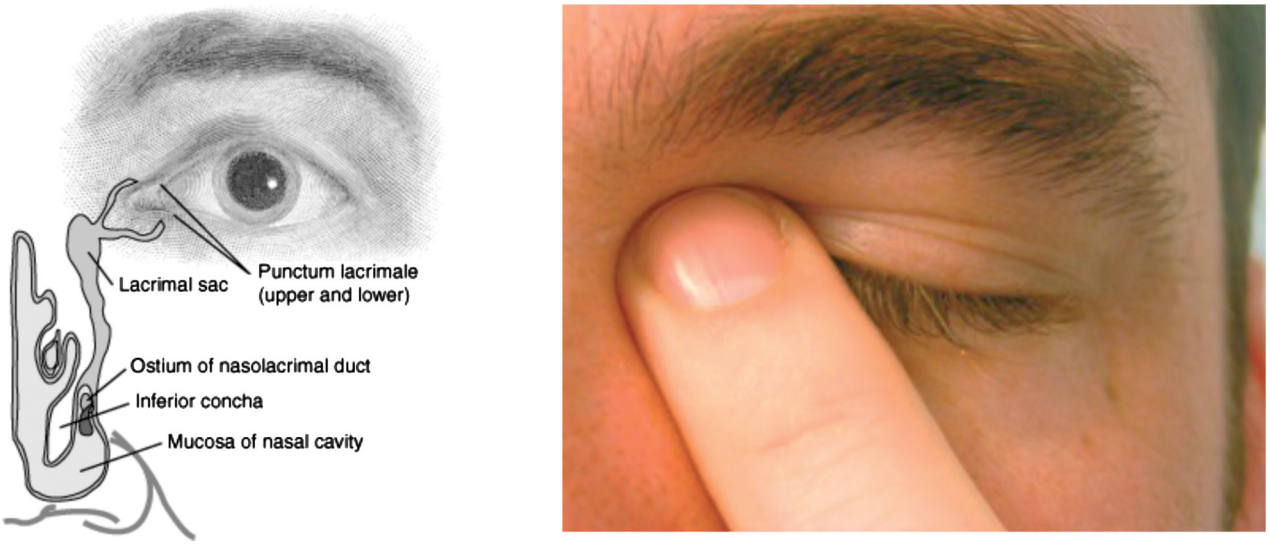

Figure 6 Lacrimal drainage system and the "double" DOT procedure.[a] *Source: Reproduced from Goldberg, I., Moloney, G., McCluskey, P., Topical ophthalmic medications: what potential for systemic side effects and interactions with other medications? Med. J. Austr. 189(7) (2008) 356 (Goldberg et al., 2008).*
[a]Don't Open the eyelids Technique (DOT) and Digital Occlusion of the Tear duct (DOT).

Screening

Community pharmacy holds a number of benefits as a setting for public health activities. With extended opening hours and no appointment needed for advice, community pharmacy can be more accessible than other settings. A systematic review of pharmacists and consumers showed that both groups believed community pharmacists should have a public health role. Glaucoma is a public health concern as it can cause irreversible blindness and half of all patients with glaucoma are undiagnosed and thus untreated—and glaucoma is a progressive disease causing irreversible visual damage (Mitchell et al., 1996; Quigley and Jampel, 2003; Tielsch et al., 1991). Those who are diagnosed are often diagnosed late sometimes with significant VF loss already present (Martus et al., 2005). Improved screening of high-risk groups would allow earlier diagnosis of glaucoma at a stage of less visual damage and enhance treatment outcomes. The highest risk group are first-degree relatives of diagnosed patients: such persons have a 23% lifetime risk for glaucoma (NHMRC, 2010). Pharmacist should repeatedly recommend to glaucoma patients filling prescriptions to ensure their relatives are aware of this and are being assessed regularly for both IOP levels and an optic nerve check.

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Management of Eye Disorders and the Pharmacist's Role: Eye Infections

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Introduction to Eye Infections

Eye infections are a common medical presentation and can vary from being self-limiting to sight threatening. Although most eye infections that present to a pharmacy are self-limiting, some may cause corneal scarring and/or permanent blindness. As such, it is important that pharmacists refer these patients appropriately.

Eye infections often manifest when the eye has been exposed to pathogens that are not part of the normal flora of the ophthalmic chamber. This usually occurs when the integrity of the eye is compromised, or there is damage to the eye due to trauma or surgery.

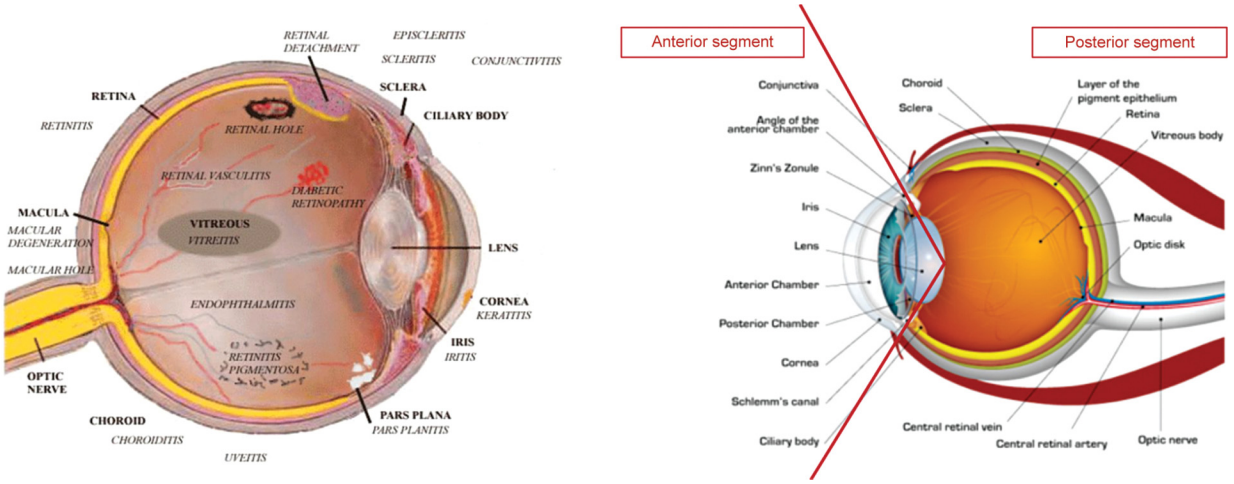

Figure 1 (A) Ocular infections categorized by location of eye. (B) Ocular infections affect both the anterior and posterior segments of the eye (Vision Best Eye Care Centre, 2019).

Infections are also more common in people who wear contact lenses or are immunosuppressed where normal microbial flora may become opportunistic (Thielen et al., 2000).

Eye infections are categorized by their etiology and anatomical location of the infection. Eye infections can occur around the eye, on the eyelid, or in the anterior or posterior segments of the eye (Fig. 1A). Eye infections are classified by the location of the infection (Fig. 1B). For instance, an infection may cause keratitis if it affects the cornea or retinitis if it affects the retina. Causative organisms for ophthalmic infections can be bacteria, viruses, fungi, or protozoa.

Common eye infections and their pathogens can usually be determined by assessing patient's history, symptoms, and clinical presentations. To confirm diagnosis, diagnostic techniques such use of fluorescein and examination through a slit lamp or microbiology testing of corneal scrapings or the vitreous may be employed. Identifying the location of the infection and the causative organism are critical in selecting a pharmacotherapeutic agent as absorption, penetration and the bioavailability of the drug will affect treatment decisions (Gerstenblith and Rabinowitz, 2012).

Epidemiology

The epidemiology and the availability of data for each eye infection vary significantly. The overall burden and the epidemiology of eye infections have not been well described, as most of the data regarding infections such as keratitis, endophthalmitis, and trachoma have been from individual studies and publications. The patterns and circumstances associated with the incidence of eye infections vary between populations and geographical locations. The factors causing the variations are based on climate and economic development (Channa et al., 2016). In less developed countries, large scale vision loss may be due to deficiency of resources and endemic infections. Trachoma, an eye infection caused by *Chlamydia trachomatis*, is more common in lower socioeconomic countries where infection spreads due to poor hygiene and high population density. It has been estimated that trachoma accounts for approximately 3% of the world's blindness with about 8 million people permanantly impaired by trachoma (World Health Organization, 2019).

In community pharmacies, red eye is the most common presentation of an eye infection. A small study in the United Kingdom showed that community pharmacies on average saw two cases of red eye per week (Rutter, 2017). Most red eye presentations are caused by conjunctivitis. Allergic conjunctivitis is the most frequent cause of conjunctivitis, affecting 15%–40% of the population (Bielory et al., 2012) and is observed more frequently in spring and summer (Høvding, 2008). Viral conjunctivitis is the most common cause of infectious conjunctivitis both overall and in the adult population (Fitch et al., 1989; Harding et al., 1987; Hørven, 1993; Rönnerstam et al., 1985; Stenson et al., 1982; Uchio et al., 2000; Woodland et al., 1992). Some studies have shown that up to 80% of conjunctivitis cases are caused by viruses, which do not require treatment with antibiotics and are usually self-limiting (Azari and Barney, 2013). Bacterial conjunctivitis is the second most common cause (Fitch et al., 1989; Hørven, 1993; Rönnerstam et al., 1985; Stenson et al., 1982; Woodland et al., 1992) and is responsible for the majority (50%–75%) of cases in children (Høvding, 2008).

Another common cause of red eye is due to an infection of the cornea, known as keratitis. Keratitis is a serious infection of the eye as it is one of the most common causes of corneal blindness and visual impairment around the world (McLeod et al., 1995). The epidemiology of keratitis varies significantly between the western and developing countries due to the fact that less industrialized countries have significantly lower number of contact lens users; hence, fewer contact lenses related infections (Al-Mujaini et al., 2009). In the United States, about 30,000 cases of microbial keratitis are reported annually (Sharma and Taniguchi, 2017). Bacterial keratitis is the most common form of microbial keratitis in temperate climates, such as United

States, accounting for 89%–96% of cases of microbial keratitis (Estopinal and Ewald, 2016; Varaprasathan et al., 2004). However, in sub-Saharan Africa, filamentous fungi has accounted for 42% of cases of microbial keratitis (Leck et al., 2002).

One of the most serious eye infections is an infection inside the eye, known as endophthalmitis. The incidence of endophthalmitis varies between studies, as the presentation of the eye infection is usually secondary to ophthalmic surgery or procedures, or is a consequence of ocular trauma. Endophthalmitis can be classified as exogenous or endogenous. Exogenous endophthalmitis refers to a cause external to the globe, such as surgery or trauma, while endogenous endophthalmitis is due to hematogenous spread. Overall, the incidence of exogenous endophthalmitis postcataract surgery appears to be decreasing. Studies from the United States show that the incidence has reduced from 0.08% over 1984–1994 to 0.025% over 2002–2009 (Ramakrishnan et al., 2009). Endogenous endophthalmitis is generally less common than exogenous endophthalmitis, with studies reporting ranges from 2% to 41% of all cases of endophthalmitis being endogenous, again varying due to geographical location and patient history (Chee and Jap, 2001).

Diagnosis

Rapid identification of eye infections is crucial as treatment regimens and visual prognosis are dependent on accurate and timely diagnosis between noninfectious, mild, and severe infections. Precise diagnosis requires a combination of analyzing clinical features that are characteristic of the infection, as well as microbiological investigation. At initial presentation, a preliminary diagnosis and empirical treatment is determined based on specific clinical features, and laboratory data enables the confirmation of a suspected diagnosis. In determining the pathogen both in vivo and in vitro, diagnostic methods are available, which include a range of conventional (such as blood testing) and molecular techniques (Sharma, 2012).

Fluorescein and Slit Lamp Biomicroscopy

The use of slit lamp biomicroscopy is the most common method to explore the cornea for eye examinations. It allows the ophthalmologist to gain a detailed assessment of the anterior and posterior segments of the eye (Martin, 2018). Fluorescein is an orange dye used during the slit lamp biomicroscopy examinations. Fluorescein is administered topically via a dropper or a strip (Gerstenblith and Rabinowitz, 2012). The action of blinking spreads the dye over the surface of the cornea, staining the eye and allowing the visualization of ocular surface disorders such as corneal ulcers, abrasions, or other epithelial defects (Martin, 2018).

Conventional Pathology and Microbiology Testing

Conventional testing requires clinical samples to be collected from the site of infection to confirm the causative pathogen. **Table 1** summarizes the type of samples required from the infected eye in order to diagnose the infection (Sharma, 2012). These samples are then processed for culture of bacteria, fungi, or parasites.

Blood samples are only required where an endogenous infection might be suspected. However, it is important to note that a negative peripheral blood results does not exclude the possibility of infection (Sharma, 2012). If a positive culture is obtained, antimicrobial susceptibility is also identified to assist clinicians in identifying an appropriate antimicrobial agent (Sehu, 2009).

Molecular Testing: Polymerase Chain Reaction

Molecular diagnosis has added sensitivity, specificity, and speed compared to the conventional techniques of microscopy and culture (Bowling, 2015; Sharma, 2012). Polymerase chain reaction (PCR) is a laboratory method to detect and measure specific genes, such as those from pathogens. PCR is the most common molecular diagnostic method used in eye infection investigations. In

Table 1 Type of sample and recommended procedure for sample collection in various eye infection

Type of infection	*Type of sample*
Conjunctivitis	Fluid/discharge from lower conjunctival sac
Blepharitis	Scales/discharge from lid margin
Dacryocystitis	Fluid/discharge from lower conjunctival sac
Keratitis	Corneal scraping
Uveitis	Anterior chamber fluid
Endophthalmitis	Anterior chamber fluid vitreous aspirate vitreous biopsy
Deep seated stromal infiltrate in keratitis	Corneal biopsy
Contact lens-associated keratitis	Contact lenses, lens cases, and lens solution
Postoperative endophthalmitis postintraocular lens implantation	Intraocular lens

Source: Modified from Sharma (2012).

cases of bacterial and fungal infections, culture is still preferred over molecular methods; however, there is increased utilization of the PCR technique in the diagnosis of bacterial and fungal endophthalmitis (Bowling, 2015; Sharma, 2012). PCR testing is also useful in the detection of organisms that are difficult to culture such as *Microsporidia*, *Propionibacterium acnes*, and *Toxoplasma gondii*, or for organisms that take a long time to grow, such as *Mycobacterium tuberculosis* (Sharma, 2012).

For many viral infections, PCR analysis has superseded less sensitive culture and pathology techniques. For instance, it is now common for conjunctivitis or keratoconjunctivitis caused by adenoviruses, herpes simplex virus, *Chlamydia*, or microsporidia to be confirmed by PCR-based techniques in the clinical setting (Bowling, 2015; Chan et al., 2005; Sharma, 2012). In fungal infections, PCR techniques are superior in improving diagnosis compared to conventional method, particularly in the diagnosis of fungal endophthalmitis (Chan et al., 2005; Sharma, 2012). Furthermore, the ability to sequence genomic fragments has assisted in the detection of organisms that are difficult to identify and can isolate new organisms associated with ocular disease.

Concepts in Ocular Pharmacotherapy

The challenge in commencing appropriate management is that there is not one therapy or regimen that can treat all the types of eye infections. Varying infections require different treatments, ranging from nonpharmacological eye care to antimicrobials and surgery. Appropriate choice of pharmacotherapy will be based on factors such as causative organism, absorption, penetration, and bioavailability of the drug and whether the infection is in the anterior or posterior segment of the eye.

Mode of Drug Delivery

Ocular drug delivery has been a major challenge due to the unique anatomy and physiology of the eye. The structure of the eye includes different layers of cornea, sclera, and retina including blood aqueous and blood–retinal barriers (Bowling, 2015; Cohen, 2009; Gaudana et al., 2010). Structural variation of each layer of ocular tissue can present a significant barrier following drug administration by any route. In theory, topical application of drugs is suitable for management of the anterior segment, and intravitreal injections or systemic medications are generally used for posterior infections. **Table 2** summarizes the types of ocular drug delivery and their associated benefits and challenges (Gaudana et al., 2010).

Antimicrobials

Eye infections can be caused by a range of microorganisms such as bacteria, viruses, fungi, or protozoa. As such, a range or antibacterial, antiviral, antifungal, and antiprotozoal agents may be used to treat eye infections. However, liberal use of antimicrobials has resulted in a rise in antimicrobial resistance rates in numerous microorganisms around the world, limiting the usefulness of antimicrobials (Grzybowski et al., 2017). For instance, patients receiving prophylactic antimicrobial eye drops prior to intravitreal injection administration for chronic retinal disease showed increased ophthalmic microbial flora resistance rates (Kim and Toma, 2011). In these patients, resistance rates to moxifloxacin rose from 26% to 65% over only one year (Kim and Toma, 2011). Clinicians should be familiar with local antimicrobial resistance patterns to ensure appropriate antimicrobials are used. Also, to prevent further rise in resistance rates, antimicrobials should be restricted to clinical cases that have been shown to provide benefit.

Table 2 Routes of delivery, benefits, and challenges in ocular delivery

Route	*Eye infections treated*	*Benefits*	*Challenges*
Topical	Keratitis, uveitis, conjunctivitis, scleritis, episcleritis, blepharitis	High patient compliance, self-administrable, and noninvasive	Higher tear dilution of drug and turnover rate Corneal barrier
Oral/Systemic	Scleritis, episcleritis, cytomegalovirus retinitis	Patient compliance, and noninvasive route of administration	Blood–Aqueous Barrier Blood–Retinal Barrier Systemic dosing with associated adverse effects and toxicity
Intravitreal	Cytomegalovirus retinitis, acute retinal necrosis, endophthalmitis	Direct delivery to vitreous and retina, sustains drug levels, evades blood—retinal barrier	Retinal detachment Possible hemorrhage Risk of cataract and endophthalmitis
Intracameral	Prevention and treatment of endophthalmitis with antibiotic delivery	Provides higher drug levels in the anterior chamber, eliminates usage of topical drops, reduces corneal and systemic side effects seen with topical steroid therapy	Toxic anterior segment syndrome Toxic endothelial cell destruction syndrome

Source: Modified from Gaudana et al. (2010).

Adjuvant Therapy

Corticosteroids

Corticosteroids are used as adjuvant therapy in the management of eye infections and aid in decreasing inflammation of the eye. The most commonly used corticosteroids are dexamethasone, prednisolone acetate, and triamcinolone. The use of corticosteroid therapy in active infection is debatable, since it can delay healing of the cornea as well as amplify the risk of opportunistic infection (Cohen, 2009). However, the benefits of both topical and systemic corticosteroid treatment in reducing the severity of corneal stromal melt, neovascularization, and subsequent scarring have been proposed (Williams and Paterson, 1987). Furthermore, corticosteroids may improve patient compliance with other eye drops by decreasing pain and discomfort from the infection (Renfro and Snow, 1992).

Anticholinergics

Topical anticholinergic eye drops include atropine, cyclopentolate, and tropicamide. They are often used for their cycloplegic effects in the management of eye infections (Rossi, 2018). Their cycloplegic effects are due to blockade of the muscarinic receptor, causing paralysis of the ciliary muscle. Immobilizing the eye can decrease the pain associated with severe eye infections (Bowling, 2015). However, clinicians should be cautious of systemic absorption of anticholinergic agents as they may cause adverse reactions such as dry mouth, headache, dizziness, hypertension, and tachycardia (Rossi, 2018). Regular review and a short duration of treatment are advised (Rossi, 2018).

Treatment of Eye Lid and Conjunctiva Infections

Blepharitis

Blepharitis is the inflammation of the margins of the eyelids, with or without the presence of ulceration. Blepharitis can be classified as either anterior blepharitis or posterior blepharitis. Anterior blepharitis affects the region of the eyelashes, with often a collarette visible at the eyelashes roots. Anterior blepharitis is usually associated with either staphylococcal or seborrheic contamination of the eye lid margin and lashes, presenting with crusting around the eyelids (Guillon et al., 2012; McCulley and Dougherty, 1985). Posterior blepharitis affects the cutaneous mucosal junction, where the meibomian glands are located and often present with sticky discharge (McCulley et al., 1982).

Anterior Blepharitis or Staphylococcal Blepharitis

Anterior (Staphylococcal) blepharitis is an infection that involves inflammation of the eyelid and hair follicles. It is characterized by crusting on the eyelid edges. Patients may present with painful, burning eyes, with ulceration or abscesses and the feeling of a foreign body in the eye or grittiness (Bowling, 2015; Therapeutic Guidelines, 2014). The most common causative pathogen is *Staphylococcus*. Other pathogens include *Pneumococcus* and *Haemophilus*.

In most cases, appropriate lid hygiene is sufficient as the condition is self-limiting and does not require topical antibiotic treatment (Therapeutic Guidelines, 2014). Lid hygiene involves applying warm compresses for 2–5 minutes to soften the crusts followed by gentle scrubbing of the eye lashes (Therapeutic Guidelines, 2014). Commercially available lid solutions can be used, alternatively patients may use a dilute sodium bicarbonate solution (1 teaspoon in 500 mL cooled boiled water) or diluted baby shampoo solution (5 drops in 100 mL cooled boiled water) (Therapeutic Guidelines, 2014). If the infection is unresolved after one to two weeks, treatment with a topical antibiotic ointment, such as chloramphenicol, may be considered (Bowling, 2015; Therapeutic Guidelines, 2014).

Posterior Blepharitis or Seborrheic Blepharitis

Posterior (seborrheic) or nonulcerative blepharitis is the most common form of blepharitis. It is characterized by burning and itchy eyes, with discharge, especially in the morning upon waking. Red and inflamed eyelids are also typical of posterior blepharitis, and in some cases, patients may also present with a secondary chalazion infection (Bowling, 2015).

Risk factors include exposure to allergen, dust, smoke, irritating chemicals, or association with seborrhea of the scalp, eyebrows, and ears (Bowling, 2015; Therapeutic Guidelines, 2014). It can occur due to irregular oil secretion from the sebaceous (meibomian) glands on the eyelid edges allowing an environment for bacterial growth. It is also associated with other dermatological conditions such as rosacea, psoriasis, and dermatitis around the scalp and forehead (Bowling, 2015).

Similar to anterior blepharitis, lid hygiene is the mainstay for treating posterior blepharitis (Therapeutic Guidelines, 2014). In patients that are unresponsive to lid hygiene alone, long-term (minimum of eight weeks) systemic antibiotics such as low-dose doxycycline or erythromycin are prescribed. In this case, these antibiotics are used for their anti-inflammatory effect rather than their antibacterial effects (Therapeutic Guidelines, 2014).

Ophthalmic Cellulitis

Ophthalmic cellulitis is an acute infection of the subcutaneous tissue around the eye and is categorized as periorbital (preseptal) or orbital (postseptal).

Periorbital Cellulitis

Periorbital cellulitis typically affects the soft tissue of the eyelid. It is usually secondary to an existing infection either originating from the orbital septum, which is the main fibrous section of the eyelid, or from the sinus region (Duane et al., 2013). The causative organisms are usually staphylococcal, *Streptococcus pyogenes* or *Streptococcus pneumoniae*. *Haemophilus Influenza type B* (Hib) can also be a source of infection in children who have not been vaccinated. Patients with a history of trauma, wound, or existing stye, dacryocystitis, or impetigo are at higher risk of developing periorbital cellulitis (Bowling, 2015; Duane et al., 2013; Moorfields Eye Hospital, 2006; Sehu, 2009).

Symptoms are usually unilateral, with swelling, pain, tenderness of the eyelid, and redness of the eyelid and adjacent soft tissue (e.g., forehead). Visual disturbances are not common for periorbital cellulitis (Bowling, 2015; Duane et al., 2013).

Treatment of periorbital cellulitis should target the most likely and common causative organisms, *Staphylococcus* and *Streptococcus* (Renfro and Snow, 1992; Rossi, 2018). Systemic antibiotics such as flucloxacillin and cefalexin are recommended. Periorbital cellulitis associated with *H. influenza type b* requires treatment with amoxicillin/clavulanic acid, cefuroxime or clindamycin (Gerstenblith and Rabinowitz, 2012; Therapeutic Guidelines, 2014). In cases where periorbital cellulitis remains unresolved after full course of antibiotic treatment or in severe infection, a systemic source of infection may be suspected and sampling of blood cultures should be considered.

Orbital Cellulitis

Orbital cellulitis is an infection of the tissue that surrounds the orbital septum. The infection may extend to ocular muscles and nerves including the optic nerve and is considered an ophthalmic emergency. Rapid diagnosis is essential for timely management of orbital cellulitis, as intracranial spread of the infection may be life threatening (Bowling, 2015; Rossi, 2018). Increased pressure of the eye and surrounding regions can result in blindness and other life-threatening manifestations (Duane et al., 2013). Orbital cellulitis usually occurs with preceding or concurrent infection of the sinus region, dental infections, or other endogenous source of bacteremia. A history of upper respiratory infection is also a determinant factor. Unlike preorbital cellulitis, it is more common in adults than children (Channa et al., 2016).

The most common causative organisms include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and other anaerobes. *H. influenzae* can also be present in unvaccinated patients. Taking blood cultures and swabs from the sinus regions is important to determine the primary infective organism. In the immunocompromised patient, the source of infection may also be fungal (Channa et al., 2016)

Orbital cellulitis requires intravenous broad-spectrum antibiotic therapy to prevent intracranial spread of the infection. A reasonable choice in therapy may include both ceftriaxone, a third-generation cephalosporin with broad activity against Gram-positive and Gram-negative organisms, in conjunction with flucloxacillin (Gerstenblith and Rabinowitz, 2012; Therapeutic Guidelines, 2014). To ensure full resolution of orbital cellulitis, antimicrobial therapy should be continued for 10 days (Bowling, 2015; Gerstenblith and Rabinowitz, 2012; Therapeutic Guidelines, 2014). In some cases, surgery may be required to drain the patients' sinuses or abscesses in the orbital or intracranial space (Bowling, 2015; Therapeutic Guidelines, 2014).

Bacterial Conjunctivitis

Conjunctivitis is the inflammation of the conjunctiva and is the most common presenting ophthalmic infection in community pharmacies. Acute conjunctivitis is classified into infectious, which includes bacterial and viral conjunctivitis, or noninfectious, which includes allergic and nonallergic conjunctivitis. Bacterial conjunctivitis is more prevalent in children than adults. The most common causative pathogens include *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus* (Fitch et al., 1989; Therapeutic Guidelines, 2014).

Although patients with contact lenses are at a higher risk of developing bacterial conjunctivitis, a referral to a physician is generally required to exclude a diagnosis of keratitis. Patients with contact lenses are more predisposed to keratitis because the space between the contact lens and cornea can act as an incubator for bacteria and enhance mechanical abrasion (Rutter, 2017).

Bacterial conjunctivitis is characterized by purulent discharge, with a "sticky" eye and crusting on the eyelid upon waking. The discharge can continue throughout the day and is described as green, yellow, and globular. Symptoms initially occur unilaterally but may be transmitted to the adjacent eye after one or two days if proper hygiene is not observed (Bowling, 2015).

Bacterial conjunctivitis can resolve spontaneously within five days without treatment in 65% of cases (Rutter, 2017). However, it is highly contagious and can be spread by contamination of ophthalmic discharge on surfaces and sharing of objects. As such, patients are encouraged to wash their hands often with soap and warm water and avoid touching or rubbing their eyes. It is also recommended that patients wash their pillowcases, sheets, and towels often in hot water and detergent (National Center for Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases, 2019).

In some cases, symptoms of bacterial conjunctivitis can last for up to 14 days. If symptoms remain after five days, topical antibiotic (chloramphenicol or framycetin) may be used to hasten the recovery (Sheikh et al., 2012).

Chlamydial Conjunctivitis

Chlamydia trachomatis conjunctivitis, or also known as inclusion conjunctivitis, occurs in neonates and patients with sexually transmitted infections. In adults, it has also been documented to be a chronic and latent infection. Concurrent, asymptomatic, urogenital infection, or urethritis may also be present in mothers of neonates (Fitch et al., 1989). Clinical features of chlamydial

conjunctivitis are usually unilateral and similar or the same as bacterial or viral conjunctivitis. PCR testing can confirm diagnosis, particularly if symptoms persist for more than 14 days. Systemic antimicrobial treatment is recommended for chlamydial conjunctivitis (Nakagawa, 1997; Therapeutic Guidelines, 2014). Azithromycin, administered as a single 1g dose, may be used for its long half-life and high ocular penetration (Bowling, 2015; Nakagawa, 1997).

Trachoma is another form of chlamydial conjunctivitis, but differentiated by recurrent and severe infection resulting in extensive inflammation and scarring of the eyelid. If left untreated, the scarring can thicken causing inward turning eyelashes (trichiasis). The constant abrasion from the eyelashes can cause irreversible corneal opacity and blindness (Bowling, 2015).

The prevalence of this type of conjunctivitis is low in developed countries and occurs mainly in areas with poor hygiene and high population density (Nakagawa, 1997; Therapeutic Guidelines, 2014). Trachoma infection can initially be asymptomatic or cause mild redness or discharge which occurs 5–15 days after contact with an infected person. Trachoma diagnosis is made by clinical examination, which shows pale round spots (follicles) or further changes on the inner surface of the upper eyelid (Bowling, 2015; Nakagawa, 1997; Therapeutic Guidelines, 2014). Pharmacological treatment is the same as chlamydial conjunctivitis with a single dose of azithromycin (Bowling, 2015). Transmission prevention is an effective strategy to reduce the prevalence of trachoma.

Gonococcal Conjunctivitis

Gonococcal conjunctivitis is caused by the Neisseria species, particularly *N. gonorrhoeae*, and can be sight threatening. The organism is usually transmitted from the genitalia to the hands and then eyes. Concurrent, asymptomatic, urogenital infection, urethritis, or chlamydial infection is common (McAnena et al., 2015; Therapeutic Guidelines, 2014). Worldwide, the epidemiology of gonococcal infection in developed countries is less than 1% due to screening and treatment availability (McAnena et al., 2015). In neonates, gonococcal infection usually occurs in the first 5 days of life, and is an ophthalmic emergency as it can lead to corneal perforation of the globe and blindness (Zikic et al., 2018).

Gonococcal conjunctivitis is characterized by sudden onset of profuse and purulent discharge presenting within 12 h of acquiring the infection. Eyelids will be red, inflamed, swollen, and edematous, with the presence of corneal ulceration and perforation. Unlike other types of conjunctivitis, patients may present with systemic symptoms (Bowling, 2015; McAnena et al., 2015; Therapeutic Guidelines, 2014; Zikic et al., 2018). For the treatment of gonococcal conjunctivitis, regular irrigation of the eye with saline throughout the day is recommended until discharge decreases. Gonococcal conjunctivitis is highly contagious and eye hygiene should be observed (Cohen, 2009). Systemic antibiotic therapy, such as a third-generation cephalosporin, is recommended (Bowling, 2015). The presence of gonococcal conjunctivitis is commonly complicated by genitourinary and epipharyngeal chlamydial infections, and therefore, topical antimicrobial treatment is inadequate and is not indicated (Nakagawa, 1997; Zikic et al., 2018). In cases where there is coinfection of chlamydia, treatment with a single dose of azithromycin described in the previous section is recommended (see chlamydial conjunctivitis) (Bowling, 2015; McAnena et al., 2015; Therapeutic Guidelines, 2014).

Viral Conjunctivitis

Viral conjunctivitis is typically caused by adenovirus associated with a recent viral upper respiratory tract infection. On occasion, the conjunctivitis may be a prodromal symptom of a viral infection, which is followed by fever, pharyngitis, and upper respiratory tract infection (Azari and Barney, 2013; O'Brien et al., 2009). Symptoms of viral conjunctivitis occur unilaterally and are characterized by watery or mucous discharge, with a sensation of burning or sand in the eye (Azari and Barney, 2013). It is less contagious than bacterial conjunctivitis, but transmission to the adjacent eye can also occur after two to three days (Azari and Barney, 2013; O'Brien et al., 2009). Viral conjunctivitis can be distinguished from bacterial infection by a more watery discharge. However, patients may still experience initial morning crusting of the eye lids two weeks after the initial symptoms despite resolution of other symptoms (Azari and Barney, 2013; O'Brien et al., 2009).

Viral conjunctivitis is usually self-limiting and does not require topical or systemic antiviral therapy (Bowling, 2015; Therapeutic Guidelines, 2014). Symptoms frequently worsen for the first three to five days, with a very gradual resolution over three weeks (Azari and Barney, 2013; O'Brien et al., 2009). Viral conjunctivitis is contagious, and appropriate eye hygiene is encouraged. For the treatment of viral conjunctivitis, there is no specific effective pharmacotherapy. Antivirals and topical antibiotics are not indicated for this infection, as they have limited effect. Symptomatic management can alleviate clinical symptoms of viral conjunctivitis, and cold compresses are used for vasoconstriction to minimize watery discharge from the eye. Alternatively, topical vasoconstrictors and antihistamines may also be used. Lubricant eye drops are recommended for comfort and relief of burning, gritty sensation. In cases where pain and fever are present, paracetamol or NSAIDs can be used for analgesic and antipyretic effect (Azari and Barney, 2013; Bowling, 2015; O'Brien et al., 2009; Therapeutic Guidelines, 2014). Topical corticosteroids are not indicated as initial treatment, particularly if HSV infection is suspected (Azari and Barney, 2013; O'Brien et al., 2009). If topical corticosteroids are required, dexamethasone or prednisone eye drops can be used up to six times a day but should be ceased if symptoms do not resolve after two to three weeks (Bowling, 2015; Therapeutic Guidelines, 2014).

Treatment of Corneal Infections

Keratitis describes the inflammation of the cornea caused by microbial infection. Keratitis is associated with decreased visual acuity and, if untreated, may result in blindness. Microbial keratitis is characterized by a subacute onset of pain and redness. It is usually

manifested unilaterally but may be present in both eyes. Patients may also describe a sensation of feeling a foreign body in the eye, worsening photophobia (Bowling, 2015; Therapeutic Guidelines, 2014). Conjunctival injection (blood shot eyes), and corneal ulceration, which may result in impaired vision, may also be present. Clinical signs do not reliably distinguish between different causative organisms, and priority should be given to taking scrapings to identify pathogens as soon as possible and directing therapy accordingly (Tabbara et al., 2000).

Bacterial Keratitis

Bacterial keratitis mostly occurs among patients who wear contact lenses or with a history of ocular injury. As described in previous sections, the incidence of keratitis varies significantly between countries who have higher number of contact lens users, due to hygiene considerations (Al-Mujaini et al., 2009; Tabbara et al., 2000). The distinguishing clinical feature for bacterial keratitis is the presence of a white spot on the surface of the eye, often seen even without a slit-lamp examination (Tabbara et al., 2000; Thomas and Kaliamurthy, 2013). The most common causative organism for bacterial keratitis is *Staphylococci*, *Streptococci*, and Gram-negative *Bacilli* such as *Pseudomonas* (Austin et al., 2017; Tabbara et al., 2000; Thomas and Kaliamurthy, 2013). **Figs. 2–4** show common presentations of bacterial keratitis.

Corneal scrapings should be performed immediately before the commencement of treatment. Systemic antimicrobial treatment is generally not indicated in bacterial keratitis, but may be considered if there is suspected risk of developing endophthalmitis or bacterial scleritis (Austin et al., 2017; Bowling, 2015; Thomas and Kaliamurthy, 2013). Initial treatment should be commenced as soon as possible with a broad-spectrum antibiotic to cover both Gram-positive and Gram-negative pathogens (Austin et al., 2017).

Antibiotic management is prescribed according to the severity of the infection and the level of risk for visual loss or blindness (Austin et al., 2017; Gerstenblith and Rabinowitz, 2012; Thomas and Kaliamurthy, 2013). Mild bacterial keratitis has a lower risk of visual loss and is characterized by minimal anterior chamber involvement and no discharge. As such, the treatment of mild bacterial keratitis usually includes topical fluoroquinolones eye drops, such as ofloxacin or ciprofloxacin. Hourly treatment is essential

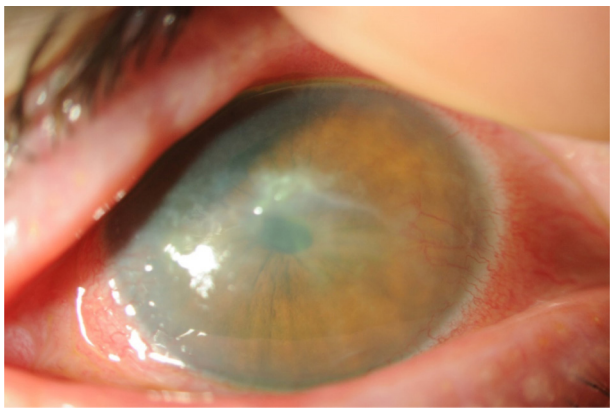

Figure 2 Bacterial keratitis characterized by a purulent opaque layer with a typical white spot on the surface of the cornea, which can be seen even without a slit lamp.

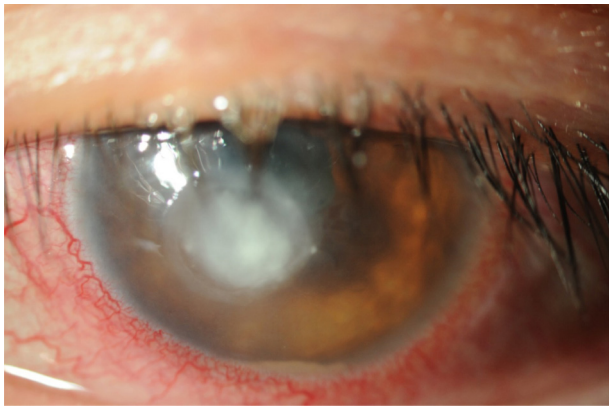

Figure 3 Bacterial keratitis with a more prominent white infiltrate on the cornea. Redness of the eye is reflective of the inflammation and pain caused by the microbial infection. White spot can also be indicative of a corneal ulcer.

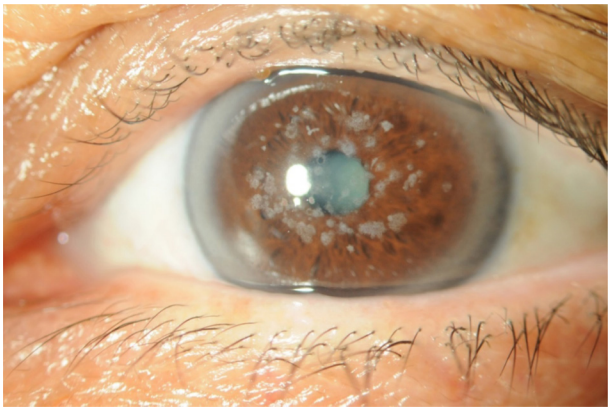

Figure 4 Typical crystalline Streptococcal bacterial keratitis, characterized by surface growth on the cornea. Hyperinflammation usually occurs at the induction of treatment before infection resolves with ongoing topical bacterial treatment.

during the first few days to ensure adequate therapeutic tissue concentrations and control of the infection. For patients who are contact lens wearers (Gokhale, 2008; Sueke et al., 2010), the addition of a topical antibiotic ointment (for example, tobramycin) at night may be beneficial for sustained effect. In cases where risk of visual loss is borderline, distinguished by epithelial and anterior chamber involvement, topical fluoroquinolones, administered hourly, are the treatment of choice (Sueke et al., 2010). Although ciprofloxacin has a better inhibitory effect against *Pseudomonas aeruginosa* and *Serratia*, moxifloxacin should be considered for superior Gram-negative cover (Hindman et al., 2009; Sueke et al., 2010).

Severe keratitis is vision threatening and is indicated with presence of large ulcers >1–2 cm, or when the infection is unresponsive to initial treatment. Fortified aminoglycoside plus cefalotin/cefazolin (5% w/v) eye drops are the recommended therapies (Ly et al., 2006; Therapeutic Guidelines, 2014; Wong et al., 2003). The aminoglycoside antibiotics used in fortified drops are gentamicin (0.9% w/v) and tobramycin (1.4% w/v) and have an excellent Gram-negative coverage (Ly et al., 2006; Wong et al., 2003). Topical treatment should be commenced every hour, and administered throughout a 24-h period.

The practice patterns in using fortified antibiotic eye drops for the treatment of bacterial keratitis has changed as antimicrobial resistance emerged. A recent international study recorded that clinicians prefer fortified antibiotics versus fluoroquinolone monotherapy, particularly in the United States where there is a greater concern with resistant organisms (Tuft and Burton, 2013). However, it is important to note that fortified preservative-free gentamicin/tobramycin and cefalotin/cefazolin ophthalmic drops are not available commercially and require manufacturing from specialized units in hospitals or pharmacies. Loading doses of topical treatment have been suggested for more severe infections, commencing at a frequency of one drop every five minutes for the first five doses or thirty minutes, and then every half hourly for the first 24 h (Bowling, 2015; Cohen, 2009; Sueke et al., 2010; Tuft and Burton, 2013). Prolonged use of topical aminoglycosides such as gentamicin may cause epithelial toxicity or necrosis and delayed recovery. In these cases, topical therapy may be replaced by topical fluoroquinolone drops, and subsequently be modified according to the results of bacterial sensitivity.

Cycloplegic agents are important adjuvant therapies in the management of microbial keratitis and are indicated when there is substantial anterior chamber inflammation. They are administered twice to three times daily, to decrease pain as well as synechia formation in bacterial keratitis. Topical corticosteroids are not usually part of the initial treatment regimen, and the place of adjuvant corticosteroids in the treatment of bacterial keratitis has been debated (Chung et al., 1998). The use of corticosteroids may be beneficial to improve outcomes by decreasing inflammation, thereby reducing scarring. However, corticosteroids may delay epithelial healing in keratitis and may even worsen infection (Chung et al., 1998; Schein, 2016). In some practices, topical corticosteroids are commenced after 24 h of topical antibiotics. Preservative-free formulations should be used where available to reduce epithelial toxicity.

In patients at risk of corneal perforation, antimetalloproteinases may be useful as they have proven anticollagenolytic activity to prevent progression of corneal necrosis and tissue breakdown (McElvanney, 2003). Tetracyclines, such as doxycycline, have been shown to display antimetalloproteinase properties and can achieve therapeutic levels in the anterior segment of the eye (McElvanney, 2003). Oral doxycycline 100 mg twice daily maybe be useful in these patients (Gerstenblith and Rabinowitz, 2012). In eyes with corneal thinning, a shield should be used to protect the ocular surface (Gerstenblith and Rabinowitz, 2012).

Fungal Keratitis

Fungal keratitis is a slower progressing form of keratitis, found more commonly in tropical climates. It is diagnosed primarily through PCR tests or cultures collected from corneal scrapings. The most common pathogens for fungal keratitis are usually *Aspergillus*, *Fusarium*, or *Candida* species (Austin et al., 2017; Therapeutic Guidelines, 2014). Compared to bacterial keratitis, the incidence of fungal infection is much lower but can have a high risk of causing loss of vision (Medoff and Kobayashi, 1980). In tropical areas, fungal infections have been documented to be responsible for 50% of corneal ulcers, and they carry a worse prognosis

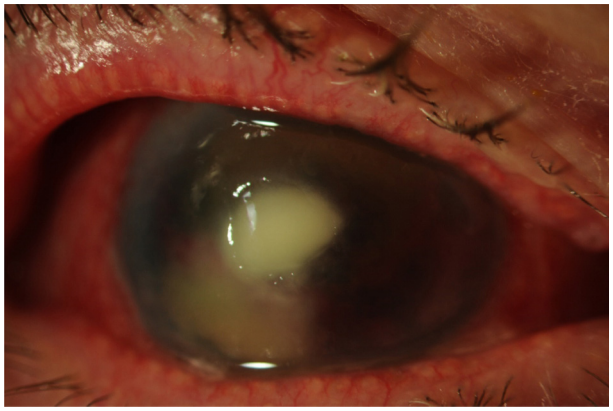

Figure 5 Slit-lamp image of fungal keratitis, typically with white spot with filamentous or "fluffy" edges. Identification of fungal keratitis, without a slit lamp, can be made with characteristic remarkable opaque infiltrate on one section of the cornea.

compared with bacterial keratitis as they are associated with higher rates of corneal perforations (Austin et al., 2017; Medoff and Kobayashi, 1980). Common presentation of fungal keratitis is shown in **Fig. 5**.

Studies have described the empirical and preferred treatment for fungal keratitis is topical natamycin, as it is active against *Fusarium* and *Aspergillus* (Xie et al., 2001). Natamycin works by binding to fungal plasma membrane and causes disruptions by altering membrane permeability and is commercially available in eye drop formulation (Xie et al., 2001). In cases of suspected fungal keratitis, and for established filamentary fungal infection, natamycin is generally administered every 1–2 h throughout the day and reduced according to clinical response (Ansari et al., 2013; Xie et al., 2001). Topical chlorhexidine 0.02% with the addition of topical voriconazole can be used as an alternative if natamycin is unavailable (FlorCruz and Evans, 2015). Topical amphotericin 0.15% every 1–2 h is the recommended treatment if *Candida* species has been isolated (Ansari et al., 2013; Yu et al., 2004).

Systemic (oral) and topical voriconazole may be beneficial in treating patients with *Fusarium* species for the treatment of deep corneal ulcers or suspected fungal endophthalmitis (Medoff and Kobayashi, 1980; Prajna et al., 2016). Therapeutic drug monitoring of voriconazole is recommended as it has a narrow therapeutic range, nonlinear pharmacokinetics and is primarily metabolized by CYP2C19 in the liver (Li et al., 2016). A meta-analysis has shown that CYP2C19 displays polymorphism with poor metabolizers exhibiting higher voriconazole trough concentrations than intermediate of extensive metabolizers (Li et al., 2016). Furthermore, the meta-analysis showed that extensive metabolizers had poorer treatment success rates than poor metabolizers, as they may not have achieved adequate levels of voriconazole (Li et al., 2016). Although limited evidence exists on the appropriate levels required in ophthalmology, it has been recommended that trough concentrations of between 1 mg/L and 4–6 mg/L are effective without causing toxicity (Rossi, 2018). To achieve therapeutic levels in a timely manner, loading doses are recommended commencing at 400 mg twice daily and reducing to 200 mg twice daily thereafter (Bowling, 2015; Therapeutic Guidelines, 2014; Yu et al., 2004).

Cycloplegic agents can be used in the management of pain associated with keratitis. Topical or oral corticosteroids are not recommended in fungal keratitis. Existing corticosteroid therapy for other comorbidities should be tapered rapidly and discontinued (Sueke et al., 2010).

Acanthamoeba Keratitis

Acanthamoeba keratitis is a rare protozoal infection of the eye, with recent increased incidence (Yu et al., 2004). The infection is commonly misdiagnosed for noninfectious or bacterial, fungal, or viral keratitis. Acanthamoeba keratitis is often caused by poor contact lens hygiene (such as swimming, showering, and face washing whilst wearing contact lenses) or corneal trauma involving soil or contaminated water.

Clinical features of acanthamoeba keratitis are not useful as a diagnostic tool, as presentation of the infection varies greatly. Patients may present with manifestations indicative of other less sight-threatening eye infections, so rapid differential diagnosis is essential by assessing clinical signs, as well as patient history (Lorenzo-Morales et al., 2015; Simitzis-Le et al., 1989; Yu et al., 2004). Symptoms of acanthamoeba keratitis include severe eye pain and sensation of foreign body. Photophobia and visual disturbances, such as deceased visual acuity, are also commonly described. Epiphora, or increased tearing of the eyes, and redness are also present. Infection presents unilaterally, but cases of bilateral infection have been reported. Immediate cultures and swabs of the eye should be taken, and therapy should be directed appropriately (Lorenzo-Morales et al., 2015; Simitzis-Le et al., 1989). **Figs. 6 and 7** show common presentations of acanthamoeba keratitis.

The aim of topical treatment is to eliminate amoebic cysts (Lorenzo-Morales et al., 2015; Simitzis-Le et al., 1989). Topical polyhexanide (also referred to as polyhexamethylene biguanide, PMHB) and chlorhexidine, administered every hour, are the recommended treatments for acanthamoeba keratitis. The two agents can be used interchangeably as there is absence of documented evidence that one is superior to the other. However, it has been suggested that polyhexanide may be superior due to its cysticidal effects (Simitzis-Le et al., 1989). In some practice settings, dual therapy of topical polyhexanide and chlorhexidine are

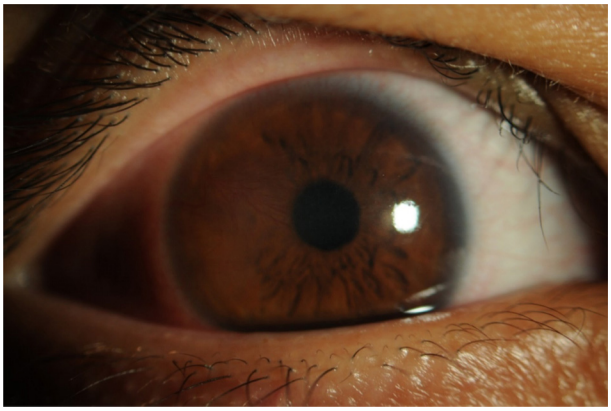

Figure 6 Acanthamoeba keratitis is difficult to differentially diagnose. At times, the typical white infiltrate may be present but in the initial stage of infection, the eye has less opacity, but with a distinct 360° stromal ring surrounding the iris.

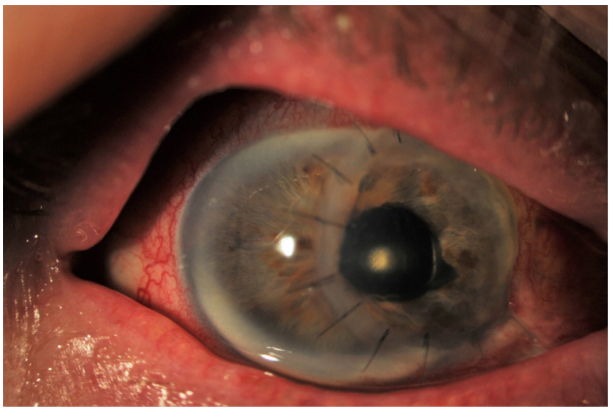

Figure 7 Enhanced slit-lamp image of Acanthamoeba keratitis with distinct stromal ring around the iris.

commonly used (Ferrari et al., 2011; Lorenzo-Morales et al., 2015; Simitzis-Le et al., 1989). In addition, the use of double biguanide therapy has been described for additional and superior treatment outcomes. Hexamidine eye drops can be prescribed in conjunction with both PMHB and/or chlorhexidine (Ferrari et al., 2011). In countries where hexamidine is not available, propamidine isethionate 0.1% eye drops may be a suitable alternative (Chu and Hu, 2013; Gerstenblith and Rabinowitz, 2012).

Corticosteroid therapy is not recommended during the initial treatment of acanthamoeba keratitis as it may affect the immune response thought to be important in elimination of acanthamoeba infection. Subsequently, this may delay recovery and adversely affect outcome (Gokhale, 2008).

Atypical Keratitis

The incidence of atypical keratitis is very rare. It is usually caused by mycobacteria or Gram-positive nocardia, which can be found in soil, dust, or water. Mycobacterium keratitis is difficult to identify, often incorrectly misdiagnosed as other forms of keratitis, and subsequently results in significant delays in treatment. Atypical keratitis can be treated with topical antimicrobials or in combination with systemic treatment. Most infections require the use of more than two types of antibiotics, such as a macrolides, fluoroquinolones, and amikacin (Gerstenblith and Rabinowitz, 2012; Kampougeris et al., 2005; Tabbara, 2007). Topical moxifloxacin is the fluoroquinolone of choice with higher ocular penetration and is used in *mycobacterium* infection (García-Sáenz et al., 2001; Tabbara, 2007). Amikacin eye drops are effective if *Nocardia* species is suspected. Initially, hourly topical therapy should be commenced, with gradual tapering of treatment according to clinical response (Grigg et al., 1992; Tabbara, 2007). If systemic antimicrobials are required, oral moxifloxacin or clarithromycin has been described as an additional therapy (Bowling, 2015; Chu and Hu, 2013).

Herpes Simplex Keratitis

Herpes simplex keratitis is caused by the herpes simplex virus (HSV) or the reactivation of latent herpes simplex virus infection. Herpes simplex keratitis (also known as HSV keratitis) may be further classified as epithelial keratitis or stromal keratitis

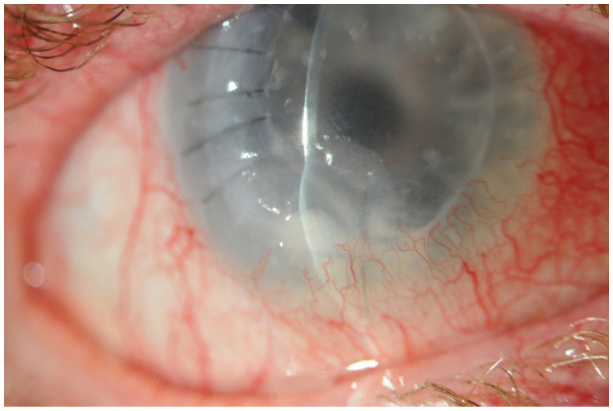

Figure 8 Typical purulent opaque layer of microbial keratitis. Herpetic infection is generally characterized by conjunctival injection (or blood shot) eyes.

(Bowling, 2015; Farooq and Shukla, 2012; Therapeutic Guidelines, 2014). Epithelial keratitis generally resolves within one to two weeks, and may not require treatment while stromal keratitis may include corneal scarring, that can lead to pain and loss of vision. Confirmation of HSV keratitis usually occurs through fluorescein corneal staining or PCR testing in conjunction with slit lamp examination (Bowling, 2015). Patients with HSV keratitis may present with similar symptoms of other ocular inflammation such as blepharitis, dacryocystitis, retinitis, or iritis (**Fig. 8**). Unilateral infection is common, though both eyes may be affected in immunocompromised patients. Other symptoms may include extensive ulceration of the cornea and associated severe pain, sensation of a foreign body in the eye, photophobia, and epiphora (Bowling, 2015).

Both oral and topical antiviral treatment is recommended in the treatment of HSV keratitis (Catron and Hern, 2008; Farooq and Shukla, 2012; Tsatsos et al., 2016). Topical aciclovir 3% ointment is commonly used, applied five times a day for 14 days. Ganciclovir 0.15% eye gel is generally reserved for refractory or severe herpes simplex keratitis not responding to other treatment (Bowling, 2015). Systemic antivirals can also be used monotherapy or in combination with a topical antiviral. Oral aciclovir (400–800 mg), valaciclovir (1 g), or famciclovir (250–500 mg) are usually given three to five times a day for 7–10 days (Bowling, 2015; Therapeutic Guidelines, 2014; Tsatsos et al., 2016).′ Oral therapy has been implicated as the preferred treatment choice in stromal keratitis as topical treatment can lead to scarring and possible nasolacrimal duct obstruction. It is also documented that oral therapy may have superior effects compared to topical therapy due to greater ocular penetration (Tsatsos et al., 2016).

Topical or oral corticosteroids are contraindicated in active and epithelial herpetic infection but may be effective to control severe inflammation and assist with pain when used with an antiviral to manage later-stage stromal involvement or uveitis. Again, topical cycloplegic adjuvant therapy can assist relieve photophobia and reduce pain (Bowling, 2015; Tsatsos et al., 2016).

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) describes shingles involving the dermatome supplied by the ophthalmic division of the fifth cranial (trigeminal) nerve (Bowling, 2015). Varicella-zoster virus (VZV) causes both chicken-pox (varicella) and shingles (herpes zoster). Reactivation of VZV is the most common cause of viral ophthalmicus (Bowling, 2015). The difference between herpes simplex keratitis and HZO is the noticeable and recognizable dermatological presentation in the latter disorder. Patients with HZO usually present with skin and mucosal involvement typical of standard zoster infection. Reactivation of the infection involves the trigeminal nerve in 15% of patients, and subsequently the eye (Therapeutic Guidelines, 2014). Initial manifestations and symptoms can be similar to other infective eye disorders and may be difficult to differentially diagnose. Confirmation of HZO can be confirmed by other VZV characteristics on the skin and past history of infection (Tsatsos et al., 2016). For the treatment of HZO, systemic antiviral therapy is recommended and commenced within 72 h of onset of symptoms. Initial treatment is the same as for herpes simplex keratitis, including systemic use of aciclovir, valaciclovir, and famciclovir (Bowling, 2015). Topical aciclovir ointment can also be used in addition in severe cases of HZO.

Treatment of Posterior Eye Infections

Posterior eye infections include those of the sclera, retina, vitreous humor, and possibly the optic nerve.

Endophthalmitis

Endophthalmitis is usually caused by infection leading to an inflammatory condition of the intraocular cavity (Bowling, 2015; Ciulla et al., 1997; Therapeutic Guidelines, 2014). Inflammation affects one or more layers of the eye and an adjacent cavity (anterior, posterior chamber) or vitreous cavity. Onset of endophthalmitis is usually acute and characterized by impaired vision,

Table 3 Most common organisms in endophthalmitis

Bacterial:
Gram-positive bacteria (75%–85%)
Staphylococcus epidermidis 43%
Streptococcus spp. 20%
Staphylococcus aureus 15%
Propionibacterium acnes 30 reports
Bacillus cereus 1%
Gram-negative bacteria (10%–15%)
Pseudomonas 8%
Proteus 5%
Haemophilus influenzae 0%–1%
Klebsiella 0%–1%
Coliform spp. 0%–1%
Fungal (rare)
Candida parapsilosis
Aspergillus
Cephalosporium

Source: Modified from Sunaric and Pournaras (1997).

edema in the eyelid, congested eye, and redness. Pain, which was initially considered essential in diagnosis, can be absent in approximately 25% of cases (Ciulla et al., 1997).

Studies have reported that the infecting organism profile is very similar to periocular microbes, which may suggest endophthalmitis is caused by the patient's own flora. **Table 3** shows the most common causative pathogens in endophthalmitis (Sunaric and Pournaras, 1997).

Bacterial Endophthalmitis

Endophthalmitis is a serious condition that can lead to vision loss. Due to the vision threatening nature of endophthalmitis, empirical treatment of intravitreal antimicrobials is given immediately, while investigations are undertaken to determine the causative organisms. A 10-year review of bacterial endophthalmitis isolates in the United States observed that no single agent provided effective treatment for all isolated microbes (Schimel et al., 2013). As such, empirical treatment includes the combination of (Therapeutic Guidelines, 2014) intravitreal vancomycin (1.0–2.0 mg in 0.1 mL) and a broad-spectrum cephalosporin, such as ceftazidime (2–2.25 mg in 0.1 mL) (Schwartz and Flynn, 2014). Vancomycin covers Gram-positive organisms, including methicillin-resistant Staphylococcus aureus (MRSA), while broad-spectrum cephalosporins and quinolones cover Gram-negative organisms (Schimel et al., 2013). Intravitreal amikacin is generally not recommended due to the possibility of retinal toxicity (Bhagat et al., 2011), although its use has been described in the Endophthalmitis Vitrectomy Study (Doft and Barza, 2004; Han et al., 1996). Intravitreal treatment can be repeated after 48–72 h if there is no improvement (Bowling, 2015). Acute-onset postoperative endophthalmitis with multidrug-resistant organisms occurs rarely (Khera et al., 2013). Alternative intravitreal agents, such as moxifloxacin, have been reported useful in these situations (Bowling, 2015).

As an adjunct, systemic fluoroquinolones have been shown to have adequate ocular penetration to achieve therapeutic levels (Pathengay et al., 2006). Ciprofloxacin is the fluoroquinolone of choice, but recently studies have suggested that moxifloxacin has superior effect with more rapid resolution of inflammation in the interior chamber and superior ocular effects compared to other quinolones. However, moxifloxacin is not active against *Pseudomonas* infection and should not be used if it is suspected.

The use of corticosteroids is controversial. Although corticosteroids have a theoretical role in reducing inflammation-related ocular damage associated with endophthalmitis, limited evidence supports its use. One pilot series of five patients showed that (Pathengay et al., 2006) the use of intravitreal triamcinolone acetonide 48–72 h after initial treatment with antibiotics was associated with favorable clinical outcomes (Pathengay et al., 2006). However, additional studies are required before recommending its routine use. If corticosteroids are used, intravitreal dexamethasone or triamcinolone (0.4 mg in 0.1 mL) or topical dexamethasone 0.5% or prednisolone acetate 1% may be suitable (Bowling, 2015; Riddell et al., 2011). Oral corticosteroid may be commenced 24 h after intravitreal injection if corticosteroid therapy is not contraindicated by patient factors or suspected fungal infection (Pathengay et al., 2006). Preservative free eye drops are recommended as high frequency treatment is required and intraocular toxicity from preservatives can occur, particularly if open globe injuries are suspected (Bowling, 2015).

Fungal Endophthalmitis

Fungal endophthalmitis is rare but occurs more frequently as a complication of candidemia compared to invasive aspergillosis (**Fig. 9**). Penetration of systemically administered antifungal agents is highly variable, as absorption of these drugs into the posterior segment of the eye is difficult. Riddell et al. (2011) documents that amphotericin B achieves very poor concentrations (Riddell et al., 2011). However, the study showed that voriconazole achieved high concentrations in the vitreous, where therapeutic concentrations were most significant for the treatment of *Candida* and *Aspergillus* (Riddell et al., 2011). Recently, intravitreal

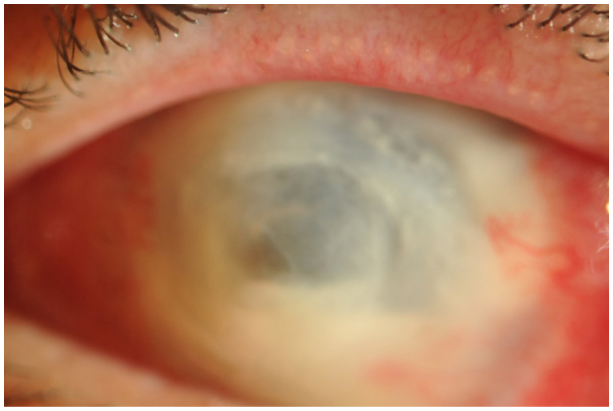

Figure 9 Severe Fungal Endophthalmitis characterized by a matt-like opacity due to infiltrate of fungal filaments.

administration has become more common, where amphotericin is administered into the vitreous space at a dose of 5–10 μg in 0.1 mL and voriconazole at 0.05 mg in 0.1 mL (Bowling, 2015; Riddell et al., 2011). Oral voriconazole may also be used for 5–6 weeks due to slow clinical response and resolution of fungal infections. Once fungal species have been confirmed, therapy can be altered to fluconazole for candida or itraconazole for aspergillus (Bowling, 2015; Gerstenblith and Rabinowitz, 2012).

Viral Retinitis

Viral retinitis can be caused by cytomegalovirus, herpes simplex virus, or varicella-zoster virus in immune compromised patient. All types of viral retinitis have a high risk of vision loss and require immediate referral.

Cytomegalovirus Retinitis

Cytomegalovirus retinitis is the most common type of viral retinitis and is predominantly described in patients with human immunodeficiency virus (HIV) infection. HIV markers are useful in diagnosing CMV retinitis as approximately 15%–40% of HIV patients are affected by the disease (Bowling, 2015). If CMV retinitis is suspected, clinicians should order a CD4 count screen, CD8+ T-lymphocyte count, CMV DNA capture PCR test, DNA PCR (from ocular fluids), viral load, and complete blood count (Bowling, 2015). Typically, patients with CMVR present with a painless, red, and inflamed eyes. Although it is painless, patients may feel some discomfort in their eye, such as a feeling of foreign objects or have specks in their visual field. CMV retinitis is often described as having a "cottage cheese with tomato sauce" appearance due to perivascular hemorrhage (Fig. 10).

Drugs used for the treatment of CMVR retinitis are virostatic and therefore do not eliminate the infection or prevent recurrence of the infection. Treatment is directed by the cause of immunosuppression. In addition, intravitreal foscarnet (2.4 mg in 0.1 mL) may be used with oral antiviral therapy. Oral valganciclovir is generally the treatment of choice and commenced at 900 mg twice daily for

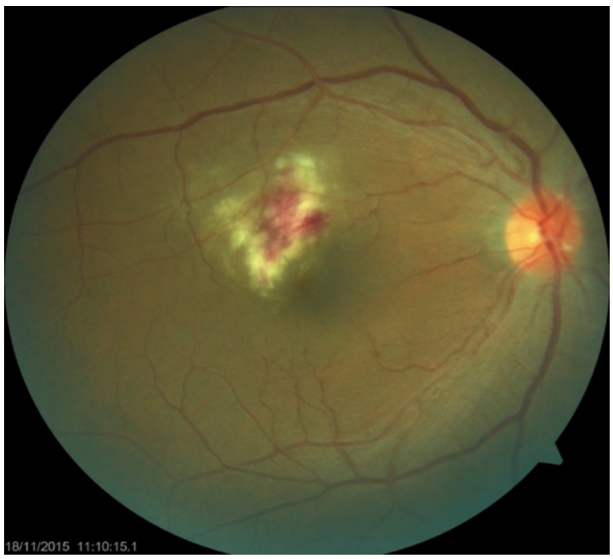

Figure 10 Cytomegalovirus retinitis slit-lamp image displaying typical opacity with red vasculature, often described as "cottage cheese with tomato sauce."

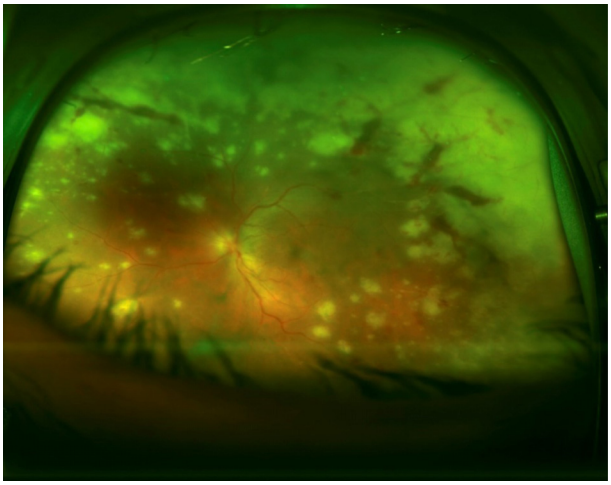

Figure 11 Acute retinal necrosis cannot be differentially diagnosed without slit-lamp imagine and PCR testing of microbial strains. Image shows characteristic opaque patches and thickening of the retina.

two to three weeks, and then reduced to 900 mg daily (Bowling, 2015; Gerstenblith and Rabinowitz, 2012). In refractory disease, intravenous cidofovir is used concomitantly with oral probenecid as a nephroprotectant (Wolf et al., 2003).

Systemic corticosteroids are not recommended in the management of CMV retinitis. The use of intravitreal, dexamethasone (unpreserved) 4 mg per 0.1 mL administered with intravitreal antivirals, topical preservative-free corticosteroid, or oral corticosteroid have also been described in literature to manage ocular inflammation (Gerstenblith and Rabinowitz, 2012).

Acute Retinal Necrosis

Acute retinal necrosis (ARN) generally presents as necrotizing retinitis caused by a viral infection of the retina, typically VZV or HSV. ARN can occur in healthy individuals but is twice as common in males than in females and is often presents with a history of immunosuppression. ARN is mostly due to HSV in younger patients, and VZV in the older population. ARN caused by cytomegalovirus, syphilis, or toxoplasmosis is rare (Bowling, 2015). ARN is characterized by acute pain and photophobia. Patients may also describe vision disturbances, decreased vision, and presence of floaters. Diagnosis of ARN is through an eye examination, which will show multiple white opaque patches and thinning of the retina is typical of the disease (**Fig. 11**). Severe inflammation may result in difficulty to differentially diagnose between ARN and other ocular disease. Confirmation of disease is via cultures obtained through a vitreous procedure and PCR results. Confirmation of sensitivities may direct therapy (Bowling, 2015; Shantha et al., 2015; Therapeutic Guidelines, 2014).

ARN should be treated immediately and aggressively with systemic and intravitreal antiviral therapy. Advancements in pharmacotherapy and experience with intravitreal injections have resulted in intravitreal foscarnet (2.4 mg in 0.1 mL) being the preferred initial treatment. A single injection can be easily administered, and then repeated once ARN is confirmed (Bowling, 2015; Kawaguchi et al., 2008; Shantha et al., 2015). Systemic therapy is also recommended with the aim to inhibit viral replication and halt disease progression in the affected eye and prevent involvement of the unaffected eye (Shantha et al., 2015). Systemic therapy for ARN includes aciclovir, valaciclovir, famciclovir, valganciclovir, foscarnet, and ganciclovir (Bowling, 2015; Kawaguchi et al., 2008; Shantha et al., 2015). Oral maintenance treatment with valaciclovir (1 g 3 times a day) or aciclovir, may be used up to 14 weeks from the onset of infection depending on clinical response.

Cycloplegic agents and anticholinergic treatments can be used as adjuvant therapies in the management of acute retinal necrosis. If inflammation is present in the anterior segment of the eye, topical corticosteroids may be used.

Studies show that vascular occlusion and ischemia of the retina are also involved in ARN. As such, aspirin 100 mg daily and oral corticosteroid treatment have a place in treatment to prevent platelet aggregation (Gerstenblith and Rabinowitz, 2012). Heparin and warfarin have also been reviewed, but currently there is no robust evidence for anticoagulation in ARN treatment (Shantha et al., 2015). Systemic corticosteroids are considered when optic nerve involvement is suspected. Delaying corticosteroid therapy is advised and should only be commenced at least 24 h after the initiation of antiviral therapy (Bowling, 2015; Kawaguchi et al., 2008; Shantha et al., 2015).

Ocular Toxoplasmosis

Ocular toxoplasmosis is a progressive and recurring necrotizing retinitis, with vision-threatening complications. Ocular toxoplasmosis can be congenital or acquired, and worldwide, toxoplasmosis is the most common cause of posterior uveitis (Bowling, 2015; Duane et al., 2013). Ocular toxoplasmosis is caused by *Toxoplasma gondii*, a single cell intracellular protozoan opportunistic organism. Primary infection can occur with exposure to high-risk environments, such as tropical, warm, and wet areas, compared

to areas that have low humidity. The most common host for *Toxoplasma gondii* is felines, but humans, reptiles, and avian hosts are also possible (Hovakimyan and Cunningham, 2002).

Toxoplasmosis is characterized by blurred vision and floaters. Infection can cause inflammation of the iris which results in eye pain and redness. Diagnosis is through PCR, and testing both the aqueous and vitreous humor for positive cultures of *Toxoplasma gondii* immunoglobulin (Duane et al., 2013; Hovakimyan and Cunningham, 2002).

Mild and non sight-threatening disease does not require medical management as it is generally self-limiting in immunocompetent patients. Pharmacological treatment is only required when major vessels, or the infection, extend beyond the peripheral section of the eye. If medications are required, a combination drug regimen is generally recommended and includes the use of pyrimethamine, folinic acid, sulfadiazine, clindamycin, and corticosteroids (Bowling, 2015; Duane et al., 2013; Stanford et al., 2003). Pyrimethamine is probably the most effective single drug as it interferes with parasite replication by inhibiting the folate production pathway. It is therefore coadministered with folinic acid (15 mg) to protect against bone marrow suppression in the host. Clindamycin interferes with protein synthesis and can be used as a single drug or in combination with corticosteroids. Clindamycin may also be given as an intravitreal injection as initial empirical treatment (Kishore et al., 2001; Stanford et al., 2003).

The Role of the Pharmacist

In acute eye infections, pharmacists have an important role to ensure resolution of infection and to improve patient outcomes. Eye hygiene is the cornerstone for most treatment to prevent the spread and worsening of the infection. These principles compliment pharmacists' role in antimicrobial stewardship to reduce antimicrobial use and resistance. As primary health-care professionals, pharmacists should also be able to recognize severe infection and ensure early referral. Pharmacists have the responsibility of ensuring patients can remain adherent to their medication regimen, which can be complicated by the use of compounded eye drops that are often used for eye infections.

Hygiene and Antimicrobial Stewardship

Nearly all eye infections require patients to maintain eye hygiene to prevent the spread and progression of the infection. Cross infection may occur through contaminated instruments, hands, communal towels, droplets, and the eye drop bottles. In addition, patients with dry eye or inadequate lid closure are more susceptible to cross infection. Pharmacists should encourage patients to wash their hands often with soap and warm water and avoid touching or rubbing their eyes. It is also recommended that patients wash their pillowcases, sheets, and towels often in hot water and detergent (National Center for Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases, 2019). Patients should also avoid sharing pillows and towels (Rutter, 2017). If possible, clear any discharge from the eye with sterile sodium chloride 0.9% before using other ocular medications (Rossi, 2018). If patients use tissues to wipe discharge from the eye, the tissue should be thrown away immediately (Rutter, 2017). Patients that wear contact lenses should also be advised not to wear them until 24 h after the infection has resolved (Rossi, 2018).

Pharmacists should also be guided by antimicrobial stewardship principles to prevent the growing rise of antimicrobial resistance. Historically, overuse of antimicrobials has been the primary driver for the rise of antimicrobial resistance. Limiting the use of antimicrobials to only clinical cases that will benefit from their use is recommended. An example of this is the treatment of conjunctivitis in the pharmacy. As up to 80% of infective conjunctivitis are caused by viruses and are self-limiting, antibiotics should not be recommended and instead pharmacists should focus on eye hygiene counseling for these patients (Azari and Barney, 2013; Rutter, 2017). However, if the patient's symptoms persist for more than 5 days, they should be reassessed and antibiotics considered (Rutter, 2017).

When antimicrobials are used, pharmacists can ensure that appropriate empirical therapy is used based on clinical symptoms. Once the causative organisms and its sensitivities are confirmed, pharmacists may recommend switching to a narrow-spectrum antimicrobial to preserve broad-spectrum antimicrobials for more difficult cases.

Pharmacists should ensure that there is an estimated length of time of drug administration for all antimicrobials used. Excessive use of antimicrobials can cause hypersensitivity or toxicity reactions. In addition, using antimicrobials longer than necessary may facilitate the development of resistant strains of bacteria. The excessive use of multiple antimicrobials increases the risk of superinfection.

Referral

Community pharmacists are often presented with vague red eye symptoms from patients, and a thorough history and examination are required to determine a diagnosis. Minor ailments such as allergic and viral conjunctivitis can be managed within the pharmacy setting without referral (Azari and Barney, 2013). For bacterial conjunctivitis, some countries allow pharmacists to supply topical chloramphenicol eye drops or ointments to patients without a prescription (Robaei et al., 2015). However, any patients presenting with severe conjunctivitis with marked redness throughout the eye are best referred (Rutter, 2017). Furthermore, patients with contact lenses should be referred as they are more predisposed to keratitis because the space between the contact lens and cornea can act as an incubator for bacteria and enhance mechanical abrasion (Rutter, 2017).

Pharmacists should also be aware that a painful red eye should generally be referred. Although it is common for conjunctivitis to present with discomfort from ocular irritation, described as gritty, true pain would indicate a more serious condition, such as scleritis, uveitis, or keratitis (Rutter, 2017). Furthermore, a patient that presents with photophobia or distortion of vision should also be referred as these are symptoms not commonly presented with conjunctivitis (Rutter, 2017; Sehu, 2009). Pharmacists should also exclude the risk of a foreign body (e.g., metal, glass, wood, plastic, sand) or infection inside the eye before recommending any treatments. Patients who have recently had eye surgery or a history or welding/woodworking should also be referred (Rutter, 2017; Sehu, 2009).

Adherence

Treatment adherence and compliance is high in eye infection due to pain and discomfort of the disease, and administration of therapy has immediate and apparent outcomes (Dolz-Marco et al., 2015). However, in severe eye infections, low adherence of treatment may be due to high frequency of eye drops, particularly in the treatment of bacterial keratitis, which requires patients to administer eye drops every 5–30 min. Low adherece may also be due to difficulty in obtaining compounded antimicrobial eye drops. Subsequently, compounded eye drops have a very short shelf-life and may require special storage conditions, such as refrigeration. All these factors may lead to poor adherence in those requiring long-term treatments. Clear communication is crucial so patients are aware of their medication regimen, supply options, and appropriate storage requirements (Dolz-Marco et al., 2015).

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Epilepsy: Management of Neurological Disorder and the Pharmacist's Role

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Learning Objectives

- To understand etiology and diagnosis of epilepsy
- To understand the therapies, as well as monitoring of efficacy and toxicity of medicines
- To understand the pharmacist role of in the management of epilepsy

Take Home Messages

1. Choice of a therapy is related to seizure type and patient demographics.
2. Most of the antiepileptic drugs AEDs are narrow therapeutic index medicines requiring counseling on adverse drug reactions ADRs and therapeutic drug monitoring.
3. AEDs have a higher degree of drug interaction and therefore need additional counseling and use of written information on medicines.
4. Knowledge of emergency treatment of seizures is important for pharmacist working in community setting as it may help avoid further complication of disease.
5. Resistant epilepsies require special dosing management both for initiation and tapering.
6. Pharmacists can play an important role in managing disease and therapy in special patient groups, women and patients with psychiatric conditions.

Introduction to Epilepsy

Seizures and Epilepsy

Epilepsy is a brain disorder typically manifested by sudden brief periods of altered and diminished consciousness, involuntary movements, or convulsions due to abnormal electrical activity in the brain (Merriam-Webster, 2018; World Health Organization, 2018). Globally, epilepsy is one of the most common and significant diseases of the central nervous system (Löscher et al., 2013), affecting approximately 50–70 million people (Ngugi et al., 2010; World Health Organization, 2018). Approximately 4.6 million people develop epilepsy every year (Fiest et al., 2017). According to the International League Against Epilepsy (ILAE), someone is presumed epileptic when he or she has an epileptic seizure and "demonstrates a pathologic and enduring tendency to have recurrent seizures" (Fisher et al., 2014). Conceptually, an epileptic seizure is "a brief occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005).

The imbalance between excitatory and inhibitory neuronal activity, overshooting and synchronous electrical discharges by groups of neurons in the brain, gives rise to epileptic seizures (Wu et al., 2015). The abnormal neuronal activity in neural pathways involved in seizure development, known as epileptic networks, may lead to inter-ictal and ictal epileptic activity (Luo et al., 2014; McCormick and Contreras, 2001). Although, the hallmark for epilepsy is the presence of epileptic seizures, it is important that seizures and epilepsies are considered and understood separately (Fisher et al., 2014; World Health Organization, 2018).

Diagnosis of Epilepsy

According to the ILAEs "new operational definition," epilepsy is diagnosed clinically, when someone has (1) at least two unprovoked or reflex seizures >24 h apart (2) one unprovoked or reflex seizure and the risk of at least 60% to have another within the following 10 years or (3) an epilepsy syndrome (Fisher, 2015; Fisher et al., 2014). A person does not necessarily become epileptic after one seizure, as at least 10% of people worldwide encounter one seizure during their lifetime (World Health Organization, 2018). However, epilepsy can be diagnosed after a single unprovoked seizure if sufficient supporting evidence such as inter-ictal EEG or brain imaging is available (Beretta et al., 2017).

Here unprovoked seizures also referred as spontaneous recurrent seizures (SRS), need to be distinguished from early or provoked or symptomatic seizures and their underlying diseases, which are therisk factors for the development of epilepsy (Löscher and Brandt, 2010; Pitkanen et al., 2016). Early seizures are caused by transient factors, for example, acute nervous system insults such as a stroke, trauma, toxicity, or infections (Beghi et al., 2010; Rizvi et al., 2017), high grade fever, concussions, or alcohol withdrawal (Scheffer et al., 2016), and are not a symptom of epilepsy, as they temporarily lower the seizure threshold of an otherwise normal brain (Fisher et al., 2014).

The burden of comorbidities in epileptic patients is often high (Keezer et al., 2016; Löscher et al., 2013; Tellez-Zenteno et al., 2007), as epilepsies are often associated with psychological, neurobiological, and cognitive disorders with social impact affecting the quality of life (Fisher et al., 2005; Jacoby et al., 2009; Rudzinski and Meador, 2013). A bilateral relationship between psychiatric disorders and epilepsy is also documented (Mula, 2017). Mood and anxiety disorders are pre-dominant in adults whereas intellectual disabilities, autism, and other developmental issues are common occurrence in pediatric patients (Mula, 2017).

Classification of Seizures

Epilepsies can be classified based upon the type of seizures and their underlying causes (Falco-Walter et al., 2018). Recently there have been revisions and updates in the classification of seizure types (Fisher et al., 2017a,b) and etiology of epilepsy (Scheffer et al., 2017). These classifications serve as an important tool for evaluating individuals presented with spontaneous seizures. It is also important to select therapy based on the seizures types (Scheffer et al., 2017) (**Fig. 1**).

Based on their key signs and symptoms, seizures can be of known (focal or generalized) or unknown origin (Fisher et al., 2017b; Scheffer et al., 2017) or considered unknown or unclassifiable (Fisher et al., 2017a), as detailed in **Table 1**.

This classification applies to seizures in adults as well as children; there is a separate classification for neonatal seizures (Falco-Walter et al., 2018). The frequency of seizure occurrence is highly unpredictable and ranges from many seizures per day to once in a year or even longer (World Health Organization, 2018) with variable severities ranging from brief losses of attention, muscle twitching, and sensory malfunctions to prolonged life-threatening seizures (Scheffer et al., 2016). The results of neuroimaging studies, electroencephalography and additional investigations exploring underlying causes of epilepsy are taken into account to classify both seizure and epilepsy type (Scheffer et al., 2017).

Classification of Epilepsies

The classification of epilepsies is broader in scope than classifying seizures. However, the seizure type provides a starting point for this classification (Scheffer et al., 2017). Additionally, the overall clinical picture, hereditary tendencies, diagnostic test outcomes and comorbidities are taken into account. Epilepsies can be classified into (1) focal, (2) generalized, (3) combined generalized and focal, and (4) unknown (Falco-Walter et al., 2018; Scheffer et al., 2017).

The patient's age, family history, types of existing sensory and motor seizures, EEG findings, and information collected from clinical observations aid in diagnosing patients with a specific epilepsy type (Falco-Walter et al., 2018). The inter-ictal EEG analysis

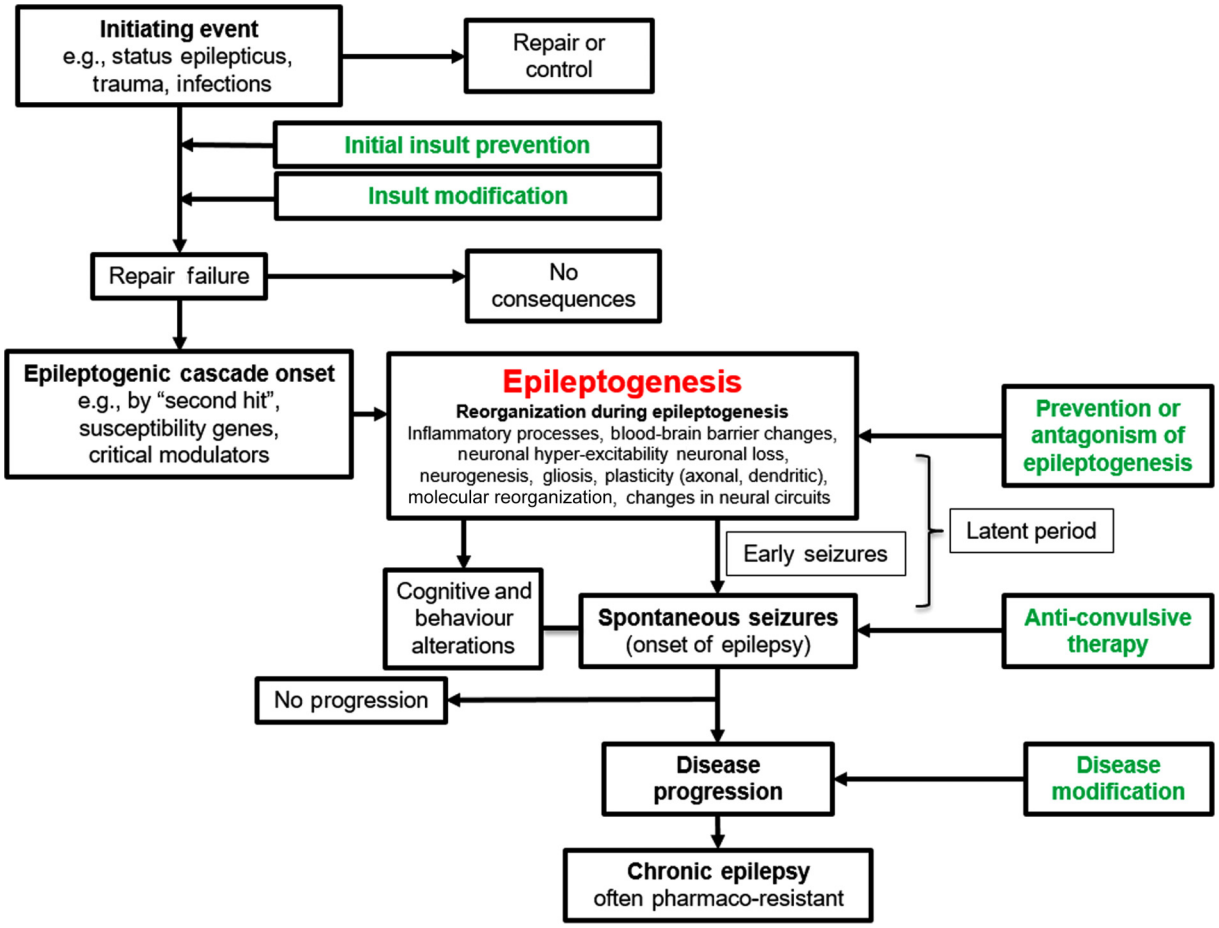

Figure 1 Steps of the development and progression of temporal lobe epilepsy and possible therapeutic interventions. *Source: Modified from Löscher and Brandt (2010)*

generally shows the presence of typical generalized spike-wave activity (generalized epilepsy), focal epileptiform discharges (focal epilepsies), and generalized spike-wave and focal epileptiform discharges (combined generalized and focal epilepsies) at the time of diagnosis. In cases when a clinician is sure of a patient having epilepsy, but neither has enough clinical evidence to support the decision nor a normal EEG, epilepsy of unknown cause is identified (Scheffer et al., 2017).

Etiology of Epilepsy

Finding the underlying cause of epilepsies on primary patient contact is desired for appropriate treatment options (Falco-Walter et al., 2018). The ILEA's recent updates has divided epileptic seizures into the following types for better clinical application and comprehension of disease (Falco-Walter et al., 2018; Scheffer et al., 2017):

1. Structural etiology including acquired (by trauma, stroke, and infection) or innate (e.g., cortical malformation) abnormalities in brain structure. Presence of hippocampal sclerosis associated with mesial temporal lobe epilepsy is one common finding (Scheffer et al., 2017).
2. Genetic etiology is linked to acquired de-novo mutations, e.g. SCN1A (sodium channel gene) mutations (Claes et al., 2001), or hereditary autosomal dominant disorders, for example, benign familial neonatal epilepsy (Grinton et al., 2015), though involvement of the environmental factors cannot be ruled out (Scheffer et al., 2017).
3. Infectious etiology is common worldwide (Vezzani et al., 2016) including infectious pathogens such as viruses (e.g., herpes viruses, West Nile viruses), parasites (e.g., Plasmodium falciparum), bacteria (e.g., mycobacteria), and fungi (e.g. *Cryptococcus* and *Candida albicans*) can cause epilepsies (Vezzani et al., 2016). The acute seizures caused by insults such as meningitis or encephalitis do not represent the disease, which is characterized by the presence of late seizures (Scheffer et al., 2017).
4. Metabolic etiology includes porphyria, uremia, and aminoacidopathies associated with seizures. They also most likely have genetic bases, but could be acquired such as cerebral folate deficiency (Scheffer et al., 2017).

Table 1 Types of seizures according to ILAE 2017 operational classification (Fisher et al., 2017a)

Seizure origin	Known							Unknown	
Confidence level	>80%							<80%	
Seizure type	Focal seizures				Generalized seizures		Focal to generalized tonic clonic seizures	Unknown onset seizures	
Hemisphere involved	One cerebral hemisphere				Both cerebral hemispheres		Focal in origin and then propagates from one to both cerebral hemispheres	–	
Awareness	Retained		Impaired		Generally impaired		Generally impaired	–	
Brain network involved	Motor	Non-motor	Motor	Non-motor (Absence)	Motor	Non-motor	–	Motor	Non-motor
Specific sub-classification based on 1st sign and symptoms	Atonic *	Autonomic	Clonic	Typical	-	-	-	Tonic-clonic epileptic spasms	Behavior arrests
	Tonic	Cognitive	Tonic	Atypical					
	Clonic	Emotional	Tonic-clonic	Myoclonic					
	Myoclonic	Sensory	Myoclonic	Eyelid myoclonia					
	Automatisms	Behavioral arrests	Myoclonic-tonic-clonic						
	Hyperkinetic		Myoclonic-atonic						
	Epileptic spasms *		Atonic						
			Epileptic spasms						

*Degree of awareness is usually not described

5. Immunological etiology refers to illnesses of the immune system with seizures as a primary symptom (Scheffer et al., 2017). Autoimmune mediated CNS inflammation may provide an indication of immune system mediated epilepsies (Vezzani et al., 2016).
6. Unknown groups include epilepsies that have limited clinical information currently to classify to any set of etiology (Scheffer et al., 2017).

Epileptogenesis

The phenomenon of developing epilepsy is called "epileptogenesis", which is a combination of the two ancient Greek words epilēpsis = attack, invasion and genesis = genesis (Löscher and Brandt, 2010). About 40% of all epilepsies have an identifiable cause, that is, they develop after an initial brain insult (Banerjee et al., 2009; Löscher and Brandt, 2010). These initial brain assaults, for example, trauma, stroke, brain tumors, status epilepticus or infections, often accompanied by early seizures, play a role in transforming an otherwise healthy brain into an epileptic brain (Löscher and Brandt, 2010; Ravizza et al., 2011). After an initial brain insult, the failure of intrinsic repair mechanisms followed by a second hit, gene sensitivity, or comorbidities provides a favoring milieu to develop late seizures (Löscher and Brandt, 2010).

Various underlying mechanisms (**Fig. 1**) such as inflammation, changes in blood brain barrier, neurodegeneration, gliosis, neuronal hyper-excitability, alterations of receptor and ion channel expression are involved in this transformation (Löscher and Brandt, 2010; Vezzani et al., 2016). The seizure free period, also known as "latency" or "latent period," between the initial insult and the occurrence of the 1st unprovoked epileptic seizure, ranges from months to years in humans and results in the manifestation of chronic epilepsy (Jozwiak et al., 2017; White and Loscher, 2014). A schematic representation of epileptogenesis and potential intervention strategies is given in **Fig. 1**

Pharmacotherapy, Pharmacoresistance, and Epilepsy Prevention

There are currently more than 20 therapeutic agents available for the management of epilepsy (Löscher et al., 2013; Pitkanen et al., 2016). Fifteen of these are 3rd generation agents, added in the past 3 decadesthat have provided clinicians more chances of attaining successful therapeutic goals (Löscher and Schmidt, 2011). Although these drugs are primarily known as "anti-epileptic drugs" (AEDs) they do not cure epilepsy itself, but rather provide symptomatic relief from seizures and are thus more appropriately called "anti-seizure or anticonvulsant" drugs (Kaminski et al., 2014). However, only 70%–80% of new onset epilepsy patients become seizure free when treated with current AEDs, while 20%–30% of patients fail to respond to these treatments (Brodie et al., 2012; Löscher et al., 2013; Sillanpaa and Schmidt, 2006).

Patients, who do not remain adequately seizure free for a prolonged period of time or do not respond to any of two or more well tolerated AEDs, are said to be pharmacoresistant (Kwan et al., 2010). The underlying mechanism of this pharmacoresistance have not been understood completely (Kwan and Brodie, 2006). Hence, the quality of life of these patients is compromised with psychological and social consequences (Weaver and Pohlmann-Eden, 2013). Currently, there are many new drugs in clinical trials or are under development that have novel mechanisms of action for pharmacoresistant epilepsy (Younus and Reddy, 2018). However if the therapy does not work then the final option for these patients is surgical resection of brain regions involved in seizure formation (Schmidt et al., 2004). However, the risks and adverse effects of these neurosurgical procedures limit the usefulness of such measures. Only 50% of such patients achieve long-term from seizure and many patients still receive the drug therapy after surgery to achieve seizure control (Loscher and Schmidt, 2006).

Choice of Therapy According to Seizure Type

The ultimate objective of epilepsy treatment is prevention of seizures. It can be achieved by maintaining a suitable dose of one or more AEDs. It is recommended to start with lowest possible dose and slowly achieve the dose where seizures stop or adverse effects appear. Dosing frequency is based on the half-life of AEDs whereas selection of AED depends on the type of seizures diagnosed. Other factors that contribute to the selection of AED are age, sex, co-medication, and co-morbidity. Important AEDs that are recommended in treating different types of seizures are listed in **Table 2**.

Status Epilepticus

The recently proposed conceptual definition by ILEA states that "SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" (Trinka et al., 2015). This definition is further explained in **Table 3** (Trinka et al., 2015).

Various treatment options are used for management of convulsive status epilepticus in community settings such as schools (described as outside emergency room), few are mentioned in **Table 4** as well, which gives a brief overview of emergency

Table 2 Type of seizures and recommended AEDs (National Institute of Health and Care Excellence, 2018; Royal Pharmaceutical Society, 2018)

Seizure type	*1st line therapy*	*Adjunctive treatment*	*By tertiary epilepsy specialist*	*Not recommended*
Focal seizures	Carbamazepine and lamotrigine. If not tolerated use oxcarbazepine, sodium valproate and levetiracetam	Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate	Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide	
Generalized seizures				
Tonic	Sodium valproate (except in premenopausal women)	Lamotrigine	Rufinamide or topiramate	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin
Tonic-clonic or generalized tonic-clonic (GTC)	Sodium valproate (except in premenopausal women)	Lamotrigine, carbamazepine and oxcarbazepine (may exacerbate myoclonic seizures)	Clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate	Myoclonic seizures
Myoclonic	Sodium valproate. If unsuitable give topiramate or levetiracetam (except in premenopausal women)	Combination of these mentioned drugs	Clobazam, clonazepam, zonisamide or piracetam	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin
Atonic	Sodium valproate (except in premenopausal women)	Lamotrigine	Rufinamide or topiramate	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin
Absence	Ethosuximide Sodium valproate or lamotrigine (except in premenopausal women)	Combination of any of these two	Clobazam, clonazepam, levetiracetam, topiramate or zonisamide	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin

Table 3 Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected (Trinka et al., 2015)

Type of SE	**Operational dimension 1** Time (t1); when a seizure is likely to be prolonged leading to continuous seizure activity	**Operational dimension 2** Time (t2); when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min	Unknown

Table 4 Doses of AEDs and anticonvulsant medications in convulsive status epilepticus

Drug	*Route of administration*	*Dose*				*Instructions for administration*
		Initial	*Increment*	*Usual dose*	*Up to*	
Lorazepam	Slow IV injection	4 mg/dose	4 mg/dose if required after 10min			Administer in large vein
Diazepam	IV	10 mg	10 mg if required after 10min			Administer at a rate of 5 mg/min
	Rectal	10–20 mg	10–20 mg if required after 10–15 min			
Phenytoin	Slow IV injection	20 mg/kg		100 mg every 6–8 h	2 g/dose	100 mg of phenytoin sodium is therapeutically equivalent to 92 mg of phenytoin base,
Midazolam	Buccal	10 mg	10 mg if required after 10min			
Fosphenytoin sodium	IV infusion	20 mg/kg		4–5 mg/kg in 1–2 divided doses		Administer at a rate of 100–150 mg/min (initial dose) and 50–100 mg/min (usual dose), 1 mg of phenytoin sodium = 1.5 mg of fosphenytoin sodium
Phenobarbital sodium	IV			10 mg/kg	1 g/dose	Rate of administration should not be more than 100 mg/min, dilute 1 in 10 with WFI

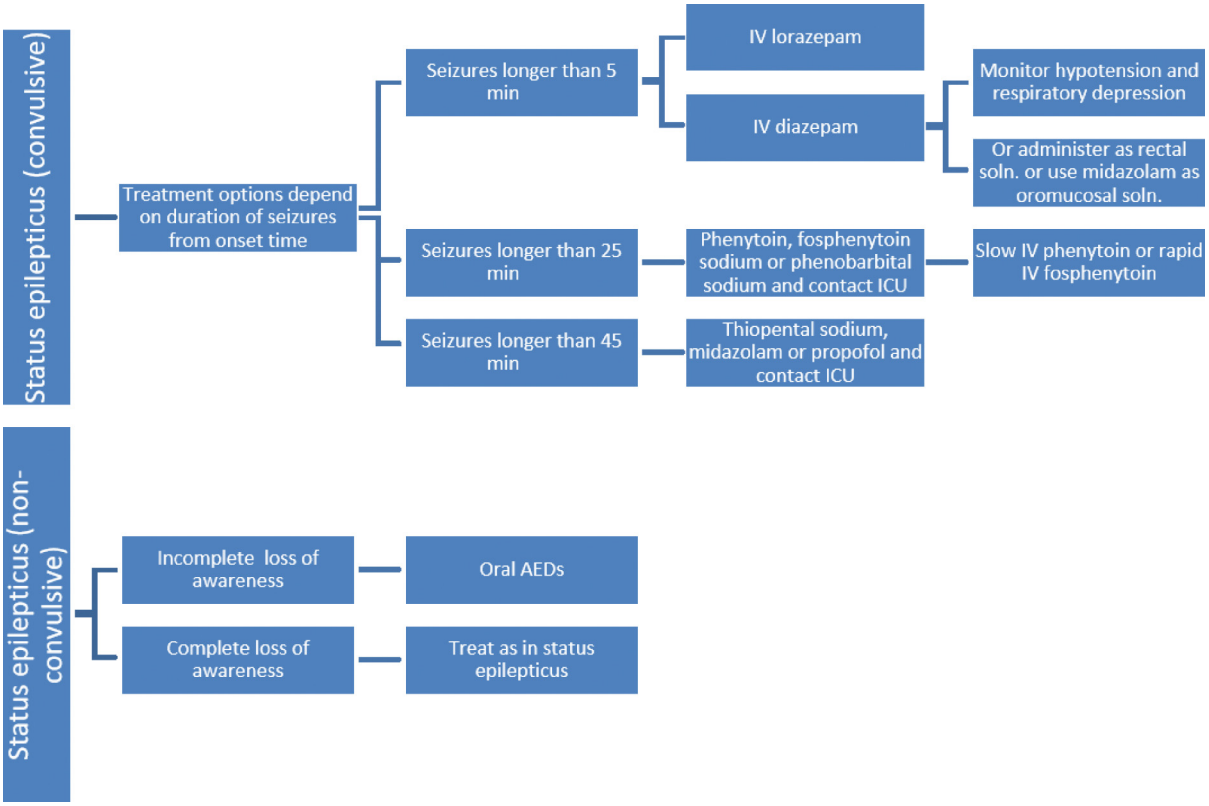

Figure 2 Decision flow in treatment of status epilepticus (Royal Pharmaceutical Society, 2018).

management. Buccal and intranasal midazolam and diazepam anema/suppository are more acceptable treatment options when trained health professional and intravenous lines are not available (Fig. 2).

Treatment of Febrile Convulsions

Febrile convulsions are common emergency conditions experienced in pediatric patients. Management of these patients includes general pharmacologic (paracetamol) and non-pharmacologic measures (sponging with tepid water) to lower body temperature. In case the duration of seizures exceed 10–15 min control of seizures must be carried out using the dosing described under convulsive status epilepticus. In-time-control-of seizures is essential in preventing brain damage associated with the prolonged seizures.

Pharmacokinetic Properties of AEDs

AEDs mostly include narrow therapeutic index drugs and the pharmacokinetics of the drugs is affected by age-related factors. Specifically, the neonates present a large volume of distribution, with a low protein binding and so a different half-life from adults. Table 5 provides an overview of the basic pharmacokinetic parameters of AEDs in adults and children.

Posology of AEDs

AEDs are given in specialized dosage regimens depending upon the age and indication (Royal Pharmaceutical Society, 2018; van Dijkman et al., 2018). Therapy is initiated with an initial dose which is build up to a usual or a routine dose using defined increments at specified intervals (Table 6). Doses can be increased up to a maximum limit depending upon the success in control of symptoms and tolerance of adverse events.

Therapeutic Drug Monitoring of AED's

TDM is a well-established tool for safe administration of AEDs because it allows the selection of individualized dosage regimen in patients with specific nature of epilepsy with variability in pharmacokinetics of AEDs. Although, the quantification of AEDs is mostly performed in plasma, however, many AEDs can be readily monitored in dried blood spot (DBS) or saliva (Patsalos et al., 2018). For AEDs with high protein-bound capacity (phenytoin, carbamazepine, and phenobarbital), saliva has proved to

Table 5 Pharmacokinetic parameters of common AEDs in adults and pediatric population (Patsalos et al., 2018)

	Oral bioavailability (%)		*Volume of distribution (L/kg)*		*Protein binding (%)*		*Time to peak conc. (h)*		*Clearance (mL/min/kg)*		*Elimination half-life (h)*	
Drug	*P*	*A*	*P*	*A*	*P*	*A*	*P*	*A*	*P*	*A*	*P*	*A*
Brivaracetam	NA	~ 100	0.5	0.5	NA	20	1–2	1–2	0.8	0.83	7–8	7–8
Carbamazepine	75–85	75–85	1.2–1.9	1.2–1.9	75–85	75–80	2–12	2–9	0.83–1.66	0.8–1.7	2–36	4–12
Eslicarbazepine	NA	~ 100	NA	2.7	NA	40	0.5–3	1–4	1.16–1.66	0.92	6–10	20–24
Ethosuximide	100	100	0.69	0.6–0.7	<10	<10	3–7	1–7	NA	0.2–0.3	14–78	30–40
Lamotrigine	NA	98	1.5–2	0.9–1.3	NA	55	1–6	1–3	1.65–1.91	0.38–0.59	8–45	24–37
Levetiracetam	100	100	0.6–0.8	0.5–0.7	< 10	< 10	0.5–3	1	1.43	0.96	6	6
Oxcarbazepine	NA	90	1.5	0.3–0.8	NA	< 40	1	1–3	1.18	1.6	5–9	1–2.5
Phenobarbital	80	90	0.6–0.9	0.6–1	25–55	20–45	3	8–12	0.05–0.07	0.05–0.07	37–69	40–117
Phenytoin	70–90	95	0.2–1.2	0.5–0.8	85–90	90	1–2	1–12	NA	NA	2–23	7–29
Rufinamide	<85	85	0.71–1.14	0.8–1.2	26–34	30	4–6	1.5–10	0.27–0.45	3–5 L/h	6–10	6–10
Topiramate	NA	81–95	0.73	0.6–1	NA	9–17	10	1–4	0.45	20–30 mL/min	24	19–23
Valproate	90	90	0.2–0.3	0.15–0.20	70–90	90	0.5–3	1–2	0.15–0.8	0.1–0.33	5–29	7–16
Vigabatrin	60–70	65	0.8–1	0.8–1.1	0	0	1	0.5–2	0.5–3	1.7–1.9	5.7–9.5	5–7
Zonisamide	100	100	0.9–1.8	1.5	40	40–60	4–6	2–5	0.45–0.55	0.30–0.35	60–100	50–70

A, adult; P, pediatric

be the most appropriate matrix with the advantage non-invasive sampling and reflecting the free, pharmacologically active, drug concentration in plasma (Carvalho et al., 2018). The DBS can be used alternatively to plasma sampling, which has simplified the effective TDM for AEDs (Linder et al., 2017). For almost all AEDs, the reference ranges have been defined that are to be considered for maintaining the plasma levels of AEDs in order to achieve safe and effective therapy. However, the drug levels outside the reference range are required for some patients due to individual variation in type and severity of seizure. The monitoring of individual therapeutic drug concentration of AEDs has advantage of administering specific dose to an individual for whom optimum seizure control with minimal adverse effects is achieved. The principal indications for TDM of AEDs are listed as follows (Patsalos et al., 2018):

- After initialization of treatment for dose adjustment
- On achievement of desired therapeutic response
- When toxicity is difficult to differentiate or assess clinically
- To regulate the extent of dose change
- When seizures persist despite of adequate dose administration
- When variability in pharmacokinetics is expected
- When formulation is changed
- When clinical response is changed, unexpectedly
- When poor compliance from the patient is suspected.

In addition to mentioned conditions, monitoring of plasma levels is also recommended during pregnancy to maintain the therapeutic levels necessary for seizure control (Royal Pharmaceutical Society, 2018). TDM is also helpful in monitoring the time-scale of drug interaction. In routine, stabilized patients are advised to undergo TDM 1–2 times a year and before initiation of the adjuvant AED it is advisable to carry out baseline level of the first AED (Whittlesea and Walker, 2011).

Population Pharmacokinetic Modeling

As the pharmacokinetics of AEDs vary among individuals due to inter-individual variability, the TDM of AEDs based only on the quantification of drugs in plasma is becoming ineffective, even for AEDs with very precisely defined therapeutic ranges. The adaptive control of dosage using computer software is effectively increased for dose tailoring (Patsalos et al., 2018) and population pharmacokinetic (popPK) modeling has been used as a valuable tool to identify sources of variability among the individuals and incorporation of these sources as covariate factors in the model. These models are then used for simulation of dosage regimens in order to design the tailored dosage regimens for individual patients (van Dijkman et al., 2018).

Contraindications and Use of AEDs in Pregnancy and Lactation

The major contraindication brought forward in the recent time includes the restriction of the sodium valproate in women of reproductive age and during pregnancy due to serious teratogenic effects (**Table 7**). If needed, it should be given in very low doses and in combination with lamotrigine for synergistic effect (Iapadre et al., 2018).

Table 6 Indications, dose regime and routes of administration for AEDs in adults (Royal Pharmaceutical Society, 2018)

		Dose				
Drug	*Indications*	*Initial*	*Increment*	*Usual dose*	*Up to*	*Route of administration*
Brivaracetam	partial-onset seizures	25–50 mg BD		25–100 mg BD		Oral or IV injection or IV infusion
Carbamazepine	Focal and secondary generalized tonic-clonic seizures: Primary generalized tonic-clonic seizures	100–200 mg 1–2 OD or BD	100–200 mg every 2 weeks	0.8–1.2 g daily in divided doses	1.6–2 g daily in divided doses 1 g daily in 4 divided doses for up to 7 days	Oral By rectum
Ethosuximide	1st line treatment for Absence seizures	500 mg daily in 2 divided doses	250 mg every 5–7 days;	1–1.5 g daily in 2 divided doses	2 g daily	Oral
Gabapentin	Adjunctive treatment of focal seizures with or without secondary generalization	300 mg OD on day 1	300 mg BD on day 2, then 300 mg TDS on day 3	0.9–3.6 g daily in 3 divided doses	1.6 g TDS	Oral
	Monotherapy for focal seizures with or without secondary generalization	300 mg OD on day 1	300 mg BD on day 2, then 300 mg TDS on day 3	0.9–3.6 g daily in 3 divided doses	1.6 g TDS	Oral
Lamotrigine	Monotherapy of focal seizures ǀ Monotherapy of primary and secondary generalized tonic-clonic seizures ǀ Monotherapy of seizures associated with Lennox-Gastaut syndrome	25 mg OD for 14 days,	50 mg OD for further 14 days, then increased in steps of up to 100 mg every 7–14 days	100–200 mg daily in 1–2 divided doses	500 mg daily	Oral
	Adjunctive therapy of focal seizures with valproate ǀ Adjunctive therapy of primary and secondary generalized tonic-clonic seizures with valproate ǀ Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome with valproate	25 mg OD alternate days for 14 days,	25 mg OD for further 14 days, then increased in steps of up to 50 mg every 7–14 days	100–200 mg daily in 1–2 divided doses		
	Adjunctive therapy of focal seizures (with enzyme inducing drugs) without valproate ǀ Adjunctive therapy of primary and secondary generalized tonic-clonic seizures (with enzyme inducing drugs) without valproate ǀ Adjunctive therapy of seizures associated with Lennox- Gastaut syndromes (with enzyme inducing drugs) without valproate	50 mg OD for 14 days	50 mg BD for further 14 days, then increased in steps of up to 100 mg every 7–14 days	200–400 mg daily in 2 divided doses,	700 mg daily	
	Adjunctive therapy of focal seizures (without enzyme inducing drugs) without valproate ǀ Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (without enzyme inducing drugs) without valproate. Adjunctive therapy of seizures associated with Lennox–Gastaut syndromes (without enzyme inducing drugs) without valproate	25 mg OD for 14 days	50 mg OD for further 14 days, then increased in steps of up to 100 mg every 7–14 days	100–200 mg daily in 1–2 divided doses		
	Monotherapy or adjunctive therapy of bipolar disorder (without enzyme inducing drugs) without valproate	25 mg once daily for 14 days	50 mg daily in 1–2 divided doses for further 14 days, then 100 mg daily in 1–2 divided doses for further 7 days	200 mg daily in 1–2 divided doses	400 mg per day	

Levetiracetam	Monotherapy of focal seizures with or without secondary generalization	250 mg OD for 1–2 weeks	250 mg BD, then increased in steps of 250 mg BD, dose to be increased every 2 weeks		1.5 g BD	O or IV infusion
	Adjunctive therapy of focal seizures with or without secondary generalization	250 mg BD,	500 mg BD, dose to be increased every 2–4 weeks		1.5 g BD	Oral
	Adjunctive therapy of myoclonic seizures and tonic-clonic seizures					Oral or IV infusion
Phenytoin	Tonic-clonic seizures Focal seizures: Prevention and treatment of seizures during or following neurosurgery or severe head injury	3–4 mg/kg daily		200–500 mg daily,		Oral
Phenobarbital	All forms of epilepsy except typical absence seizures			60–180 mg OD		Oral
Rufinamide	Adjunctive treatment of seizures in Lennox-Gastaut syndrome	200 mg BD	Increase in steps of 200 mg BD		900 mg BD (body weight 30–49 kg), 1.2 g BD ((body-weight 50–69 kg), 1.6 g BD ((body-weight 70 kg and above)	Oral
Topiramate	Monotherapy of generalized tonic-clonic seizures or focal seizures with or without secondary generalization	25 mg OD for 1 week	Increase as 25–50 mg every 1–2 weeks, in two divided doses		500 mg per day	Oral
	Adjunctive treatment of generalized tonic-clonic seizures or focal seizures with or without secondary generalization | Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome	25–50 mg OD for 1 week	Increase as 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses	200–400 mg daily in 2 divided doses	400 mg per day	Oral
Valproate sodium	All forms of epilepsy	600 mg daily in 1–2 divided doses	Increase as 150–300 mg every 3 days	1–2 g daily	2.5 g per day	
Zonisamide	Monotherapy for treatment of focal seizures with or without secondary generalization in adults with newly diagnosed epilepsy	100 mg OD for 2 weeks	Increase as 100 mg every 2 weeks	300 mg OD	500 mg per day	
	Adjunctive treatment for refractory focal seizures with or without secondary generalization	50 mg daily in 2 divided doses for 7 days	Increase as 100 mg daily in 2 divided doses, then increased in steps of 100 mg every 7 days	300–500 mg daily in 1–2 divided doses		

Table 7 Use of AEDs in pregnancy, lactation, hepatic and renal impairment

Drug	*Use in pregnancy*	*Breast feeding*	*Contra-indications*	*Hepatic impairment*	*Renal impairment*
Brivaracetam	Avoid unless potential benefit outweighs risk—limited information available.	Should avoid, present in milk in animal studies.		Require dose adjustment, starting dose of 25 mg BD in chronic liver disease; max. maintenance dose 75 mg BD in all stages of impairment.	
Carbamazepine	Monitor plasma drug concentration and adjust the dose	Amount probably too small to be harmful. Monitor infant for possible adverse reactions.	Acute porphyria. AV conduction abnormalities (unless paced). History of bone marrow depression	Withdraw immediately in cases of aggravated liver dysfunction or acute liver disease and leucopenia. Metabolism impaired in advanced liver disease.	Use with caution
Ethosuximide	Monitor during pregnancy and after birth, and adjustment on clinical basis.	Present in milk. Hyperexcitability and sedation reported.		Use with caution	Use with caution
Gabapentin	Monitor during pregnancy and after birth, and adjustment on clinical basis.	Present in milk—manufacturer advises use only if potential benefit outweighs risk.			Reduce the dose depending upon the values of eGFR
Lamotrigine	Monitor plasma drug concentration and adjust the dose	Present in milk, but limited data suggest no harmful effect on infant.	Myoclonic seizures, Parkinson's disease	Halve dose in moderate impairment. Quarter dose in severe impairment.	Caution in renal failure; metabolite may accumulate. Dose adjustments required.
Levetiracetam	Monitor plasma drug concentration and adjust the dose, also monitor fetal growth	Present in milk—manufacturer advises avoid.		In adults Halve dose in severe hepatic impairment if eGFR less than 60 mL/min/1.73m^2.	In adults Maximum 2 g daily if eGFR 50–80 mL/min/1.73m^2. Maximum 1.5 g daily if eGFR 30–50 mL/min/1.73m^2. Maximum 1 g daily if eGFR less than 30 mL/min/1.73m^2.
Phenytoin	Monitor plasma drug concentration and adjust the dose	Small amounts present in milk, but not known to be harmful	Acute porphyrias	Adjust the dose, reduce dose to avoid toxicity.	
Phenobarbital	Monitor the dose and adjust on clinical basis.	Avoid if possible; drowsiness may occur.		May precipitate coma. Avoid in severe impairment.	Use with caution.
Rufinamide	Monitor the dose and adjust on clinical basis.	Manufacturer advises avoid.		Avoid in severe impairment. Adjust the dose.	
Topiramate	Increased risk of major congenital malformations following exposure during the first trimester.	Manufacturer advises avoid—present in milk.	Avoid in active liver disease.	Use with caution in moderate to severe impairment—clearance may be reduced.	Use with caution and adjust the dose
Valproate	must not be used unless there is no suitable alternative treatment;	Present in milk—risk of haematological disorders in breast-fed newborns and infants.	In women and girls of childbearing potential unless conditions of pregnancy prevention programme are met. Acute porphyrias	Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months).	Reduce dose.
Zonisamide	Use only if clearly necessary and the potential benefit outweighs risk	Manufacturer advises avoid for 4 weeks after last dose.		Avoid in severe impairment. Dose adjustments Initially increase dose at 2-week intervals if mild or moderate impairment.	Initially increase dose at 2-week intervals; discontinue if renal function deteriorates.

Table 8 Chronic side effects with use of major AEDs

Drug	*Chronic side effects*	*Drug*	*Chronic side effects*
Carbamazepine	Antiepileptic hyper-sensitivity syndrome, Hyponatremia	**Phenobarbital**	Behavior changes, connective tissue disorders, intellectual blunting, metabolic disease, mood change, sedation
Ethosuximide	Behavior changes, headache	**Topiramate**	Kidney stones, weight loss
Gabapentin	Weight gain	**Valproate**	Polycystic-ovary like syndrome, weight gain, hyperammonemia, menstrual cycle irregularities
Phenytoin	Behavior changes, Cerebellar syndrome, connective tissue changes, skin thickening, folate deficiency, gingival hyperplasia, Hirsutism, coarsening of facial features, acne, cognitive impairment, metabolic bone disease, sedation	**Zonisamide**	Kidney stones, weight loss

Carbamazapine and gabapentin are not recommended in tonic, atonic, myoclonic or absence seizures, whereas lamotrigine and phenytoin are contraindicated in myoclonic or absence seizures. Some genetic variants in population are more prone to the cutaneous adverse effects of antiepileptic agents such as carbamazepine, oxycarbamazepine, phenytoin and lamotrigine. FDA recommends screening of the South Asian population for the HLA*B 1502 allele for preventing the serious ADRs like Steven–Johnson syndrome (SJS)and toxic epidermal necrolysis(TENS).

Side Effects of AEDs

AEDs are narrow therapeutic index medicines with many CNS and other side effects. Table 8 shows some examples of chronic side effects of commonly used AEDs.

Chronic side effects

Hypersensitivity and other serious cutaneous adverse drug reactions

SJS and TENS are the serious cutaneous ADRs associated with the AEDs carbamazepine and phenytoin. These ADRs show substantial morbidity and mortality (40%–50%). In a recent study on 480 validated cases of SJS/TENS reported in the UK on use of AEDS, highest risks were found with phenytoin (45.86 cases/100,000 exposed), lamotrigine (44.17cases/100,000 exposed), and carbamazepine (20.38 cases/100,000 exposed). No cases were observed for levetiracetam, clonazepam or topiramate whereas valproate, gabapentin, pregabalin and clobazam had a high odds ratio but no causal relationship identified using drug casualty for epidermal necrolysis (ALDEN) score used in the study (Frey et al., 2017).

Pharmacogenetic investigations for identifying the etiology of these reactions have shown that the HLA allele, HLA*-B* 1502 is associated with the increased risk of skin reactions for carbamazepine, phenytoin, oxcarbamazepine, and lamotrigine. The Population of Southeast Asia (China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan) are found to be more prone to these reactions than India and Japan. Owing to this relationship, FDA has introduced screening for HLA-B*1502 commencing the carbamazepine and phenytoin therapy in Southeast Asian Population (Whittlesea and Walker, 2011).

Drug Interactions of Antiepileptic Drugs

AEDs are used as long-term monotherapy, in combination or as adjunctive therapy and mostly consist of drugs that are likely to exhibit drug interactions. (van Dijkman et al., 2018) The classical AEDs cause inhibition (valproate) or induction (carbamazepine, phenobarbital, phenytoin, primidone) and affect the plasma concentration of other AEDs. It also affects other drug classes including anti-depressants, anti-psychotics, anti-microbial drugs and many more. These drug interactions could be classified depending upon the severity of clinical complications. Level 1 enlists serious clinical complications that develop due to AED interactions and should be avoided. Level 2 include drug interactions that usually require dose adjustments and co-administration of these drugs is possible. The interactions where dose adjustment is not necessarily required are categorized under Level 3. Updated information on the possibility and severity of drug interactions may help to treat the seizure more effectively. AED interactions with other co-administered AEDs (Table 9) and other drugs (Table 10) are described later.

Table 9 Drug interactions of AEDs with co-administered AEDs

Brivaracetam	**Brivaracetam**													
Carbamazepine	2, m, St	**Carbamazepine**												
Ethosuximide			**Ethosuximide**											
Fosphenytoin	2, m, St	2, s, St, Ad		**Fosphenytoin**										
Gabapentin					**Gabapentin**									
Lamotrigine		2, m, St, Ad		2, m, St, Ad		**Lamotrigine**								
Levetiracetam							**Levetiracetam**							
oxcarbazepine		1, m, St, Ad		2, m, St, Ad		2, m, St, Ad		**Oxcarbazepine**						
Phenobarbital		2, m, St, Ad		2, m, St					**Phenobarbital**					
Phenytoin	2, m, St	2, s, St, Ad		2, m, St				2, m, St, Ad	2, m, St	**Phenytoin**				
pregabalin											**Pregabalin**			
Rufinamide												**Rufinamide**		
Topiramate		3, m, St		2, m, St, Ad					2, m, St	2, m, St, Ad			**Topiramate**	
Valproate				2, s, St		1, s, St, Ad			2, m, St, Ad	2, s, St		1, m, St, Ad	3, s, St	**Valproate**
Zonisamide		2, m, St, Ad		2, m, St, Ad					2, m, St, Ad	2, m, St, Ad			3, s, Th	

Key: 1. Affects the efficacy or exposure of drugs, 2. Affects the concentration of drugs, 3. Produces toxic effects Ad, adjust; An, anecdotal; Av, avoid; m, moderate; Mo, monitor; s, severe; St, study; Th, theoretical; U, unknown.

Table 10 Drug interactions of AEDs with co-administered drugs.

Drug	*Interaction with*	*Effect*	*Method*	*Severity*	*Advice*
Brivaracetam	Enzalutamide (1, Th, m), rifampicin (1, St, m, Ad), St John's Wort (1, Th, m)				
	Neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium, vecuronium).	AED decrease the effects of (but acute use increases the effects of drug)	Study	Moderate	
	Suxamethonium	Co-administration increases the risk of prolonged neuromuscular blockade	Study	Moderate	
	Theophylline	Potentially increase the clearance of theophylline	Anecdotal	Moderate	
Carbamazepine	Thyroid hormones	Increase the risk of hypothyroidism	Study	Moderate	
	Oral cladribine	increase the risk of haematological toxicity	Theoretical	Moderate	
	Clozapine	Increase the risk of myelosuppression	Anecdotal	Study	Avoid
	Coumarins	AED decrease the anticoagulant effect	Study	Severe	Monitor and adjust the dose
	Procarbazine	Combine administration may increase the risk of hypersensitivity reaction.	Anecdotal	Severe	
	afatinib (1, Th, m), aliskiren (1, Th, m), antifungals, azoles (miconazole, fluconazole, posaconazole) (3, An, s, Ad), antimalarials (quinine) (3, St, u), Calcium channel blockers (diltiazem, verapamil) (2, Th, m, Av or Mo, Ad), caspofungin (1, Th, m, Ad), dabigatran (1, St, s, Av), Danazol (2, St, s, Mo, Ad), edoxaban (1, St, m), efavirenz (1, St, s), Grapefruit juice (1, St, m, Mo, Ad), H_2 receptor antagonists (cimetidine) (2, St, s, Mo, Ad), HIV-protease inhibitors (1, Th, s, Mo, Ad), ketoconazole (2, Th, m, Av, or Mo, Ad), ledipasvir (1, Th, s, Av), Macrolides (clarithromycin and erythromycin) (2, St, s, Mo, Ad), mianserin (1, St, m, Ad), modafinil (1, Th, m), monoamine-oxidase A and B inhibitors, irreversible (3, Th, s, Av), monoclonal antibodies (brentuximab vedotin) (1, Th, s), nintedanib (1, St, m), olanzapine (1, St, m, Mo, Ad), ombitasvir (1, Th, s, Av), opioids (tramadol) (2, St, s, Ad), raltegravir (1, Th, m), selexipag (1, St, m, Ad), sofosbuvir (1, St, s, Av), St John's Wort (2, Th, m, Mo, Ad), statins (atorvastatin) (1, Th, m, Mo, Ad), statins (simvastatin) (1, St, s, Mo, Ad), trazodone (2, An, m, Ad), tricyclic antidepressants (1, St, m, Ad), vitamin D substances (1, St, m), zolpidem (1, St, m),				
	Isoniazid	Increases the risk of hepatotoxicity administered together	Study	Severe	Monitor and adjust the dose
	Lithium	Increases the risk of neurotoxicity administered together	Anecdotal	Severe	
Ethosuximide	Not available				
Fosphenytoin	Antifungals, azoles (miconazole, fluconazole, posaconazole, voriconazole) (3, An, s, Av), Sulfonamides (sulfadiazine) (1, St, m, Mo, Ad),				
Gabapentin	Antacids	Antacid decrease the absorption of gabapentin		Take AED 2 h after taking antiacids	

(*Continued*)

Table 10 Drug interactions of AEDs with co-administered drugs. (*cont.*)

Drug	*Interaction with*	*Effect*	*Method*	*Severity*	*Advice*
Lamotrigine	Desmopressin	Increase the risk of hyponatraemia when given together	Theoretical	Severe	Adjust the dose
	Rifampicin	The drug increases the clearance of AED	Study	Moderate	Adjust the AED dose
	Combined hormonal contraceptives (1, St, m, Ad), Desogestrel (1, St, m), HIV-protease inhibitors (ritonavir) (1, St, s), Hormone replacement therapy (1, Th, m)				
Levetiracetam	Methotrexate	AED decreases the clearance of drug	Anecdotal	Severe	
oxcarbazepine	ciclosporin (2, An, s), cobicistat (2, Th, s), combined hormonal contraceptives (1, St, s), daclatasvir (1, St, s), dolutegravir (1, Th, s, Av), etonogestrel (1, Th, s), glecaprevir (1, Th, s, Av), guanfacine (1, Th, m, Mo, Ad), hormone replacement therapy (1, An, m), imatinib (1, St, m, Av), levonorgestrel (1, Th, s), pibrentasvir (1, Th, s, Av), rilpivirine (2, Th, s, Av), simeprevir (1, Th, s, Av), ulipristal (1, An, s), velpatasvir (1, Th, s, Av), voxilaprevir (2, Th, s, Av)				
	Lithium	Increases the risk of neurotoxicity administered together	Anecdotal	Severe	
Phenobarbital	Antifungals, azoles (itraconazole, ketoconazole, voriconazole) (1, St, m, Av), beta blockers, non-selective (carvedilol, labetalol, propranolol, acebutolol, bisoprolol, metoprolol, nebivolol) (1, St, m), calcium channel blockers (diltiazem, verapamil) (1, St, m, Mo, Ad), chenodeoxycholic acid (1, Th, m, Mo, Av), chloramphenicol (2, St, m), cholic acid (1, St, m, Av), clozapine (1, An, m), efavirenz (1, Th, s), Folates (2, St, s, Ad), griseofulvin (1, St, m), HIV-protease inhibitors (1, Th, s), metronidazole (1, St, m), metyrapone (1, St, m, Av), mianserin (1, St, m), modafinil (1, Th, m), monoamine-oxidase A and B inhibitors, irreversible (1, Th, s), norethisterone (1, An, s), Phenothiazines (chlorpromazine) (2, St, m), raltegravir (1, Th, m, Av), rifampicin (1, St, m, Ad), St John's Wort (2, Th, s, Av), thyroid hormones (1, Th, m), tricyclic antidepressants (1, St, m), vitamin D substances (1, Th, m)	Decreases the exposure	Study	Moderate	Avoid and for 14 days after stopping fosphenytoin
	Volatile halogenated anesthetics (methoxyflurane)	Co-administration increases the risk of nephrotoxicity	Theoretical	Severe	Avoid
	Procarbazine	Combine administration may increase the risk of hypersensitivity reaction.	Anecdotal	Severe	
	Coumarins	AED decrease the anticoagulant effect	Study	Moderate	Monitor INR and adjust the dose
	Dapsone	Given together can increase the risk of methemoglobinemia	Theoretical	Severe	
Phenytoin	Antifungals, azoles (miconazole, fluconazole, posaconazole, voriconazole) (3, An, s, Ad), antifungals, azoles (itraconazole) (1, St, m, Av), .anaesthetics, local (ropivacaine) (1, Th, m), melatonin (1, Th, m), duloxetine (1, Th, m), olanzapine (1, St, m, Mo, Ad), Sulfonamides (sulfadiazine) (2, St, m, Mo, Ad)				
	Antimalarials (pyrimethamine)	Increase the risk of haematological toxicity	Study	Severe	
	Enteral feeds	Drug decrease the absorption of AED	Study	Severe	
Pregabalin	Not available				
Rufinamide	combined hormonal contraceptives (1, St, s), etonogestrel (1, Th, s), hormone replacement therapy (1, An, m), levonorgestrel (1, Th,s), norethisterone (1, An, s), ulipristal (1, An, s)	AED decrease the efficacy of other drug	Study	Severe	
Topiramate	Combined hormonal contraceptives (1, St, s), etonogestrel (1, Th, s), hormone replacement therapy (1, An, m), levonorgestrel (1, Th,s), norethisterone (1, An, s), ulipristal (1, An, s)	AED decrease the efficacy of other drug	Study	Severe	

Valproate	Bupropion (1, St, s), Carbapenems (2, An, s, Av), glycerol phenylbutyrate (1, Th, m), guanfacine (2, St, m, Mo, Ad), HIV-protease inhibitors (ritonavir) (2, An, s), paliperidone (1, St, m, Ad), propofol (2, Th, s, Ad), selexipag (1, Th, u), sodium oxybate (1, St, m, Ad), sodium phenylbutyrate (1, An, m), zidovudine (1, St, m),				
	Penicillins (pivmecillinam).	Increase the risks of side effects when given together	Anecdotal	Severe	Avoid
	Quetiapine	Combined administration may increase the risk of neutropenia	Study	Moderate	
Zonisamide	Antihistamines, sedating (hydroxyzine), Haloperidol, Oxybutynin, Tricyclic antidepressants (clomipramine, imipramine)	Potentially increase the risk of overheating and dehydration	Theoretical	Severe	Avoid in children
Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone	Abacavir (1, Th, m), Abiraterone (1, Th, s, Av), Albendazole (2, St, m), aldosterone antagonists (eplerenone) (1, Th, m, Av), alprazolam (1, Th, m, Ad),antiarrhythmics (disopyramide, dronedarone, propafenone)(1, St, s, Av), anticholinesterases, centrally acting (donepezil) (1, St, m), antifungals, azoles (isavuconazole) (1, St, s, Av), antimalarials (artemether, piperaquine) (1, St, s, Av), apixaban (1, St, s, Av), premilast (1, St, s, Av), aprepitant (1, St, s, Av), aripiprazole (1, St, s, Av), axitinib (1, St, s, Av), bazedoxifene (1, St, s, Av), bedaquiline (1, St, s, Av), bortezomib (1, St, s, Av), bosentan (1, St, s, Av), bosutinib (1, St, s, Av), bupropion (1, St, s, Av), buspirone (1, St, s, Av), cabozantinib (1, St, s, Av), calcium channel blockers (amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine) (1, St, m, Ad), cannabis extract (1, St, s), ceritinib (1, St, s, Av), ciclosporin (2, St, s), cilostazol (1, Th, m), cinacalcet (1, St, m, Mo, Ad), clomethiazole (1, St, m, Mo, Ad), cobicistat (1, Th, s, Av), cobimetinib (1, Th, s, Av), combined hormonal contraceptives (1, St, s), corticosteroids (budesonide, deflazacort, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone) (1, St, m, Mo, Ad), corticosteroids (fluticasone) (1, Th, u), crizotinib (1, St, s, Av), dasabuvir (1, Th, s, Av), dabrafenib (1, Th, m, Av), daclatasvir (1, St, s, Av), dasatinib (1, St, s, Av), darifenacin (1, Th, m), delamanid (1, St, m, Av), desogestrel (1, Th, s), dolutegravir (1, St, s, Ad), elbasvir (1, St, s, Av), elvitegravir (2, Th, s, Av), ergotamine (1, Th, m), erlotinib (1, St, s, Av), etonogestrel (1, Th, s), etoposide (1, St, m), etravirine (1, Th, s, Av), everolimus (2, St, s, Ad), exemestane (1, St, m), fesoterodine (1, St, m, Av), fosaprepitant (1, Th, m, Av), gefitinib (1, St, s, Av), glecaprevir (1, St, s, Av), grazoprevir (1, St, s, Av), guanfacine (1, St, m, Ad), haloperidol (2, St, m, Ad), hormone replacement therapy (1, An, m), ibrutinib (1, St, s, Av or Ad), idelalisib (1, St, s, Av), imatinib (1, St, m, Av), irinotecan (1, St, s, Av), iron chelators (deferasirox) (1, Th, m, Mo, Ad), ivabradine (1, Th, m, Ad), ivacaftor (1, St, s, Av), ixazomib (1, St, s, Av), lapatinib (1, St, s, Av), levonorgestrel (1, Th,s). linagliptin (1, St, m), lomitapide (1, Th, m, Mo, Ad), Lumacaftor (1, Th, s, Av), lurasidone (1, St, m, Av), macitentan (1, St, s, Av), maraviroc (1, St, s, Ad), midazolam (1, St, m, Mo, Ad), midostaurin (1, St, s, Av), mirtazapine (1, St, s, Ad), montelukast (1, St, m), naloxegol (1, St, m, Av), nateglinide (1, St, m), netupitant (1, St, s, Av), Nevirapine (2, St, s), nilotinib (1, St, s, Av), nitisinone (1, Th, m, Ad), norethisterone (1, An, s), olaparib (1, Th, m, Av), ondansetron (1, St, m), opioids (alfentanil, fentanyl) (1, St, m), opioids (buprenorphine) (1, Th, m, Mo, Ad), opioids (methadone) (1, St, s, Mo, Ad), opioids (oxycodone) (1, St, m, Mo, Ad), osimertinib (1, St, m, Av), palbociclib (1, St, s, Av), paliperidone (1, St, s, Mo, Ad), panobinostat (1, Th, m, Av), paracetamol (1, St, m), paritaprevir (with ritonavir and ombitasvir) (1, St, s, Av), pazopanib (1, Th, s, Av), phosphodiesterase type-5 inhibitors (avanafil, tadalafil) (1, St, s, Av), phosphodiesterase type-5 inhibitors (sildenafil, vardenafil) (1, Th, m), pibrentasvir (1, St, s, Av), pitolisant (1, St, m), ponatinib (1, Th, m, Av), praziquantel (1, St, m, Av), quetiapine (1, St, m), ranolazine (1, St, s, Av), reboxetine (1, An, m), regorafenib (1, St, m, Av), repaglinide (1, St, m, Mo (blood glucose), Ad), ribociclib (1, St, s, Av), rilpivirine (1, St, s, Av), risperidone (1, St, m, Ad), rivaroxaban (1, St, s, Av), roflumilast (1, St, m, Av), rolapitant (1, St, s, Av), ruxolitinib (1, St, m, Mo, Ad), saxagliptin (1, St, m), simeprevir (1, St, s, Av), sirolimus (2, St, s, Av), sofosbuvir (1, Th, s, Av),				

(*Continued*)

Table 10 Drug interactions of AEDs with co-administered drugs. (*cont.*)

Drug	*Interaction with*	*Effect*	*Method*	*Severity*	*Advice*
	solifenacin (1, Th, m), sorafenib (1, Th, m), sunitinib (1, St, m, Ad or Av), tacrolimus (2, St, s, Mo, Ad), taxanes (cabazitaxel, paclitaxel) (1, St, s, Av), taxanes (docetaxel) (1, Th, s), temsirolimus (2, St, s, Av), tenofovir alafenamide (1, Th, m, Av), tetracyclines (doxycycline) (1, St, m, Mo, Ad), ticagrelor (1, St, s, Av), tivozanib (1, St, s), tofacitinib (1, St, s, Av), tolvaptan (1, St, s, Av), toremifene (1, St, m, Ad), trabectedin (1, Th, s, Av), ulipristal (1, An, s), vandetanib (1, St, m, Av), velpatasvir (1, St, s, Av), vemurafenib (1, Th, s, Av), venetoclax (1, St, s, Av), vinca alkaloids (vinblastine, vincristine, vindesine) (1, Th, s), vinca alkaloids (vinflunine and vinorelbine) (1, th, s, Av), vismodegib (1, Th, m, Av), vortioxetine (1, St, m, Mo, Ad), voxilaprevir (2, St, s, Av), zopiclone (1, St, Mo, Ad)				
Fosphenytoin, phenytoin	agomelatine (1, Th, m), Aminophylline (1, St, m, Ad), antiarrhythmics (lidocaine) (1, An, s), Antiarrhythmics (amiodarone) (2, St, s, Mo, Ad), antifungals, azoles (itraconazole) (1, St, m, Mo, Av)	AED decreases the effect of other drug			
	calcium channel blockers (diltiazem, verapamil) (1, St, s), Capecitabine (2, An, s), caspofungin (1, Th, m, Ad), Intravenous chloramphenicol (2, St, s, Mo, Ad), Chlordiazepoxide (2, St, s), Clobazam (2, An, s), Clonazepam (2, An, s), clozapine (1, An, m), Disulfiram (2, St, s, Mo, Ad), Diazepam (2, St, s, Mo, Ad), Diazoxide (2, An, m), Digoxin (2, St, s), efavirenz (1, Th, s), Fluorouracil (2, An, s, Ad), Folates (2, St, s, Ad). H_2 receptor antagonists (cimetidine) (2, St, s, Mo, Ad), HIV-protease inhibitors (1, Th, s), Isoniazid (2, St, m), levodopa (1, St, m), loop diuretics (furosemide) (1, St, m), metyrapone (1, St, m, Av), modafinil (2, Th, m, Mo, Ad), Monoclonal antibodies (tocilizumab)(1, Th, m, Mo, Ad), pirfenidone (1, Th, m), Quinolones (ciprofloxacin) (2, St, s, Mo, Ad), raltegravir (1, Th, m, Av), rifampicin (2, St, m, Ad), selexipag (1, St, m, Ad), SSRIs (fluoxetine, fluvoxamine) (2, An, s, Mo, Ad), SSRIs (sertraline) (3, An, s, Mo, Ad), SSRIs (paroxetine) (2, St, m), St John's Wort (2, Th, s, Av), statins (atorvastatin, simvastatin) (1, An, m), Sulfinpyrazone (2, St, m), suxamethonium (1, St, m), Tegafur (2, An, s, Mo, Ad), theophylline (1, St, m, Ad), tizanidine (1, St, m), Trimethoprim (2, St, m), vitamin D substances (1, St, m)	Increase the concentration of antiepileptics	Study	Severe	Monitor and adjust dose
	Caffeine citrate	moderately increase the clearance of caffeine citrate.	Study	Moderate	Monitor and adjust dose
	Coumarins	AED alters the anticoagulant effect	Anecdotal	Moderate	
	Dapsone	Given together can increase the risk of methemoglobinemia	Theoretical	Severe	
	Procarbazine	Combine administration may increase the risk of hypersensitivity reaction.	Anecdotal	Severe	
	Neuromuscular blocking drugs, non-depolarising (atracurium, cisatracurium, pancuronium, rocuronium, vecuronium).	AED decrease the effects of (but acute use increases the effects of drug)	Study	Moderate	
	Thyroid hormones	Increase the risk of hypothyroidism	Study	Moderate	
	Topotecan	AED increase the clearance of drug	Study	Moderate	
	Topical anaesthetics, local (prilocaine),	Combine administration may increase the risk of methemoglobinemia	Theoretical	Severe	Avoid or use with caution

Ad, adjust; *An*, anecdotal; *Av*, avoid; *m*, moderate; *Mo*, monitor; *s*, severe; *St*, study; *Th*, theoretical; *U*, unknown

Role of Pharmacists in Management of Patients with Epilepsy

Epilepsy being a chronic disease requires years long duration of treatment and in many cases life-long management at outpatient basis. Hence, it stands as a strong candidate for pharmacists to contribute especially in community settings including:

1. Empowering patient on disease management
2. Medication adherence and compliance aids/approaches
   Non-compliance or failure to medication adherence is long been identified as a major challenge in the epilepsy management (Leppik, 1988) with the consequence of increasing treatment cost and increased rate of hospitalization due to episodes of uncontrolled seizures. A properly planned counseling session that empowers patient on the management of side effects and information on the consequences of deviation from the treatment plan, as well as constant follow up and reiteration of the message play key role in medication adherence. Provision of adequate information on the use of medication should remain the prime focus of the pharmacy personnel with the use of written information where necessary. Use of simple dosage regimens and less frequent dose administrations like sustained release preparations should also be encouraged.
   Assessment of adherence is a complicated area where direct assessment using invasive approach is not always and frequently applicable. Indirect methods involve use of medication adverse events monitoring system (MEMS) by using MEMS devices and dosage unit counts. The former method is expensive whereas the latter one is not a confirmatory approach due to errors and incomplete information at many instances.
   Use of self-reported medication adherence using questionnaires like medication adherence reporting scale (MARS) is a practical approach with its limitations involving underestimation of adherence. A short study with limited number of participants accessed on telephone showed significant increase in the number of patients perfectly adherent to their AED prescriptions assessed suing MARS after the pharmacist led epilepsy consultation (Fogg et al., 2012). Especially showing improvement in quality of life by decreasing seizure worry, coping with physical effects of AEDs, and emotional well-being. Participants reported to be more aware on the information on medicines and their working, how they interfere with other medicines and side effects after the consultation by pharmacist.
3. Monitoring of efficacy (recording seizure control/seizure diary)
4. Monitoring of toxicity (information on symptoms of toxicity)
5. Drug interactions
6. TDM
7. Adverse drug reaction monitoring and management of side effects
8. Specialized dosing protocols (low starting dose and slow tapering)
9. Management of status epilepticus and prevention of development of refractory seizures/importance of emergency management in epilepsy
10. Counseling on the decision for stopping the treatment
    Upto 40% of patients who are seizure free for more than 2 years may have a risk of relapse. The longer the patient remains seizure free the lesser the chances of relapse. Relapse of seizures may have serious social consequences as well as the complication that the seizures might not be controllable by the initial drugs and dosage regime. Hence, it is important to inform and involve the patient of the possible risks and benefits of the termination of AED therapy in before making the decision. In any case, the withdrawal should be carried out very slowly with tapering of one drug at a time (Whittlesea and Walker, 2011).
11. Management of withdrawal symptoms
12. Management of poisoning and over dose
13. To inform what to do when the dose is missed
14. Generic substitution and use of therapeutic equivalence for AEDs
    Prescribing generic AEDs is challenging because of these being narrow therapeutic index drugs as well as due to the associated apprehensions and actual events of loss of seizure control, chances of pharmacoresistance, and withdrawal symptoms that force the practitioners and patients to weigh down the expected cost savings of generic substitution (Gidal, 2009). Certain patients show more vulnerability to the variations in blood levels associated with the formulation changes (Gidal, 2009). Difficulty in generic substitution also makes the AEDs a complex area regarding the access issues especially affordability of medicines. In a study on lamotrigine, it was estimated that the increased hospital visits and more chances of emergency services and hospitalization due to generic substitutions may in some instances prove to be more expensive when total per annum projected costs were considered (LeLorier et al., 2008). Care should be taken for drugs like phenytoin where drug dose–serum level relationship does not behave linearly. The publications and reports on potential harms of switching the branded AED with generic drug has been reviewed by Commission Human Medicine (CHM) and concluded that the loss of seizure control could be chance associations and could not be related to switching therapy. AEDs have been sub-divided into three categories depending upon brand substitution advice (**Table 11**).
15. Quality of life assessment
    Use of self-administered questionnaires for assessing health related quality of life in epilepsy inventory (QOLIE-32) or general health questionnaire (GHQ-12) can help pharmacist in assessing the patient's well being and identifying the need for change in prescription or information to patient on managing ADRs and drug interactions

Table 11 Medicines and Healthcare Regulatory Authority (MHRA)/Commission on Human Medicine (CHM) advice on brand substitution of AEDs (Royal Pharmaceutical Society, 2018)

Category	*AEDs*	*Advice*
1	Phenytoin, carbamazepine, phenobarbital, primidone	Patient should be maintained on a particular manufacturer's product
2	Valproate, lamotrigine, perampanel, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine acetate, zonisamide, topiramate	Need of particular manufacturer's product is based on clinical judgment and consultation with the physician and patient
3	Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin	Unnecessary to maintain the patient on a particular manufacturer's product, unless risk of patient confusion, dosing error or patient anxiety is expected.

Apart from the earlier mentioned generalized role of pharmacists for patients with epilepsy, some patient groups may exhibit additional needs for which pharmacists can provide more diverse range of services in helping the patient achieve the treatment objectives.

1. Role of pharmacists for patients with psychiatric comorbidities
   Epilepsy and psychiatric disorders have bidirectional relationship. Mula enlists a checklist for patients with epilepsy and psychiatric comorbidities which comprises three prime components closely related to the medication use presenting potential roles of the pharmacists in the care of epileptic patients. It states that the potential treatment-emergent psychiatric problems of AED's must be discussed with the patient, low starting dose and slow titration of AEDs must be ensured, and potential side effects and drug interaction should be discussed with the patients (Mula, 2017).
   Patients with aggressive behavior receiving topiramate are at 4 times higher risk of developing depression when started with AEDs. A study on epileptic patients shows that the use of rapid titration schedule increases the risk of depression with topiramate to 23 times and 12.7 times higher in patients with history of depression and febrile seizures, respectively (Mula et al., 2009).
   Attention deficit hyperactivity disorder (ADHD) has been identified as an important comorbidity which adversely affects the quality of life of patients with epilepsy in children and adolescents. Contrary to the reluctance of clinicians on co-prescription of AEDs and methylphenidate, RCTs have shown a positive response rate from 60% to 70% in this respect. However, due to inhibitory effect of methylphenidate on hepatic isoenzymes a low starting dose, slow titration rate and clinical monitoring are advised during therapy.
   In case of psychiatric comorbidities, there are higher degree of chances of pharmacokinetic interactions of psychotropic drugs with inducers drugs carbamazepine, barbiturates and phenytoin. Increased risk of seizures (especially with clozapine), weight gain, higher risk of sedation and sexual dysfunction are some of the complications that arise in the concomitant therapy with AEDs and antiepileptic medicines (Mula, 2017)
2. Role of pharmacists for women with epilepsy
   Gender is an important consideration for designing the counseling and pharmaceutical care services for the patients receiving AEDs. Adverse effects such as hormonal disturbances, weight gain, menstrual irregularities as well as the hormonal phases (menstruation, contraception and menopause), reproductive phases (fertility, pregnancy and lactation) require special counseling and interventions to prevent decline in the patient's quality of life, a problem that is documented for women with epilepsy. Girls taking enzyme-inducing AEDs are advised to avoid concomitant use of progestogen pill and implants (National Institute of Health and Care Excellence, 2018). Difficulty in control of number of seizures, need of multiple AEDs and depression are the challenges faced in clinical care of these patients. **Table 7** provides the key information on the use of AEDs during pregnancy and lactation along with the recommended actions to be taken. Losada-Camacho et al. (2014) have studied provision of pharmacy services in women with epilpesy. **Table 12** describes various pharmacist-led interventions and varous assesment methods used to performs these services.
3. Role of pharmacists in dealing with pediatric patients and their caregivers

Table 12 Few examples of pharmacy services provided in epilepsy management for women with epilepsy and their assessment methods (Losada-Camacho et al., 2014)

	Pharmacy service/ pharmacist-led intervention	*Assessment methods*
1.	Medication review	Dader's method
2.	Group education session	
3.	Adherence	Haynes–Sackett test and Moriski-Green test
4.	Adverse drug reaction	Liverpool adverse event profile (Liverpool AEP)
5.	Depression	Questionnaire of the center for epidemiologic studies depression scale (CES-D),
6.	Seizure frequency record	Using seizure diary
7.	Health related quality of life (HRQOL)	Quality of life in epilepsy inventory-31 (QOLIE-31

Epilepsy Management and Importance of Multidisciplinary Clinical Team

Multidisciplinary clinical team approaches are encouraged for the management of epilepsy. The need of constant evaluation of efficacy and toxicity of the therapy has led to involvement of many non-prescribers to deliver this role including nurses and pharmacists. Pharmacist-led epilepsy consultation provide more information on medication adherence, addressing the queries of the patient regarding therapy, advise in time, changes in the prescription due to reported ADRs and the changes needed to suite the patient preferences and life style.

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Management of Neurological Disorders and Pharmacist's Role: Multiple Sclerosis

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Learning Objectives

At the end of this chapter, the reader should be able to:

- Describe the epidemiology, etiology, pathophysiology, clinical manifestations, and diagnosis of multiple sclerosis (MS).
- Discuss the course of illness and complications associated with MS.
- Identify the pharmacological and nonpharmacological approaches used in the management of the different forms of the disease.
- Identify the current and future role of pharmacists in the management of MS.

Take-Home Message

MS is an autoimmune chronic inflammatory condition that affects the central nervous system (CNS) and is associated with an unpredictable clinical course. Although MS has no cure, different therapeutic modalities hold a great promise for the treatment of MS at different stages. The challenging safety profiles and trajectory of prices of the different therapeutic agents call for the need of emphasizing the pharmacist's role in the management of MS. Pharmacists contribute to the management of MS through serving as patients advocates and collaborating with other health care professionals to generate better health outcomes.

Introduction

MS is an autoimmune disease, characterized by chronic inflammation that affects the CNS (i.e., the brain, spinal cord, and optic nerves) (Goldenberg, 2012). MS causes an immune-mediated axonal damage and demyelination of the protective myelin sheaths covering the nerve cells. Inflammation and absence of myelin interrupt the transmission and affect numerous elements of the

human body. This can result in various reversible and irreversible consequences, including potential disability (Goldenberg, 2012). However, due to the unpredictability of the disease course, some patients may present with a worsening disease associated with major disability over time, while others may experience a milder course with little to no disability. Although one cannot anticipate how the disease may progress with each individual patient, most patients often experience short periods of symptoms or acute exacerbations followed by longer periods of partial or full recovery (Leray et al., 2016). Recently, several environmental and genetic factors have been associated with the development of MS; however, the etiology of the disease remains unclear (Ascherio and Munger, 2016; Reich et al., 2018).

Moreover, depending on the severity and course of disease progression, MS could be classified into four different disease forms with variable responses to therapy: (1) relapsing remitting MS (RRMS), (2) primary progressive MS (PPMS), (3) secondary progressive MS (SPMS), and (4) progressive relapsing MS (PRMS) (Ascherio and Munger, 2016; Reich et al., 2018). Consequently, patients with MS may experience a variable range of clinical signs and symptoms. Most common among these are acuity and visual disturbances, walking difficulties, helplessness, and clumsiness in attitude and emotions, changes in pain perception, and peculiar sensation like tingling (Swann, 2008). In addition, while there is currently no cure for MS, a number of pharmacologic and nonpharmacologic approaches are available for the management of MS, including injectable and oral disease-modifying therapies (DMTs) (Ascherio and Munger, 2016; Reich et al., 2018). Furthermore, newer challenges have surfaced with the emergence of novel MS treatments. Thus, research is still ongoing in this area in order to improve the overall quality of care of MS patients. MS is associated with a significant economic burden globally (Schafer et al., 2010). Pharmacotherapy as well as MS-related hospitalizations, physical/occupational therapy, and polypharmacy are among the major contributors to MS cost burden (Asche et al., 2010; Schafer et al., 2010).

Epidemiology of Multiple Sclerosis

MS is the most common neurologic disorder worldwide. Its prevalence has been steadily increasing globally; according to the Atlas of MS, the number of MS patients increased from 2.1 million in 2008 to approximately 2.3 million in 2013 worldwide. Nonetheless, the likelihood of underestimation cannot be ruled out owing to limited data from India and China (Browne et al., 2014). In addition, with an uneven global distribution, the prevalence of MS is highest in North America (140/100,000 population) and Europe (108 per 100,000 population) and lowest in East Asia and Sub-Saharan Africa (Browne et al., 2014). Although the prevalence of MS is highest in Europe and North America (Heydarpour et al., 2015; Leray et al., 2016), a shift toward a moderate-to-high prevalence of MS has been evident in several gulf countries, including Qatar (Deleu et al., 2013), Kuwait, and Iran (Ascherio and Munger, 2016; Leray et al., 2016; Reich et al., 2018).

Generally, there is a 2:1 ratio of women-to-men with MS, indicating an increasing incidence of MS in women worldwide. In America, the incidence of MS in women is more than twice that in men with a ratio of 2.6. The reason pertaining to the higher difference of MS risk in women as compared with men has not been fully established; however, it is believed to be related to different social and environmental aspects, including genetic differences (Browne et al., 2014). Moreover, MS is often diagnosed between the ages of 15–45 years, with an average age of MS onset is 30 years (Awad and Stüve, 2010; Leray et al., 2016).

Pathophysiology of Multiple Sclerosis

There are several suggestions pertaining to the involvement of the immune system in the pathogenesis of MS. Although still debatable, the autoimmunity theory of MS has been well established to be the underlying mechanism that guides the understanding of the pathogenesis of MS (Korn, 2008). Briefly, according to several lines of evidence, in MS myelin antigen-specific CD4+ T helper cells are activated in the peripheral immune compartments. The activated T cells then cross the blood–brain barrier into the CNS, resulting in further differentiation of autoreactive T cells and production of effector cytokines. This, in turn, contributes toward dissemination of immune cells (e.g., macrophages) into the CNS parenchyma. Consequently, the immune cells mediate the inflammation and demyelination of the myelin sheaths resulting in axonal damage and secretion of toxic oxygen species. With time, the immune-mediated CNS destruction and axonal damage may become irreversible causing severe disability in MS patients. In addition, chronic inflammation and continued neurodegeneration may promote secondary progressive forms of the disease (Korn, 2008; Wu and Alvarez, 2011). While the actual trigger for the activation of this autoimmune inflammatory activity in MS patients remains elusive, evidence suggests that certain infectious agents (e.g., Epstein–Barr virus) may be responsible for initiating this peripheral immune activation (Korn, 2008; Wu and Alvarez, 2011).

Etiology of Multiple Sclerosis

As mentioned previously, the etiology of MS, like other autoimmune disorders, is still unclear. However, several modifiable and nonmodifiable environmental, hereditary, and epigenetic risk factors have been identified as possible contributors to the overall risk of developing MS. Such factors include genetic variations, female gender, smoking, and low vitamin D levels. While an increased risk is inevitable with MS-associated genetic factors, some environmental and lifestyle-related risk factors can be modified to minimize interactions with genetic events, thus serving as possible preventative mechanisms for MS (Olsson et al., 2017).

Genetic Susceptibility of Multiple Sclerosis

The strongest known genetic element attributed to MS susceptibility may be the HLA-DRB1*1501 haplotype (Patsopoulos et al., 2013). However, it is not fundamental for the development of MS because it only escalates the risk by two to fourfolds and exists in about 20%–30% of healthy individuals. In contrast, there is a strong association between hereditary elements and the development of MS, whereby an up to 40-fold increase in the risk of disease development is evident in first-degree relatives of patients with MS. In addition, the risk is increased by up to 30% in monozygotic twin (Zwibel and Smrtka, 2011).

Environmental Factors Associated With Multiple Sclerosis

Environmental factors, such as vitamin D levels, viral infections, sunlight exposure, geographic latitude, and place of birth, play a key role in determining the risk of developing MS. One proposed explanation for the potential association of MS with latitude is that contact with sunlight could be protective, either due to the impact of ultraviolet radiation or due to that of vitamin D (Ascherio and Munger, 2007). Moreover, research highlights a relationship between sunlight exposure, ultraviolet radiation, serum vitamin D levels, and the risk of MS (van der Mei et al., 2003; Munger et al., 2004); such that some of these factors are thought to be inversely correlated with MS disease activity in established MS cases (Mowry et al., 2012; Ascherio et al., 2014).

In view of the evidence, the distribution of MS is higher in areas away from the equator. Caucasians and residents of Northern European descents are at a significantly higher risk of developing MS as compared with other ethnicities. In addition, although the chance of developing MS is higher in individuals residing in areas of Northern Europe, the degree of disease risk may differ with respect to their place of residence in early life. According to a research conducted by Dean and Kurtzke (1971), migration from low to high-risk zones in childhood does not increase the risk or chance of developing MS. However, the complete cutoff is relatively indeterminate, considering that Hispanic Americans and Black Americans encounter more rapid disease development than White Americans (Ventura et al., 2017). Moreover, environmental triggers unrelated to geography are also possible risk factors for the development of MS. Such triggers include tobacco smoking, obesity, contraception, and late childbirth (Franklin and Nelson, 2003; Koch-Henriksen and Sørensen, 2010). Interestingly, the risk of MS relapse is significantly reduced during pregnancy, but increases again postpartum (Lee and O'Brien, 2008).

Clinical Presentation—Signs and Symptoms of Multiple Sclerosis

Clinical signs and symptoms are widely variable among different MS patients. Similarly, symptoms severity and degree of disease progression may also vary extensively within the same individual over time (Schapiro, 2005). Initially, patients commonly present with sensory deficits like tingling or numbness, optic neuritis manifested as blurry or doubled vision, muscle pain or weakness, and problems in gait or bladder control. At a later stage, symptoms such as cognitive impairment, mood swings, and physical fatigue may become more prominent. Accordingly, complications secondary to primary disease symptoms may arise over time, such as urinary tract infections secondary to MS-related urinary retention (Schapiro, 2005). Eventually, patients may develop symptoms that affect their daily life activities and overall quality of life (Schapiro, 2005).

As mentioned earlier, the clinical course of MS has four clinical classifications (Lublin et al., 2014). First is the RRMS phase in which 85% of patients present with exacerbations that last for at least 24 h, following a clinically isolated syndrome (CIS). These new symptoms, also known as relapses, correspond with magnetic resonance imaging (MRI) findings and are subsequently followed by clearly defined periods of complete or partial disease remission. Due to the unpredictable nature of the disease, the occurrence of MS attacks cannot be anticipated (Lublin et al., 2014). However, certain circumstances have been associated with symptoms or exacerbations such as heat, stress, infections, and malnutrition. Subsequently, most RRMS patients enter a progressive phase, referred to as SPMS, which is characterized by evidence of significant disability with undistinguishable periods of relapses and remissions (Lublin et al., 2014). On the contrary, around 10%–15% of patients begin with a progressive form of MS at disease onset, a phase referred to as PPMS (Lublin et al., 2014). PPMS is equally common in men and women and is characterized by a worsening disability which is diagnosed at a later age (Tremlett et al., 2005). Finally, at onset, fewer patients (~5%) present with a mixture of both a progressive and a relapsing form of MS known as PRMS (Lublin et al., 2014). Notably, although the life expectancy of MS patients is not directly affected by the condition, several factors may be associated with a better disease prognosis, such as the female gender, or a less favorable one, such as an age of disease onset later than 40 years.

Diagnosis of Multiple Sclerosis

The diagnosis of MS is challenging because it shares common features with other neurological disorders. A complete neurological examination and collecting a comprehensive medical history are essential for excluding other causes and confirming a correct MS diagnosis (Ghasemi et al., 2017). Despite the lack of a specific diagnostic test for MS, a set of criteria, known as "McDonald Criteria," were established by an international panel of MS experts in association with the National MS Society of America for the purpose of achieving a prompt diagnosis to allow for a sooner initiation of MS treatment (McDonald et al., 2001). Briefly, according to the McDonald Criteria, a diagnosis of MS is established upon the identification of two different neurological attacks that have occurred

at two different time points and are in at least two distinct locations in the CNS (brain, spinal cords, or optics nerves) (McDonald et al., 2001; Polman et al., 2005). The attacks could be identified through the patient's clinical history, MRI examination, or both, given that other possible causes for such events are ruled out. The first attack is referred to as CIS, for which several medications are approved for use at this stage to prevent progression to a clinically definite MS diagnosis (Swanton et al., 2007). On the contrary, patients may initially present with a radiologically isolated syndrome (RIS), which may progress to a CIS and eventually to a clinically definite MS over time (Lebrun et al., 2009). RIS is a newly identified concept whereby asymptomatic patients present with incidental MRI findings suggestive of MS; however, unlike CIS, the initiation of MS treatment at this stage is still elusive (Lebrun et al., 2009; Gerber et al., 2017).

In addition to the typical clinical symptoms, data from MRI are generally considered in order to support the diagnosis of the condition, given the characteristic CNS lesions associated with MS, also known as plaques or sclerosis (Ghasemi et al., 2017). On the contrary, cerebrospinal fluid (CSF) evaluation, blood analysis, and neurophysiological testing could provide major evidence toward a more accurate diagnosis. Moreover, characteristic biomarkers in MS are objectively measured and evaluated as indicators of normal biological processes, disease activity, disease progression, and pharmacological response to therapeutic interventions (Lesko and Atkinson, 2001; Paul et al., 2018). The most established biomarkers in MS are linked to MRI of the brain, which permits the identification and quantification of MS lesions of progressive nature (Martin et al., 2006). Although the biological biomarkers in MS have already been identified in various bodily fluids, such as urine, blood, tears, and CSF, each kind of specimen has its own merits and demerits. In addition, as MS lesions are hardly ever biopsied, the CSF evaluation remains the optimal indictor of the disease pathology and could better reflect on relevant inflammatory mechanisms (Sospedra et al., 2010). Furthermore, the use of optical coherence tomography for the evaluation of the retina is also noteworthy because the ganglion-cell axon loss in the retina corresponds to changes in the brain MRI and can predict the development of disability in MS patients (Saidha et al., 2015).

Management of Multiple Sclerosis

Pharmacological Therapy

The pharmacotherapy of MS is grouped into three different classifications: (1) treatment of acute MS exacerbations; (2) management of the underlying disease course; and (3) management of MS-related symptoms. These three treatment categories are aimed at minimizing the duration and severity of attacks, halting the disease progression, and optimizing patients' quality -of -life, respectively. Moreover, slowing the progression of disability over time and maintaining the quality -of -life in patients with MS mandate an early detection of the disease followed by an immediate initiation of drug therapy (Polman et al., 2005). Although international MS guidelines and relevant professional associations have proposed several treatment algorithms, a universally accepted algorithm is yet to be established. Hence, due to the complexity of MS and the heterogeneity of symptoms among different patients, a treatment algorithm is often tailored as per each individual patient case, while constantly weighing for the benefit-to-risk ratio. One example of a simple treatment algorithm adopted from a clinical review published in the *British Medical Journal* is demonstrated in **Fig. 1** (Wingerchuk and Weinshenker, 2016).

In addition, owing to the demanding monitoring schedules, the need for comprehensive educational sessions, and the introduction of new pharmacological agents, the management of MS could become challenging for health care practitioners, patients, and patients' caregivers (Förster et al., 2019). However, different evidence-based therapeutic categories, both pharmacological and nonpharmacological, have been proven efficacious in treating the relapsing-remitting stages, slowing the disease progression, and reducing the treatment burden.

Treatment of Acute Attacks

The goal of the acute management of MS is to reduce the duration and severity of initial or recurrent attacks (Kaufman et al., 2000; Ontaneda and Rae-Grant, 2009; Rae-Grant et al., 2018). MS exacerbations could be defined by a number of findings that must solely be attributed to the natural course of the disease: (1) new or enhancing MRI lesions of the brain, spinal cord, or optic nerves; (2) a new MS-related symptom or one that is worsening over a period of 2 weeks; and (3) clear functional limitations. Findings secondary to other causes, such as heat, stress, or infections, are referred to as "pseudo-exacerbations" and should be carefully ruled out before administering an acute therapy or modifying a current disease-modifying therapy (DMT).

According to the European Committee of Treatment of Research in Multiple Sclerosis and European Academy of Neurology (ECTRIMS/EAN), American Academy of Neurology (AAN), and the NICE guidelines, a high-dose intravenous (i.v.) corticosteroid (500–1000 mg i.v. methylprednisolone) should be administered for 3–5 days as first-line therapy in patients with acute MS attacks (Kaufman et al., 2000; Perry et al., 2014; Montalban et al., 2018). Although the mechanism of action of corticosteroids in MS remains unclear, they presumably speed up recovery by exerting an anti-inflammatory effect in the CNS (Ontaneda and Rae-Grant, 2009). Moreover, i.v. methylprednisolone has also been shown to delay subsequent MS attacks by 1–2 years (Kaufman et al., 2000), although this did not directly affect MS progression (Zivadinov et al., 2001). On the contrary, guidelines recommend the use of plasma exchange or i.v. immunoglobulin as second-line treatments if an exacerbation fails to respond to i.v. corticosteroid or if a patient initially presents with a severe attack (e.g., paraplegia).

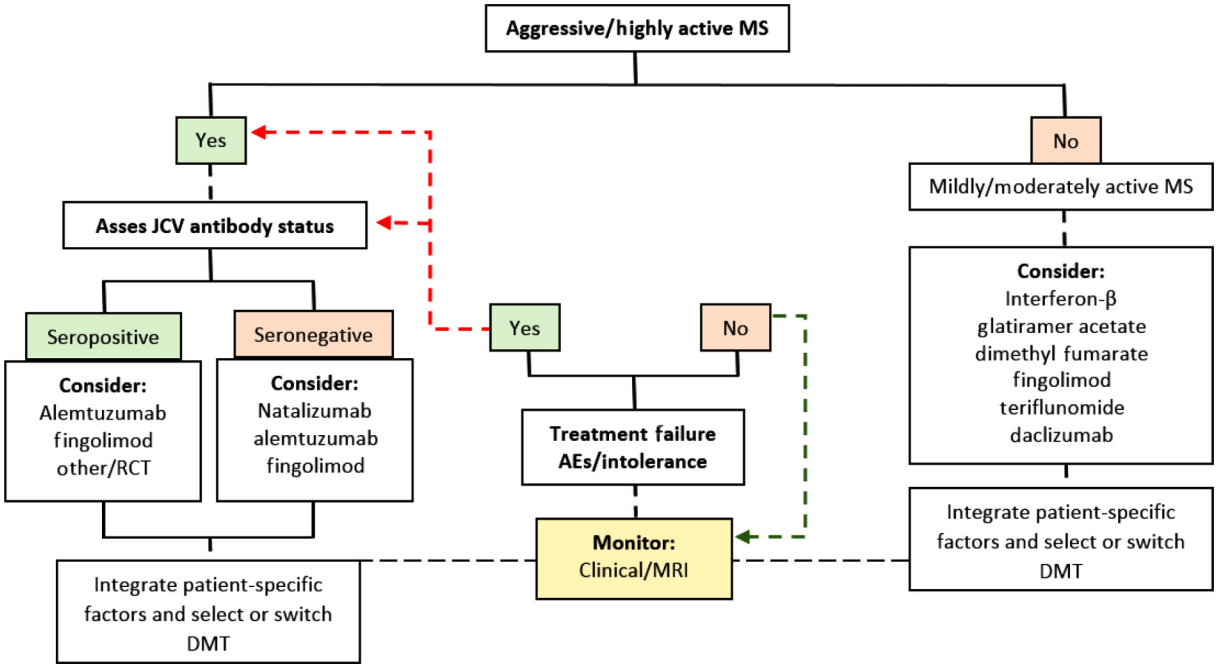

Figure 1 A proposed algorithm for the treatment of multiple sclerosis.

Disease-Modifying Therapy

While some clinicians may choose to defer the use of DMT until the nature of the disease course is clearly identified, current evidence recommends conducting a more comprehensive diagnostic work-up to allow for a sooner initiation of therapy (McDonald et al., 2001; Polman et al., 2005). On that note, the available DMTs do not cure MS; however, they can alter the immune system either through immunomodulation or through immunosuppression. Although both therapies target the inflammatory activity of MS (Katsavos and Anagnostouli, 2013), immunosuppressant drugs tend to cause direct cytotoxic activity and bone marrow suppression, while immunomodulatory agents do not. With this in mind, selecting a DMT is generally based on determining the severity of the initial disease presentation, availability of treatment options, safety profiles of the medications, and patients' preferences and expectations (Montalban et al., 2018).

Moreover, patients are usually assigned either to an induction or an escalation treatment algorithm depending on the intensity of their initial clinical presentation. In the escalation approach, FDA-approved self-injected medications, that are associated with better safety profiles yet partial effectiveness, are considered first-line treatments (four interferon-β [IFN- β] formulations and glatiramer acetate) (Kasarełło et al., 2017). However, upon evidence of ongoing treatment failure, patients are consequently switched to second-line DMTs (natalizumab, ocrelizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab) owing to their higher effectiveness (Kasarełło et al., 2017). On the contrary, the induction strategy involves using second-line DMTs as initial therapies in the earlier phases of the disease, followed by long-term maintenance treatment. Despite their high therapeutic effectiveness, second-generation DMTs are also associated with higher risk of more serious side effects (De Jong et al., 2017). Therefore, the induction treatment approach is generally reserved for patients with poor prognosis or highly active disease at onset. On the contrary, DMTs can be subclassified into three other categories based on the premises of safety (e.g., INF-β and galtiramer acetate), convenience (e.g., oral DMTs: fingolimod, teriflunomide, and dimethyl fumarate), and effectiveness (e.g., natalizumab, ocrelizumab, and alemtuzumab). Lastly, an investigational or non-FDA-approved drug, such as rituximab, is recommended in the case that both the first- and second-generation DMTs fail to improve the disease progression, that a patient initially presents with aggressive forms of MS, or that a patient is unable to tolerate the initial therapy (Montalban et al., 2018).

The common DMTs used in the treatment of MS are summarized in **Table 1** (Comi et al., 2017).

Additionally, it is important to recognize that DMTs do not improve symptoms secondary to MS. Several pharmacological agents such as methylphenidate, gabapentin, baclofen, and propantheline are recommended for the treatment of MS-related fatigue, sensory complaints, spasticity, and abnormal bladder control, respectively (Schapiro, 2005).

Summary of Recommendations from Clinical Practice Guidelines

According to most recent evidence-based clinical practice guidelines in Europe, the United Kingdom, the United States, and Australia/New Zealand, all patients with recent evidence of active RRMS should be started on a DMT (Ontaneda and Rae-Grant, 2009; Broadley et al., 2014; Montalban et al., 2018; Rae-Grant et al., 2018). However, the guidelines recommend individualizing the choice of a specific DMT as per the patient's clinical presentation, personal values, expected goals, medical comorbidities, and medications tolerability. The ECTRIMS/EAN guidelines also recommend the initiation of a low-risk DMT, either INF-β or

Table 1 Disease-modifying therapies used in the treatment of multiple sclerosis

Medication	*Trade name*	*Indication*	*Dose and route of administration*	*Side effects*	*Comments*
First-generation DMTs (safety -preference)					
Interferon-β1a	Avonex	CIS; RRMS. SPMS	30 μg IM every week	Injection-site reactions, elevated liver enzymes, depression	Self-injectable
Interferon-β1a	Rebif	CIS; RRMS. SPMS	44 μg SQ three times a week	Injection-site reactions, elevated liver enzymes, depression	Self-injectable
Interferon-β1b	Betaferon/ Extavia	CIS; RRMS. SPMS	250 μg SQ every other day	Injection-site reactions, elevated liver enzymes, depression	Self-injectable
Pegylated interferon-β1a	Plegridy	RRMS	6.3 μg SQ day 1, then 94 μg SQ on day 15, then 125 μg SQ on day 29, then 125 μg SQ every 14 days	Injection-site reactions, elevated liver enzymes, depression	Self-injectable
Glatiramer acetate	Copaxone	CIS; RRMS	20 mg SQ once daily	Injection-site reactions, flu-like symptoms, lipoatrophy	Self-injectable; pregnancy category B
Second-generation DMTs (convenience -preference)					
Fingolimod	Gilenya	RRMS	0.5 mg orally once daily	Bradycardia, infections	Risk of PML
Teriflunomide	Aubagio	RRMS	14 mg orally once daily	Diarrhea, hair thinning	Teratogenic (pregnancy category X)
Dimethyl fumarate	Tecfidera	RRMS	240 mg orally twice a day	Flushing, gastrointestinal symptoms	Risk of PML
Second-generation DMTs (effectiveness -preference)					
Natalizumab	Tysabri	RRMS	300 mg i.v. every 4 weeks	Infusion reactions; infections	i.v. infusion; risk of PML
Ocrelizumab	Ocrevus	RRMS; SPMS; PPMS	300 mg i.v. once, and 300 mg i.v. once after 2 weeks, then 600 mg i.v. once every 6 months	Infusion reactions; infections	i.v. infusion; contraindicated in active hepatitis B virus infection
Alemtuzumab	Lemtrada	RRMS	12 mg i.v. once a day for 5 consecutive days and, after 12 months, 12 mg i.v. once a day for 3 days	Infusion reactions; infections	i.v. infusion

CIS, Clinically isolated syndrome; *DMTs*, disease-modifying therapies; *IM*, intramuscular; i.v., intravenous; *PPMS*, primary progressive multiple sclerosis; *RRMS*, relapsing-remitting multiple sclerosis; *SPMS*, secondary-progressive multiple sclerosis; *SQ*, subcutaneous.

galtiramer acetate, for patients with a CIS and characteristic radiological finding who do not fulfill the criteria of definite MS diagnosis (Montalban et al., 2018).

Upon the progression of RRMS to SPMS, it is recommended that patients be started on, or switched to, an INF-β1a/1b formulation. Ocrelizumab and mitoxantrone have also demonstrated efficacy in reducing relapse rates in patients with SPMS (Montalban et al., 2018). Moreover, a randomized clinical trial showed that mitoxantrone reduced the progression of disability in patients with PRMS (Hartung et al., 2002). However, owing to its high -risk of serious adverse events, mitoxantrone should only be offered to MS patients if the benefits significantly outweigh the risks. In addition, according to the AAN and ECTRIMS/EAN guidelines, ocrelizumab should be offered to patients with PPMS following a careful evaluation of its benefit-to-risk ratio. Generally, given that patients are adherent to current therapy, clinicians should consider switching to another DMT upon evidence of frequent disease activity over a period of 1 year, a long enough duration to determine the full efficacy of a DMT.

Finally, all guidelines recommend that DMTs should be stopped and should not be initiated during pregnancy, unless the risk of MS during pregnancy outweighs the risk of DMT use during pregnancy. Women of childbearing age are strongly advised to follow strict contraceptive methods and discuss pregnancy planning with their health care providers. According to the ECTRIMS/EAN guidelines, women who plan to become pregnant despite pervious recommendations should be offered either INF-β or glatiramer

acetate until pregnancy is confirmed. In the event that women becomes pregnant, the use of glatiramer acetate, natalizumab, or alemtuzumab throughout pregnancy may be considered.

Non-pharmacological Treatment

Nonpharmacologic approaches are interventions offered either by health care practitioners or by caregivers to alleviate the sufferings and symptoms of patients with MS for the purpose of minimizing disease-related morbidity. As MS is associated with a wide range of symptoms, several nonpharmacological approaches are recommended to minimize MS-related pain, fatigue, spasticity, and mood disorders. Such approaches include transcutaneous electrical nerve stimulation, psychotherapy, moderate physical exercise, transcranial random noise stimulation, transcranial direct stimulation, hydrotherapy, reflexology, neuromuscular electrical stimulation, modified Paleolithic diet, stress management, meditation, and massages. In addition, lifestyle modifications can improve MS symptoms and reduce symptoms or exacerbations (Bowling, 2014). Therefore, MS patients are also advised to adhere to self-management activities such as drinking plenty of fluids, reporting signs of infections or disease relapse, avoiding extreme temperatures, and avoiding excessive exercise (Bowling, 2014).

Moreover, incorporation of physical exercise in the clinical care of MS can positively affect patients' wellness, quality -of -life, and participation in daily life activities (Motl et al., 2017). A large body of evidence demonstrated mixed findings with regard to the effect of physical exercise on the disease progression in patients with MS (Roehrs and Karst, 2004; Ratchford et al., 2010; Pilutti et al., 2011; Straudi et al., 2013; Fornusek and Hoang, 2014; Pilutti et al., 2016). However, results showed improvements in thigh circumference, endurance and severe spasticity, walking rate, gait, fatigue, and quality -of -life (Roehrs and Karst, 2004; Ratchford et al., 2010; Pilutti et al., 2011; Straudi et al., 2013; Fornusek and Hoang, 2014; Pilutti et al., 2016).

Monitoring Therapy in Multiple Sclerosis

MRI is the most commonly recommended tool for the quantification of lesions in MS patients. It is used for estimating disease progression and identifying response to therapy. MS is characterized by a buildup of plaques in white matter and gray matter, which are presented as quantifiable volumes of deviant magnetic properties in conventional MRI (i.e., in T2-weighted imaging data T2 lesions). New or enhancing T2 lesions that appear during therapy are reliable indicators of subclinical disease evolution and inflammatory activity. In addition, the most widely used means of measuring the progression of MS over time is the clinical rating scale called the "Expanded Disability Status Scale" (EDSS) (Kurtzke, 1983). The EDSS is used to evaluate the change in patients' neurological and daily functioning (Kurtzke, 1983).

MS is associated with a complex array of symptoms and possible risk of disability issues. Therefore, monitoring of physical, social, and cognitive parameters is important to ascertain adequate counseling and treatment measures (Köhler et al., 2018). Likewise, one cannot underestimate the concept of self-monitoring, which not only benefits the patients but also provides health care professionals with more relevant information about the patient's condition. The International Organization of Multiple Sclerosis Nurses (IOMSN) highlighted the need of a self-assessment scale that enables close monitoring of MS patients for the goal of achieving better care outcomes.

"Monitoring My Multiple Sclerosis", a web-based monitoring algorithm which incorporates various patient outcome measures, along with computerized cognitive batteries (such as the CogState Brief Battery), wearable biosensors, and a recently developed application (MS Sherpa) is used in examining disability, functional mobility, and cognitive impairment in MS patients. Although periodic assessments in clinical settings remain imperative for the evaluation of MS progression, active and passive smartphone-based self-monitoring strategies are more explicit in nature. Despite being user-friendly and convenient, those monitoring devices could be subject to several limitations including potential measurements' inaccuracy, non-adherence by users, and the issues with data management.

Prevention

With more than 2 million people afflicted globally and the burden of disease being substantial both on individuals and society, modifiable risk factors need to be identified to prevent morbidity and mortality. Given that vitamin D is one of the key regulators of the immune and nervous function, low vitamin D can increase the chances of developing MS. Studies suggestive of reduced relapse rate with increased vitamin D levels demonstrate the positive role of vitamin D in preventing the development of MS. In the present era of vaccine being marketed for every disease, it is imperative to remember that no single microorganism is implicated in MS and therefore developing a vaccine to prevent MS cannot be of substantive significance, although BCG vaccine was reported to decrease the number of active brain lesions in MRI scan of MS patients. Furthermore, maintaining a healthy lifestyle with normal BMI, abstinence from smoking and alcohol, and gearing up with dietary modifications such as omega-3 oils are expected to keep MS at bay.

The Role of Pharmacist in the Management of Multiple Sclerosis

The idea behind medication therapy management (MTM) is to assess patients from a holistic viewpoint, identify and resolve all patients' drug-related problems, promote concordance and adherence to drug and nondrug therapy, and create customized care plan

with emphasis on regular follow-ups for better health care outcome (Anderson and Philbrick, 2014). Pharmacists can be viewed as educators and counselors for MS patients and assist them in setting realistic goals for their therapy and lifestyle modifications, and prior inform the patients regarding the barriers related to adherence (Anderson and Philbrick, 2014). In the context of MS, therapeutic agents have challenging safety profiles and may require regular laboratory monitoring with close follow-up for undesirable effects. For instance, consistent laboratory monitoring is essential for many medications and therefore, in patients prescribed with dimethyl fumarate (Tecfidera [Biogen Idec]), lymphocyte counts need to be assessed every 6 months.

The presence of a skillful clinical pharmacist is expected to minimize the chances of medication errors and treatment delays and promotes improved adherence, culminating into better clinical outcomes for the patients (Schultz et al., 2016). A pharmacist can be an active member in an MS multidisciplinary team who can improve the treatment outcome by carefully reviewing individual patient's therapeutic plan. In the backdrop of initiating new line of treatment, the pharmacist collaborates with other team members and patients to comprehensively appraise the different aspects of medication use followed by response to queries from the patients or other health care professionals.

Studies have been conducted on the effect of MTM and MS with regard to patients administrating their own injections. In a behavioral study, it was observed that patients who self-inject compared with those who rely on other caregivers were found to be more likely adherent to their drug therapy (Mohr et al., 2001). The impact of patient adherence to interferon beta-1b SQ (MS relapse) on prices and health care resource usage was studied among individuals with RRMS over an interval of 3 years. The outcomes reported that medication taking behavior is the key to minimizing direct or indirect expenses of disease exacerbation and enhanced adherence (Steinberg et al., 2010). Pharmacists need to be aligned with the MS patient's health care team and can make efforts in shifting the mindset toward "getting the drug therapy right for each patient." Hanson et al. (2014) cited a few of the known reasons for patient's poor adherence in MS: the misperception of DMT benefits, needle phobia, lack of social support, and insufficient understanding regarding their disease condition. Because of the complexity of the condition, care coordination among different health -care providers is necessary for long-term benefits.

There are numerous reasons why persons living with MS might neglect to stick to their valuable therapy. Factors like adverse drug reactions, inconvenient usage, cost of therapy, mood, and education need to be improved through effective communication. According to Taddei-Allen et al. (2017), pharmacist-led effective communication is divided into two levels for MS patients. During this first level of communication, once a new individual is identified with MS, a clinical pharmacist contacts her or him to establish a therapeutic relationship and perform a preliminary screening. This is followed by establishing a baseline on the patient's condition, evaluating their regular MS symptoms and recording the prior medical history, evaluating risk elements, and measuring the patient's knowledge and understanding of medications (Taddei-Allen et al., 2017).

The second level of communications involves patients who either discontinue their treatment or no longer respond to the pharmacy's outreach efforts. The findings showed that communication is also substantially associated with adherence and thus better communication is advocated between a health care provider, office staff, and patient to increase adherence (Patty Taddei-Allen, 2017)

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Selected Reading/Resources

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https://www.msif.org/about-us/who-we-are-and-what-we-do/advocacy/
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Attention-Deficit Hyperactivity Disorder Management and the Role of the Pharmacist

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General Overview of Attention-Deficit Hyperactivity Disorder

History

Attention-deficit hyperactivity disorder (ADHD) is a common childhood neurobehavioral disorder that often persists into adolescence and adulthood (Gintner and Mooney, 2015). The history of ADHD dates back to the early 20th century when a British pediatrician, Sir George Still found that some children lacked the ability to control their behaviors compared to other children. He described this condition as "an abnormal defect of moral control in children" (Conners, 2000). Later in 1915, after the epidemic of encephalitis, it was noted that children who survived the infection developed behavioral problems such as hyperactivity and impulsivity. This condition was initially termed as "brain-injured child syndrome," which was later changed to "minimal brain damage" and then to "minimal brain dysfunction" (Lange, 2017).

In 1952, the American Psychiatric Association issued the first Diagnostic and Statistical Manual of Mental disorders (DSM) in which all mental disorders were recognized except ADHD. However, in 1968, the disorder was introduced for the first time in DSM-II by the name of "hyperkinetic reaction of childhood" (Barkley, 2014). The 1970s saw changes in ADHD research as scholars began to emphasize the issues of impulse control and lack of attention in addition to hyperactivity (Lange, 2017). In 1980, DSM-III incorporated those changes and the disorder was named as "attention-deficit disorder" (ADD) (Barkley, 2014). However, in 1987, the disorder was renamed as "attention-deficit hyperactivity disorder" (ADHD) in the revised version of DSM-III (DSM-III-R) (Conners, 2000). During the 1990s, it was recognized that ADHD is not exclusively a childhood disorder, but it may persist into

adolescence and adulthood (Barkley, 2014). Hence, the DSM-IV included examples of occupational difficulties in the diagnosis of ADHD. Moreover, DSM-IV also introduced the three specific subtypes of ADHD identified as predominantly inattentive, predominantly hyperactive/impulsive, and combined (Barkley, 2014). The recent publication of DSM-V named the disorder as ADHD and placed it under the umbrella of neurodevelopmental disorders. The revisions included the elaboration of diagnostic criteria with specific examples, change of terminology from ADHD "types" to "presentations," and the use of modifiers (mild, moderate, severe) to specify the severity of the disorder (Rosales et al., 2015).

In contrast, the International Classification of Diseases, Tenth Revision (ICD-10), published by the World Health Organization (WHO) in 1992, classifies ADHD as hyperkinetic disorders (HKD) (F90) (Doernberg and Hollander, 2016). This group of disorders is classified under "behavioral and emotional disorders with onset usually occurring in childhood and adolescence" (F90-F98), in a section of Chapter 5: "Mental and behavioral disorders" (F00-F99) (Doernberg and Hollander, 2016). HKD are further classified into disturbance of activity and attention (F90.0), hyperkinetic conduct disorder (F90.1), other kinetic disorders (F90.8), hyperkinetic disorder, and unspecified (F90.9). Hyperactive disorders are characterized by an early onset (within the first 5 years of birth) in which a child with excess activity moves from one activity to another without completion (Santosh et al., 2005).

Epidemiology

ADHD is a childhood disorder but often persists into adolescence and adulthood. The prevalence of ADHD varies among children, adolescents, and adults (Polanczyk et al., 2007). Although there is no global consensus on the prevalence of ADHD, a meta-analysis of 175 studies worldwide reported a pooled estimate of 7.2% in children under 18 years of age (Thomas et al., 2015). Approximately, 129 million children in the age group 5–19 years worldwide have ADHD (Thomas et al., 2015). The prevalence in adults varies from 1.2% to 7.3% globally (Fayyad et al., 2007). The variation in the prevalence of ADHD in different parts of the world is mainly due to behavioral and environmental changes, use of different diagnostic criteria, and methodological differences between studies (Polanczyk et al., 2007).

A study published in January 2018 reported that 5.4 million children (8.4%) in the United States (US) have a current diagnosis of ADHD (Danielson et al., 2018). Of these, 2.9 million are adolescents aged 12–17 years, 2.2 million are school-aged children aged 6–11 years, and 0.3 million are young children aged 2–5 years (Danielson et al., 2018). In Europe, the prevalence varies from 1.2% in Spain to 7.3% in France (Fayyad et al., 2007). In Brazil, a study reported a prevalence of 6.7% (Ponde and Freire, 2007). In Australia, ADHD is regarded as the most common mental disorder among children and adolescents with a prevalence of 7.4% (Australia Institute of Health and Welfare et al., 2018).

In the United States, ADHD results in an extra burden of $143 billion to $266 billion annually (Doshi et al., 2012). In the United Kingdom, the cost associated with the management of ADHD is reported as £670 million (Telford et al., 2013). The higher costs associated with ADHD invite efforts for early diagnosis and better management of the disorder.

Etiology

ADHD has a multifactorial etiology due to its complex nature. Researchers have proposed four factors that are likely to be responsible for the development of ADHD, pregnancy and birth complications, psychosocial adversity, exposure to toxins, and genetics (Willcutt et al., 2010). Although the exact cause is unknown, a large portion of the published literature strongly suggests that ADHD develops due to the interplay between environmental and genetic factors (Faraone and Buitelaar, 2010).

Diagnosis

The use of DSM-V to diagnose ADHD is common in different parts of the world including the United States and Australia. For children, DSM-V requires the presence of at least six symptoms of inattention and/or six symptoms of hyperactivity/impulsivity to be persistent for at least 6 months in a way that is not consistent with development and adversely affects social and academic/occupational functioning (American Psychiatric Association, 2013). For adolescent and adults (aged 17 years and over), at least five symptoms are required. According to DSM-V, patients should have experienced most symptoms before the age of 12, and in at least two different settings (DSM-V, 2013). It must be clear that the symptoms are interfering with social and academic/occupational activities. Moreover, symptoms should not occur during the course of any other psychiatric disorder (e.g., schizophrenia, personality disorder, mood disorder, substance abuse, and anxiety disorder) (DSM-V, 2013).

Clinical Presentation

Inattention, hyperactivity, and impulsivity are the three hallmark symptoms of ADHD. Symptoms of inattention include the inability to pay attention to details, self-focused behavior, increased frequency of careless mistakes at school or workplace, difficulties in following directions, reduced alertness, and difficulties in maintaining focus (Milich et al., 2001). For example, a child may lose concentration while reading or writing or may make careless mistakes and then have to start over with the task. Symptoms of hyperactivity include the inability to sit still, excessive talking, being highly energetic, excessive fidgeting, problems with playing quietly, difficulties in settling down, and roaming around the classroom (Wilens et al., 2009). Symptoms of

impulsivity include interrupting others at school or workplace, intrusion in other's space, trouble waiting for their turns, initiating tasks without listening to instructions, problems with finishing the task, and starting new projects or assignments that catch their interest before finishing previous ones (Wilens et al., 2009). It is important to note that the symptoms are only considered clinically relevant if they start to interrupt daily functioning and occur in multiple settings (American Psychiatric Association, 2013).

The Management of ADHD

Successful management of ADHD requires careful history taking and observation of the child. This process involves both parents and teachers of the child, as a child may behave differently at home and at school, considering the different environments, tasks, and demands. This, however, is conducted in two phases (Burcham and DeMers, 1995). The first phase involves the clinician's and parent's assessment of ADHD symptoms followed by a physical and neurological examination.

The second phase involves a detailed teacher's report of the child's behavior at school. A range of standardized rating scales for clinicians, parents, and teachers are available that can be used in this process (Pappas, 2006). After detailed analyses of all collected information, the clinician makes informed recommendations tailored to the needs of the child. As there is no cure for ADHD, management strategies aim to minimize the symptoms and improve functioning (Abikoff et al., 2004). Management strategies include the use of pharmacotherapy and behavioral therapy. The short-term effectiveness of both strategies has been supported by a number of scientific publications (Connor et al., 2002; Emilsson et al., 2011; Jadad et al., 1999). However, given the limitations of the strategies, the literature supports the use of a multimodal approach to achieve optimal outcomes (Murphy, 2005; Pelham and Gnagy, 1999).

International Guidelines for the Management of ADHD

The National Institute for Health and Care Excellence (NICE), a widely referred to public body in Europe, supports the use of nonpharmacological management as first-line management in children with ADHD (NICE, 2018). If symptoms persist, medication, preferably methylphenidate, is recommended to be commenced in children aged 5 years and above. A course of cognitive behavioral therapy (CBT) is also recommended to be considered for people who have shown some improvements in symptoms after medication use but are still experiencing problems with social skills, peer interactions, self-control, and controlling emotions (NICE, 2018). The NICE recommends the same strategy for adults with the added flexibility that nonpharmacological interventions, such as CBT, may follow environmental modifications if the patient makes an informed decision to not take ADHD medications. In contrast, the American Academy of Pediatrics (AAP) recommends a combination of FDA approved ADHD medications, preferably stimulants, and parent- or teacher-administered behavior therapy as first-line management in patients aged 6–18 years (ADHD, 2011). The National Health and Medical Research Council (NHMRC) in Australia recommends the use of psychosocial strategies and/or behavioral interventions as first-line management. If those strategies fail, pharmacotherapy stimulants are indicated (NHMRC, 2018; Tonge, 2013). Health professionals should refer to the latest version of the above-mentioned guidelines for detailed guidance.

Pharmacological Management

Pharmacological management is one of the well-established approaches to the management of ADHD (Dopheide, 2009). With growing evidence, the use of pharmacotherapy has increased significantly in the past two decades. Specifically, the use of pharmacotherapy has increased by 75% in children and 18% in adults (Dopheide, 2009). An Australian study reported an increase of 101.8% from 2007 to 2015 (Brett et al., 2017). Medications are highly effective in reducing the symptoms of ADHD and improving the academic, occupational, and social functioning of people with ADHD. It is important to note that the use of ADHD medications requires extensive monitoring by health professionals to maximize the effectiveness of the medications and at the same time minimize the side effects which could be experienced.

Psychostimulants

Methylphenidate and dextroamphetamine are the two most commonly used psychostimulants. The use of psychostimulants is supported by numerous clinical trials, which have demonstrated improvements in core symptoms of ADHD (Jensen, 1999; Pelham et al., 2014). Evidence from the literature has also suggested that these agents have greater effectiveness in improving the social, behavioral, and academic functioning in 50%–95% of people with ADHD (Barkley, 2014).

Psychostimulants are the first-line pharmacological agents for the management of ADHD (Banaschewski et al., 2004). These medications are indicated in patients who are hyperactive, impulsive, and inattentive. It has been suggested that psychostimulants are also effective in comorbid disorders associated with ADHD (Jensen et al., 2001; Scheffer et al., 2005). Although psychostimulants may be indicated in patients with any subtype of ADHD, patients with combination-type ADHD are more likely to respond to psychostimulants (Millichap, 2010).

Psychostimulants do not cure ADHD (Advokat, 2009). Their use is limited to symptomatic management (Advokat, 2009). The benefits of psychostimulants usually prevail as long as the therapy is continued, but once the therapy stops, symptoms start to

reappear. Furthermore, the long-term beneficial effects of psychostimulants are still debatable because of limited evidence. The increased frequency of side effects also limits the use of psychostimulants. According to research, more than 50% of children taking psychostimulants experience at least one side-effect (Kos et al., 2006).

Nonstimulants

Nonstimulants are usually the second choice of agents and are only reserved for people who do not respond to or cannot tolerate the side effects of psychostimulants. It has been estimated that approximately 10%–30% of children and adults with ADHD who take medications are on nonstimulants (Banaschewski et al., 2004). Like psychostimulants, nonstimulants provide symptomatic management in patients with ADHD. Currently, three nonstimulant medications (atomoxetine, guanfacine, clonidine) are approved by the Food and Drug Authority (FDA) for use in people with ADHD. Atomoxetine and guanfacine are the two nonstimulants approved by the European Medicines Agency for use in ADHD in the European Union, while atomoxetine is the only Therapeutic Goods Administration approved nonstimulant in Australia.

Atomoxetine

Atomoxetine (ATMX) is the most commonly used nonstimulant in the management of ADHD. It is the first nonstimulant to receive approval for use in ADHD by the FDA in 2002 (Hammerness et al., 2009). ATMX is an effective nonstimulant and is generally well-tolerated. A number of randomized control trials have provided evidence of ATMX efficacy and safety in patients with ADHD (Kelsey et al., 2004; Michelson et al., 2001; Michelson et al., 2003; Weiss et al., 2005).

Studies have reported the significant benefits of atomoxetine in improving the core symptoms of ADHD; inattention, hyperactivity, and impulsivity (Banaschewski et al., 2004; Bushe and Savill, 2014). Atomoxetine is more effective than stimulants in patients with comorbid disorders such as tics, sleeping disorder, and Tourette disorder (Garnock-Jones and Keating, 2009). Atomoxetine has demonstrated improved ADHD outcomes in both children and adults (Upadhyaya et al., 2013). Furthermore, atomoxetine is also effective in patients with substance abuse due to its reduced ability to be misused (Upadhyaya et al., 2013). Some patients respond to ATMX at an early stage, but it may take up to 10 weeks to get the full benefits of ATMX (Lorberg and Prince, 2010). The unique advantage of ATMX is its usefulness in people with ADHD who also have anxiety and mood disorder (Adler et al., 2009).

One limitation of atomoxetine is that it takes approximately 4 weeks of continuous use to reach full effectiveness (Garnock-Jones and Keating, 2009). ATMX may not be the best choice for people with ADHD who only use the medication when needed to gain focus and attention.

Other nonstimulants

Other nonstimulant medications such as clonidine and guanfacine have also shown some effectiveness in symptomatic improvements in patients with ADHD (Arnsten et al., 2007). Other medications such as antidepressants and bupropion, although not approved, have been shown to be moderately effective in improving ADHD symptoms (Biederman and Spencer, 1999).

Clonidine and guanfacine have been shown to be useful in improving the three core symptoms of ADHD. However, these medications are mainly reserved for patients with ADHD who have a history of Tourette syndrome or tics (Rizzo et al., 2013). The use of extended-release guanfacine in the clinical management of ADHD increased after it received FDA approval in 2009. Since FDA approval, alpha 2 agonists are mainly used as stimulant extenders, soporifics (sleep aid), or stimulant enhancers. As stimulant extenders, these agents limit the dose of stimulants and extend the duration of therapeutic action (Palumbo et al., 2008). People with ADHD are prone to sleep disturbances, and if they are on a stimulant, it can further aggravate the problem. Alpha 2 agonists, as soporifics, are well suited for such situations because of their profound sedative effects. As stimulant enhancers, alpha 2 agonists are combined with a stimulant to enhance their effect. This use is mainly occasioned by the presence of a comorbid disorder such as Tourette disorder, oppositional defiant disorder, or aggressive/impulsive behavior.

With the advent of an extended-release formulation of stimulants, the use of alpha 2 agonists in ADHD has been limited to complex and comorbid ADHD (Scahill et al., 2001). Even in those complex cases, the evidence for the efficacy of alpha 2 agonists as monotherapy is sparse, and their use is limited to adjunct therapy along with stimulants (Pliszka, 2007).

Novel Pharmacotherapy for ADHD

In the past few decades, many pharmacological agents have been evaluated for their effects in people with ADHD. Nicotinic agents, such as donepezil, galantamine, metadoxine, are some of the medications that have been studied for the treatment of ADHD (Prince et al., 2015). Though these medications show some efficacy in small-scale trials, their role in the management of ADHD remains investigational (Prince et al., 2015).

Most of the recently approved medications for ADHD and the medications under trial are the modified forms of already established methylphenidate, amphetamine, and guanfacine and other approved salts (De Sousa and Kalra, 2012). For example, in 2017, FDA approved a new medication for ADHD aiming to control all-day symptoms in patients older than 13 years (Wigal et al., 2018). This triple-bead, mixed amphetamine salt (MAS) is a long-acting medication planned for once-daily use (Wigal et al., 2018). This formulation employs a unique triple-bead technology to extend its duration of action. It contains three beads of MAS; an immediate-release bead, a pulse-delayed bead, and an extended-release bead. Similarly, another formulation of guanfacine was approved in 2017 for use in children between the ages of 6 and 17 years (Childress, 2017). This medication offers a time-release

pharmacokinetics compared to the original guanfacine formulation, resulting in a once-daily dose and reduced side effects (Li et al., 2018).

Preliminary data have suggested that metadoxine, a novel nonstimulant therapy, may improve attention in people with ADHD (Manor et al., 2014); however, the medication failed to reach its primary endpoint in a phase III trial in 2017 (Alcobra, 2015). On the other hand, dasotraline, a serotonin-norepinephrine-dopamine reuptake inhibitor, which showed promising results in a phase II trial (Koblan et al., 2015), is now under review by the FDA. Mazindol, a stimulant, also showed positive results in phase II trials, resulting in both a reduction in symptoms and gain in function (Konofal et al., 2014; Wigal et al., 2018).

Certainly, there are gaps in the optimal pharmacotherapy of ADHD that need to be filled by newer medications. Specifically, there is a need for newer compounds with improved efficacy and tolerability to address the limitations of existing medications.

Psychoeducation

Psychoeducation refers to providing didactic psychotherapeutic intervention to enhance patients' and their families' knowledge of mental health illness and its treatment and empowering them to cope with their condition in an optimal manner (Lyman et al., 2014). It is considered an important part of ADHD management. Its use is well supported by several studies (Ferrin et al., 2014, 2016; Montoya et al., 2011) and is recommended by The National Institute of Health and Care Excellence (NICE) guidelines to be used as first-line management of ADHD (NICE, 2018; Taylor et al., 2004). It provides patients and their families/carers with essential and comprehensive information about their disease and its management, as well as possible difficulties they can face at school, workplace, or at home, and the skills to create environments that foster success (Montoya et al., 2011). Psychoeducation can be delivered in many ways such as providing affected people and their families with an expert's view on the disorder, didactic discussions, and providing materials and online resources (Knouse et al., 2008). It is important to note that effectiveness of psychoeducation programs only remains valid as long as the process is active and ongoing (Ferrin and Taylor, 2011). It is also highly important that these programs should not only be limited to the affected people and their families but also to a broader environment including teachers and carers (Ferrin and Taylor, 2011).

Behavioral Management

Behavioral therapy is an important component of nonpharmacological management that can help patients with ADHD manage their symptoms. The characteristic symptoms of ADHD often put a lot of pressure on affected families and teachers. These therapies do not aim to target the symptoms of ADHD but teach affected people and their families the skills needed to control them. Research supports the use of behavioral therapies in the management of ADHD (Emilsson et al., 2011). Behavioral therapies can be further classified as parent-led, classroom-based, and cognitive behavioral therapy.

Parent-Led Behavioral Therapy

Evidence suggests that involving parents in the process of disease management can improve health outcomes (Chronis-Tuscano et al., 2016). Various strategies can be employed in this process. One such strategy could be using a daily report card in which a child is given a plan to improve behavior, and the child is awarded upon the execution of the set plans (Horn et al., 1991). Another strategy could be the use of proactive antecedent actions to prevent misbehavior by deploying rules and providing instructions and awarding the child based on compliance (Fabiano, 2007).

Classroom-Based Behavioral Therapy

Evidence from the literature suggests that effective classroom interventions can enhance the learning of children with ADHD (DuPaul et al., 2011). These interventions if delivered in an actual classroom will result in marked improvements in social skills, anger management, and self-control in children (DuPaul and Stoner, 2014). These interventions are mainly delivered by trained teachers at school. The important consideration for the teachers is to identify and address the unique needs of students and the demands of the environment. Nonverbal support, such as verbal tone, gestures, and facial expression, rewarding children, and time management are some of the examples of preventive strategies that could be implemented in classroom settings to help students becoming academically and behaviorally successful.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a fusion of behavioral therapy and cognitive therapy that identifies and then subsequently negates the person's negative feelings and behavior through discussion and home exercises (Toplak et al., 2008). CBT has been well-established over the years for the management of anxiety, depression, obsessive–compulsive disorder, and other related conditions (Hofmann et al., 2012). A review of studies evaluating CBT has shown mixed results in children with ADHD (Mongia and Hechtman, 2016). However, another review has shown no additional benefits of using CBT in children (Sonuga-Barke et al., 2013), while some have suggested that CBT can help in improving core ADHD symptoms, academic performance, and social adjustments (Froelich et al., 2002; Pelham et al., 1998). In contrast, CBT can be more helpful in adults with ADHD (Safren et al., 2005). CBT can help adults to deal with their problems associated with time management, organizing short-term and long-term plans, stress management, and emotional self-regulation (Solanto et al., 2008).

Prevention

To date, medical science has not been able to find ways to prevent ADHD. The major emphasis in clinical practice is on managing symptoms and maximizing the functional behavior of people with ADHD. Evidence suggests that early interventions may alter the trajectory of ADHD and thus prevent the long-term impact of the disorder (Halperin et al., 2012). Research has demonstrated that a number of factors increase the likelihood of ADHD, and therefore strategies to minimize these factors can help to decrease the likelihood of ADHD (Halperin et al., 2012).

Antenatal and Postnatal Care

Poor diet, alcohol use, drug addiction, and smoking during pregnancy increase the likelihood of ADHD in a child (Hausknecht et al., 2005; Kim and Chang, 2011; Thapar et al., 2013). A mother's exposure to lead during pregnancy may put her child at risk of developing ADHD (Rodriguez and Bohlin, 2005). Premature birth and low birth weight have also been associated with ADHD (Mick et al., 2002). Moreover, a study found breastfeeding newborns for at least 3 months could have a protective effect from developing ADHD later in life (Mimouni-Bloch et al., 2013).

Balanced Diet

Although not universally accepted, some researchers believe that processed sugar and carbohydrates play an important role in the development of ADHD (Millichap and Yee, 2012). Artificial colors, flavoring agents, and preservatives should be avoided or minimized to improve a child's behavior. These ingredients are believed to contribute to hyperactivity in children by producing an adrenalin rush (Breakey, 1997). Excessive consumption of food additives, sugar, and salt may negatively affect a child's behavior (Tomlinson et al., 2009). It is important to use a balanced approach while deciding on a balanced diet.

Preschool Strategies

Effective behavioral modifications in preschool children aged 3–6 years may help in reducing the likelihood of ADHD symptoms (Young and Myanthi Amarasinghe, 2010). These strategies focus on the start and stop techniques such as encouraging children to participate in activities and stopping them from running around and being disruptive. These techniques can be easily taught and are applicable to different school settings. They can positively influence ADHD-related symptoms while not harming children without such symptoms (Egger and Angold, 2006).

Parenting Quality

Although the quality of parenting is not the primary cause of ADHD, it is one of the important risk factors that may influence the severity and/or impairment of the disorder (Halperin et al., 2012). A randomized control trial showed that parenting quality plays an important role in improving ADHD-related symptoms in school-aged children (Thompson et al., 2009). This evidence suggests that the quality of parenting can have a profound effect on ADHD. It is also suggested that improving parenting quality may help to prevent the worsening of ADHD-related symptoms (Modesto-Lowe et al., 2008). A study suggested that parents' higher involvement with a child, consistent discipline, and supervision can play a role in the child's expression of symptoms (Ellis and Nigg, 2009). The current evidence therefore suggests the need to target parents to optimize the quality of their parenting, which support the focus of intervention programs being on parents, as the key strategy to improve a child's behavior.

Role of Pharmacists in the Management of ADHD

The role of general physicians, pediatricians, and psychiatrists in the identification, assessment, and management of ADHD has been well-defined in the literature; however, there is a huge gap in the literature about the role of pharmacists in the management of ADHD. Given that approximately 129 million people are affected by ADHD worldwide, and medications remain a major source of treatment, pharmacists are well-positioned to play an important role in reducing the burden associated with ADHD and deliver effective pharmaceutical services to the patients and their parents or carers.

Evidence for the Role of the Pharmacist

The potential contributions of pharmacists in the management of ADHD have not been well explored. Although previous researchers have highlighted the roles pharmacists can play to increase quality use of medicines (Kehoe, 2001; Levin, 1995), no attempt has been made to examine the effectiveness of these roles on a larger scale. An extensive search of the literature yielded only a couple of pilot/small-scale studies that established the role of pharmacists (Reutzel et al., 2008; Tobaiqy et al., 2010). There is a need for further studies to validate the existing findings and strengthen the body of evidence.

Educational Programs for School Personnel

Ruetzel et al. demonstrated that pharmacists can effectively deliver educational programs to school staff in collaboration with a mental health therapist to enhance their understanding of ADHD and medication use (Ruetzel, 2008). The school environment can be challenging for children with ADHD. It was demonstrated that providing education to teachers and other school personnel about

ADHD can improve their knowledge of the medications used in ADHD and give them the confidence to recognize the symptoms of ADHD. Ruetzel et al. stated that increased knowledge and confidence levels in school personnel should reduce the occurrence of medication errors and improve the overall effectiveness and safety of the therapy (Ruetzel, 2008). Moreover, it would enable them to be aware of important issues relating to managing children with ADHD at school.

Pharmacist-Led ADR Monitoring

Tobaiqy et al. reported that community pharmacists can be very effective in monitoring adverse drug reactions (ADRs) in people taking medications for ADHD (Tobaiqy et al., 2010). The use of long-term ADHD medications may result in ADRs; however, in most cases, these ADRs do not pose a serious threat to a patient. Nonetheless, it is important to continue monitoring for ADRs throughout the course of treatment. Pharmacists with their comprehensive knowledge of medications can play a crucial role by detecting and subsequently reporting ADRs to their respective national ADR reporting authority.

Expanding the Role of Pharmacists

The role of pharmacists in the identification, support, and management of ADHD has not been recognized universally. Limited effort has been made in the past to examine the role of pharmacists in managing patients with ADHD. Therefore, the published evidence that supports the role of pharmacists in ADHD is presently very limited. However, the role of pharmacists has evolved considerably in other mental health diseases, such as depression, in the last decade (Rubio-Valera et al., 2014). Pharmacists with their unique set of skills and knowledge are well placed to expand these roles to patients with ADHD. This section will discuss a range of services that pharmacist could provide to optimize ADHD management.

Medication Optimization

The role of pharmacists is well established in optimizing medication use in patients with chronic diseases such as hypertension, diabetes, asthma, arthritis, and depression. Given the increase in the use of medications in people with ADHD, the opportunity exists for pharmacists to contribute to the management of ADHD by ensuring optimum use of medications. Pharmacists can promote medication optimization through patient engagement and risk communication, medication reviews, health-care interface pharmacist services, and improving medication adherence.

Patient engagement and risk communication

In recent years, the health-care model has shifted from disease-focused to patient-centered care. The new model involves consideration of patient's values, goals, and concerns about the effectiveness and risk of therapy. This model encourages health professionals to make clinical decisions in consultation with a patient. Research has demonstrated the positive effects of shared decision making (SDM) between parents/carers of children with ADHD and pediatricians (Brinkman et al., 2013). There remains an opportunity to replicate a similar model in people with ADHD with their pharmacist. Pharmacists should enhance their understanding of this approach to engage patients, build relationships, and play their part in promoting the optimum use of medications.

Another advantage of patient engagement is risk communication. Risk communication is an important process through which health professionals use a scientific approach to communicate with patients about the benefits and harms of the medication and enable them to make an informed decision about their treatment. This is a very important concept in the management of ADHD as it is often seen that parents/carers do not start or adhere to their child's medication regimen due to the fear of side effects or lack of effectiveness. Therefore, it is essential for pharmacists to embrace effective patient communication and positively influence patient's decision making about the use of medications.

Regular medication reviews

People receiving ADHD medications, such as stimulants, are required to attend regular medication reviews to ensure the safety and effectiveness of their medications (Swanson et al., 1993). Furthermore, stimulant medications are associated with drug misuse (Volkow and Swanson, 2003). Drug diversion is another issue that is gaining the attention of many researchers (Wilens et al., 2008). Adolescents with ADHD are more susceptible to being involved in drug diversion (Wilens et al., 2006). Drug diversion has been defined as a transfer of prescribed medication from one person (whom it was prescribed for) to another person (whom it was not prescribed for) for illicit use (Cooper et al., 1992). Pharmacist-led medication reviews can be very helpful in examining these issues. As medication experts, pharmacists are well aware of such possibilities and can use a holistic approach in reviewing ADHD medications.

Health-care interface pharmacy services

The diagnosis of ADHD is usually carried out by a psychiatrist, pediatrician, or health professionals with specialized training in ADHD or relevant psychiatric conditions. The specialist then takes the decision to put the person with ADHD on medication. Once the therapy starts, the information/plan about medication use is passed on to a primary care provider who is responsible to ensure the effectiveness and safety of the medication. Studies have shown that the chances of medication errors increase as a patient moves between primary and secondary care (Kvamme et al., 2001; Preston et al., 1999). For example, general practitioners may not receive clear explanation about the future course of medication use so continue to prescribe medication, which may not

be effective. Pharmacists can team up with general practitioners (GPs) and specialists to facilitate medication management across the interface.

Furthermore, other professionals, such as psychologists, behavioral therapists, social workers, teachers, school nurses, and educational therapists, are also involved in caring for children with ADHD. Hence, a leadership opportunity exists for pharmacists to work at multiple interfaces and ensure that good communication is maintained, and all efforts are aligned toward quality use of medications and improved health outcomes of the person with ADHD.

Improving medication adherence

The first step in understanding the issue of medication adherence is to assess patient or carer understanding about ADHD and its treatment options. Pharmacists are required to communicate effectively to determine what a patient or carer thinks about a medication or what they expect from a medication. Most patients/carers may not realize that medications do not cure ADHD rather they help improve the academic, social, and behavioral outcomes of the person with ADHD. Similarly, there may be a lack of awareness among patients and/or carers about the expected side effects of medications. Pharmacists are encouraged to take initiatives to speak to patients/cares about medication-related issues and establish rapport with patients/carers to ensure that they express their concerns about the use of a medication. This will help to identify knowledge gaps and patients'/cares' beliefs toward ADHD and its medication.

The second step is to assess adherence and identify the factors influencing medication adherence. This is an important step, and pharmacists need to be aware of the methodological and practical issues associated with the measurement of adherence. It has been suggested to measure medication adherence and assess factors influencing medication adherence at three phases, namely, initiation, implementation, and discontinuation (Khan et al., 2018; Vrijens et al., 2012). It is important to first look at the factors that influence patients' or their parent's/carer's decision to start medication. Second, it is important to examine if they continue to take medication as prescribed on a daily basis, and finally, assess the reasons for early discontinuation of medication. It is imperative that a distinction is made between the three phases as the factors influencing one phase may differ from the other phases. Moreover, consideration should be given to the person with ADHD to see if they are children, adolescents, or adults, as factors influencing medication adherence in one group may differ from the other groups. In the case of children and to some extent, adolescents, the role of parents in decision making about medication use is important. Hence, it is also important to examine the parental factors that may affect adherence to medications.

The last step is to deliver tailored interventions to promote adherence at the appropriate phase of adherence. Pharmacists can play an active role in this step as their involvement would increase the likelihood of positive outcomes (Dopheide, 2009). Pharmacist-led interventions have successfully improved medication adherence in patients with other disease states, for example, in psychiatric conditions, such as depression (Rubio-Valera et al., 2014).

Pharmacist-Led ADHD Screening Services

Early detection of ADHD-related symptoms is important to start early management and therefore reducing the long-term impact of the disorder (Sonuga-Barke et al., 2006). Pharmacists, as the first point of contact for parents and carers of children, can provide ADHD screening services in community settings. There is considerable evidence of pharmacists providing cost-effective screening services in other psychiatric conditions such as depression (Rubio-Valera et al., 2014). There is therefore a great opportunity for pharmacists and researchers to take this initiative to build an evidence-based role for pharmacists in this area. It is possible that not all pharmacists will feel confident in providing such services. Therefore, to establish their role in ADHD screening, pharmacists are required to have a thorough understanding of ADHD screening procedures and available tools. Specialized mental health education or training in assessment and screening of ADHD can help pharmacists reach their true potential in providing such services. Pharmacy practice regulatory authorities may consider regulating such services by allowing pharmacists to deliver the services only after successful completion of relevant training.

Given the shortages of medical doctors and other health-care facilities in rural areas, there is an opportunity for pharmacists to take a lead role in increasing awareness of ADHD among rural communities, particularly in developed countries, and provide screening services to children or adults who are suspected of having ADHD. Rural pharmacists can influence people (Nissen and Tett, 2005). Previous research has established the role of pharmacists in providing mental health counseling to rural communities (Scott et al., 2016). It is therefore a timely opportunity for appropriately trained and accredited pharmacists to expand their role in public health by delivering ADHD screening services in rural communities.

Reducing Stigma

Studies suggest that pharmacists can be very effective in providing education to people about mental health in a proactive and individualized manner (Crump et al., 2011; Finley et al., 2003). Pharmacists-led ADHD awareness campaigns may help to spread the correct information about the condition and the role of medicines taking. The campaigns could target people with ADHD, parents/carers, teachers, health professionals, and the community in general. Effective strategies need to be designed to customize information as per the needs of each group being targeted. For example, parents can be provided with comprehensive information about ADHD and its treatment options.

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Anxiety Disorders

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Learning Objectives

- Describe the prevalence, epidemiology, and etiology of anxiety disorders and list the four most common conditions.
- Explain the pharmacological and nonpharmacological management options for GAD, panic disorder, PTSD, OCD, and describe which treatment option would be used and in what situations.
- List the most common side effects and interactions associated with SSRIs, SNRIs, pregabalin, and benzodiazepines, and describe how to manage these.
- Describe the role of the pharmacist in managing anxiety disorders and give examples where pharmacists can contribute to the pharmaceutical care of anxiety disorders.

Take Home Messages

- Anxiety disorders are the most prevalent psychiatric disorder.
- There are different types of disorders, which fall under the wider category of anxiety disorders, each with their own preferred treatment options.
- Treatment should be tailored to the individual—taking account of his or her comorbidities, treatment preferences, adverse effects, and prior experience with pharmacotherapy.
- SSRIs and SNRIs remain the mainstay of anxiety treatment, though efficacy varies depending on the exact anxiety condition being managed.
- Benzodiazepines should be used at the lowest effective dose for the shortest period of time (maximum 4 weeks) and should only be used while waiting for medium- to long-term treatments to take effect.
- The pharmacist plays a key role in anxiety management as individuals may first come to the attention of health services through primary care, and long-term management responsibility will mainly reside in the community, making the pharmacist well placed to the treatment of anxiety.
- Opportunities to optimize medicines use in anxiety include side effect management, managing interactions, and benzodiazepine withdrawals.

Introduction to Condition

Anxiety is common and can occur as an isolated, short-lived, and self-limiting symptom. From an evolutionary perspective, anxiety is known to occur in the context of an adaptive response to environmental threats and prepare the person for the "fight or flight" response (Cannon, 1915). However, when persistent or disabling, it can lead to impaired functioning and be part of an umbrella of clinical disorders termed anxiety disorders. Anxiety disorders are the most prevalent of psychiatric disorders and often show comorbidity with other anxiety or depressive disorders (Kessler et al., 2005b; Thibaut, 2017).

There are numerous anxiety disorders with each having its own set of etiology, epidemiology, physiology, and prognosis. In this chapter, there will be an exploration of overlaps between anxiety disorders as a group and then selective focus on certain subtypes. It is beyond the scope of this chapter to explore the various anxiety disorders in significant detail. This chapter will focus on generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) (see **Table 1** for key features). While there is much overlap in symptomatology between various anxiety disorders, at the core of these disorders are a set of physical, behavioral, and cognitive attributes that show variation between them and are therefore classified as discrete conditions. There are numerous treatment options available, which can involve monotherapy or combinations of pharmacotherapy, psychotherapy, and social interventions.

Brief History of Anxiety Disorders

Though the description of anxiety disorders is often thought to be a recent development (since the 19th century), historical records suggest that they have been recognized since antiquity (Crocq, 2015). Situations such as going to battle/facing one's own mortality, a loved one dying, public speaking and romantic courtship, among others, were recognized as possible triggers for states of anxiety and potentially influenced by the Greek or Roman Gods.

Consistent with the theory of body humors by Hippocrates, anxiety was thought to arise from an imbalance in humor levels. This theory persisted till the Renaissance; subsequently, till roughly the 19th century, anxiety was grouped together with depression as contributing to states of melancholy and not recognized as a condition of its own. However, since then, the classification of anxiety has moved toward a medical model and recognition as a separate disorder (Stone, 2009). Medically, there was conceptualization of anxiety being driven by weaknesses of the nervous system, which was termed *neurosis* by the Scottish physician William Cullen. However, while neuroses contained a wide number of possible neurological, psychiatric, psychological, and other disorders, it also captured situations when behaviors were not socially acceptable (Bienvenu et al., 2010). The neurologist Jean Marie Charcot and his

Table 1 Summary of key features in various anxiety disorders

Disorder	*Key features*
Generalized anxiety disorder (GAD)	• Excessive, difficult to control anxiety and worry (apprehensive expectation) about multiple events or activities (e.g., school/work difficulties) • Accompanied by symptoms such as restlessness/feeling on edge or muscle tension
Panic disorder	• Recurrent unexpected panic attacks, in the absence of triggers • Persistent concern about additional panic attacks and/or maladaptive change in behavior related to the attacks
Posttraumatic stress disorder (PTSD)	• Exposure to actual or threatened death, serious injury, or sexual violation • Intrusion symptoms (e.g., distressing memories or dreams, flashbacks, intense distress) and avoidance of stimuli associated with the event • Negative alterations in cognitions and mood (e.g., negative beliefs and emotions, detachment), as well as marked alterations in arousal and reactivity (e.g., irritable behavior, hypervigilance)
Obsessive–compulsive disorder (OCD)	• Obsessions: recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted and that cause marked anxiety or distress • Compulsions: repetitive behaviors (e.g., hand washing) or mental acts (e.g., counting) that the individual feels driven to perform to reduce the anxiety generated by the obsessions

Source: Adapted from (American Psychiatric Association, 2013; Katzman et al., 2014b)

protégé, Sigmund Freud (who started his career as a neurologist) encountered several cases of what appeared to be medically driven neurosis but were able to clarify possible psychological contributors for states such as *anxiety neurosis*, *hysteria,* and *neurasthenia*, and applied psychoanalysis as a modality to understand and treat these conditions (Bogousslavsky and Dieguez, 2014; Perez-Rincon, 2011).

Following World War I, there were several documented cases of "shell-shock," a precursor to what is now known as PTSD. After World War II, psychopharmacology and biological treatments for anxiety became much more developed including the emergence of benzodiazepines and tricyclic antidepressants. Later in the 20th century, discussions around "state" versus "trait" representations of anxiety emerged (Cattell and Scheier, 1960) but it was not until the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) that there was delineation of the various types of anxiety disorders under an anxiety disorders chapter. Therefore, while concepts of anxiety were historically in the domains of astrology, theology, and philosophy, in more modern times, it has moved toward being recognized as discrete disorders under psychiatry and psychology (Berrios, 1996).

Condition Information

Definition/Classification of Anxiety Disorder and Diagnosis

Transient anxiety is recognized as a normal symptom or an experience that can occur in the context of a response to a stimulus. However, when it is disruptive to normal functioning, excessive or persistent, it is regarded as a disorder. For example, it can be secondary to a medical disorder (e.g., in association with hyperthyroidism or pheochromocytoma) or be part of discrete clinical psychiatric disorders e.g., GAD, panic disorder, or specific phobias. Physical symptoms associated with anxiety disorders include sweating, dizziness, shortness of breath, muscle tension, or a racing heart.

While anxiety disorders demonstrate core features involving excessive levels of anxiety and fear, they have associated cognitive features, which can contribute to behavioral disturbances (American Psychiatric Association, 2013). Cognitive symptoms include a sense of impending doom or a fear of dying/embarrassment/humiliation. It is thought that anxiety corresponds to future threat and is associated with vigilance and preparing for a threat; in contrast, fear relates to a real or perceived threat and is associated with autonomic arousal. However, there is often overlap between anxiety and fear within the rubric of anxiety disorders and they are differentiated by the context where symptoms arise, associated cognitions, and behaviors such as avoidance.

Looking across the lifespan, the anxiety disorders as described by DSM-V include specific phobias, selective mutism, separation anxiety disorder, social anxiety disorder, GAD, panic disorder, and agoraphobia. Additional anxiety disorders include substance-induced or medication-induced, other specified and unspecified anxiety disorders and due to other medical conditions. PTSD and OCD used to be historically included under the anxiety disorders chapter but since DSM-V, these have been moved to adjacent chapters (obsessive-compulsive and related disorders and trauma- and stressor-related disorders) (American Psychiatric Association, 2013).

Usually, the diagnosis of an anxiety disorder is based on clinical criteria such as the DSM or the International Statistical Classification of Diseases and Related Health Problems (ICD) (American Psychiatric Association, 2013; World Health Organization, 1992). Prior to diagnosis, it is necessary to assess and consider other differential diagnoses such as mental health, medical, physiological, or medication/substance-induced conditions. Anxiety disorders are frequently underdiagnosed or diagnosed as another mental health disorder such as depression (Ormel et al., 1991; Wittchen et al., 2002). There are several tools that can be used to help diagnosis and are relatively straight forward to use and can be completed quickly. Such screening tools for anxiety

disorders include the Generalized Anxiety Disorder 7, which is a 7-item rating scale (GAD-7) (Spitzer et al., 2006), hospital and anxiety depression scale (HADS) (Zigmond and Snaith, 1983), PHQ-4 (Kroenke et al., 2009), Beck's Anxiety Inventory (BAI) (Beck and Steer, 1993), as well as ones for anxiety states (Rose and Devine, 2014). A recent systematic review done by Herr and colleagues reviewed the use of tools to help in the diagnosis of anxiety. They found that the GAD-7 and the PHQ-4 screening tool were most effective (Herr et al., 2014). These screening tools are used for case-finding purposes and not for diagnosis. As such, these can be used by pharmacists when screening for "at-risk" patients, who can then be referred for further work-up and diagnosis (see Role of the Pharmacist section for further details). Although these screening instruments are useful and may be used as part of the initial diagnostic evaluation, a criterion-based diagnosis should be established through further evaluation by a primary care physician or by a mental health professional to whom the patient is referred. Such confirmation will also help rule out psychiatric disorders with related symptoms (e.g., PTSD, depression) and medical causes of symptoms suggestive of anxiety (Kroenke et al., 2007).

Epidemiology

As a group of psychiatric disorders, anxiety disorders are the most prevalent (Narrow et al., 2002) with lifetime prevalence estimates as high as 31% (Kessler et al., 2005a, 2007). Prevalence rates appear higher in high-income relative to low-income countries (Lewis-Fernandez et al., 2010). They are underdiagnosed in primary care (Sartorius et al., 1996; Vermani et al., 2011) and other settings and are overall undertreated (Martin-Merino et al., 2010; Weisberg et al., 2007; Wittchen et al., 2002). There are a variety of reasons for this including people feeling uncomfortable discussing their emotions or general practitioners not routinely screening for these or a lack of training in diagnosis.

There is a gender imbalance with women demonstrating higher rates of anxiety disorder across all age bands, with lifetime rates approximately 1.5–2 times higher than men, and being generally more disabling (McLean et al., 2011). There are often higher rates of quality of life impairments, disability, health-care utilization, and wider impacts to society, for example, through lost productivity (Barrera and Norton, 2009; Wittchen, 2002; Wittchen et al., 2011). With the move of PTSD and OCD from the anxiety disorders chapter in DSM-V to their own separate chapters, it is possible that prevalence estimates of anxiety disorders will fall (American Psychiatric Association, 2013).

Anxiety disorders are often associated with comorbidities such as other anxiety disorders and depression (Wittchen et al., 2000). Moreover, alcohol and substance use and gambling are overrepresented in populations with anxiety disorder (el-Guebaly et al., 2006; Petry et al., 2005). Although anxiety disorders are associated with increased risk of suicide and self-harm attempts, when comorbid with other mental health disorders such as depression, these risks are further enhanced by odds ratios between 1.5 and 4 (Sareen et al., 2005).

Etiology

The etiology of anxiety disorders is complex and often multifactorial involving biological, psychological, social, environmental, cultural, cognitive, and behavioral mechanisms (Gross and Hen, 2004; Humble, 1987; Lau et al., 2007). It can also be helpful to consider factors that contribute to stress causation versus stress continuation (Uliaszek et al., 2012). Possible contributors to anxiety include exposure to threat and can be an adaptive response and there have been theories suggesting an evolutionary basis to fear/anxiety states but classical Pavlovian conditioning as a longer term maintenance factor for anxiety disorder (Gross and Canteras, 2012; LeDoux, 2000; Mineka, 2002). Fear and threat neural system circuits have also been suggested to contribute (LeDoux and Pine, 2016).

Endogenous production of catecholamines such as adrenaline prepares the individual for the fight or flight response in the context of fear but can be chronically overactivated in an anxiety disorder. The sympathetic nervous system contributes to physical symptoms of anxiety e.g., sweating, tachycardia, hypertension, dyspnea, nausea, and light-headedness.

Exogenous substances including nonprescribed agents such as caffeine and stimulants (e.g., cocaine, amphetamine) as well as prescribed methyldopa, theophylline, salbutamol, and corticosteroids can contribute to states of anxiety. Additionally, when someone develops dependence to substances such as benzodiazepines or alcohol, when withdrawing from the substance, this is likely to precipitate anxiety symptoms and autonomic arousal. Neurodegenerative, endocrine, and other physical disorders can also contribute to secondary anxiety states e.g., dementia, asthma, cardiac failure, and epilepsy (Craske et al., 2017).

Place of Pharmacotherapy in Context of Treatment Options

Treatment options for anxiety and related disorders include psychological and pharmacological treatments. The choice of treatment depends on factors such as patient preference and motivation, ability of the patient to engage in treatment, severity of illness, clinician skills and experience, availability of psychological treatments, patient's prior response to treatment, and the presence of comorbid medical or psychiatric disorders (Katzman et al., 2014a).

Psychotherapy and pharmacotherapy generally demonstrate about equivalent efficacy for the treatment of most anxiety and related disorders (Bandelow et al., 2007; Roshanaei-Moghaddam et al., 2011). The choice between psychotherapy and pharmacotherapy as first-line treatment can depend on the severity of anxiety, patient preference (e.g., beliefs associated with the treatments, medication side effects, and the time needed for psychotherapy), and treatment availability. Those with milder symptoms that do

Table 2 Summary of pharmacotherapy options for anxiety disorders

	First-line drug treatment	*Second-line drug treatments*	*Other (PRN) treatment*
Generalized Anxiety Disorder	SSRIs or SNRIs • May initially exacerbate symptoms • A lower starting dose often required Pregabalin • Not approved for GAD in the US	Some TCAs • Imipramine, clomipramine Buspirone • Delayed onset of action Second-generation antipsychotics	Benzodiazepines • Normally for short-term use only (maximum 2–4 weeks) • Usually as an adjunct to antidepressant therapy
Panic Disorder	SSRIs or SNRIs • Therapeutic effect can be delayed • Patients can experience an initial exacerbation of panic symptoms	Some TCAs • Imipramine, clomipramine	Benzodiazepines • Panic symptoms can return quickly if the drug is withdrawn • NICE does not recommend benzodiazepines
Posttraumatic Stress Disorder	Drug treatment should not be used as a routine first-line treatment • SSRIs may be recommended where there is minimal/incomplete response to psychological therapy		α-Blockers may be useful for trauma-content nightmares Benzodiazepines not usually appropriate
Obsessive-Compulsive Disorder	SSRIs • Citalopram is not approved or authorized for this indication • Doses licensed for OCD are higher than those for depression	Clomipramine	Benzodiazepines not usually appropriate

not interfere significantly with functioning may be managed with psychotherapy based on cognitive behavioral therapy (CBT). However, when patients do not benefit from CBT or have a limited response, the addition of pharmacotherapy may be advisable. See Table 2 for a summary.

Benzodiazepines

All guidelines and consensus states recommend that benzodiazepines should be used only to treat anxiety that is severe, disabling, or subjecting the individual to extreme distress. Due to their potential to cause physical dependence, sedation, cognitive impairment, and withdrawal symptoms, benzodiazepines should be used at the lowest effective dose for the shortest period of time (maximum 4 weeks) while medium- to long-term treatment strategies are implemented. They should also be used with caution in patients with a history of substance misuse. However, a small number of patients with severely disabling anxiety may benefit from long-term treatment with a benzodiazepine; this should be done in consultation with a specialist.

GAD

Benzodiazepines have been shown to be beneficial in the treatment of GAD as they work quickly and generally lead to a reduction of emotional and somatic symptoms within minutes to hours, depending on the specific medication (Davidson, 2004; Offidani et al., 2013). While benzodiazepines should be used with caution, their use need not be entirely avoided. They may be used for acute, maintenance, or long-term treatment of GAD, either as monotherapy or, more commonly, as an adjunct to antidepressant treatment. They are most commonly used for acute management of anxiety and worry during the period before serotonergic reuptake inhibitors (SSRIs/SNRIs—described later) take effect. They can counteract the initial activation caused by serotonergic reuptake inhibitors. Once the patient responds to the SSRI/SNRI, the benzodiazepine can be tapered off gradually.

Panic Disorder

Benzodiazepines are the least preferred monotherapy for patients with panic disorder and co-occurring depression or substance use disorder. They may be useful adjunctively with antidepressants to treat residual anxiety symptoms, or in patients with very distressing or impairing symptoms in whom rapid symptom control is critical (American Psychiatric Association, 2009).

PTSD

Although the efficacy of benzodiazepines in treating the core symptoms of PTSD has not been established, they are frequently used to treat symptoms of anxiety and hyperarousal. However, clinical observations include the possibility of dependence (there is high prevalence of comorbid substance abuse in patients with PTSD), increased incidence of PTSD after early treatment with benzodiazepines, or worsening of PTSD symptoms after withdrawal of these medications. Thus, benzodiazepines are not recommended as monotherapy in PTSD; however, they can be useful as an adjunct to other long-term treatments (see below) (American Psychiatric Association, 2004).

OCD

There is limited evidence for efficacy of benzodiazepines in the treatment of OCD; therefore, they cannot be recommended for monotherapy (American Psychiatric Association, 2007). They may be used cautiously for short periods to counteract the early activation effects of SSRIs (National Institute for Health and Care Excellence, 2005a).

Serotonergic Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have "broad spectrum" efficacy in both short- and long-term treatment of anxiety, and are generally well tolerated. These are widely considered the first-line pharmacological approach for patients with anxiety disorders and OCD. SSRIs have potentially troublesome adverse effects, including initial increased nervousness, insomnia, nausea, and sexual dysfunction (Gartlehner et al., 2011; Serretti and Chiesa, 2009; Sinclair et al., 2009). There may be an increased risk of gastrointestinal bleeding; therefore, gastroprotective drugs may be appropriate for some patients e.g., those taking nonsteroidal anti-inflammatory drugs (Laporte et al., 2017; Paton and Ferrier, 2005). SSRIs may also cause activation—a distinct constellation of behavioral side effects including agitation, restlessness, anxiety symptoms, insomnia, or akathisia. It may occur any time during the treatment, but is most common during the first few weeks (Warden et al., 2010). When stopped abruptly, and even when tapered slowly, SSRIs can produce a discontinuation syndrome characterized by dizziness, insomnia, and flu-like symptoms (Baldwin et al., 2007); this appears more likely with shorter half-life SSRIS, e.g., paroxetine (Tint et al., 2008).

Serotonin-norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have proven efficacy for the short- and long-term treatment of GAD (Baldwin et al., 2011), and placebo-controlled trials have shown that venlafaxine is efficacious in the acute treatment and prevention of relapse in panic disorder (see Panic Disorder section) (Batelaan et al., 2012). Although the tolerability profiles of SSRIs and SNRIs in patients with anxiety disorders are not established fully, systematic reviews of studies in depressed patients suggest that duloxetine and venlafaxine may be less well tolerated than the SSRIs (Cipriani et al., 2012; Schueler et al., 2011). The most common side effects include nausea, constipation, dizziness, insomnia, sedation, and changes in sexual function. Venlafaxine may also cause elevated blood pressure and increased risk for gastrointestinal bleeding. Both agents have been associated with discontinuation symptoms after withdrawal due their short half-lives (Baldwin et al., 2007).

GAD

SSRIs and SNRIs are generally considered to be first-line pharmacotherapies for GAD, with response rates in the range of 30%–50% (Reinhold and Rickels, 2015). There is a lack of data available directly comparing the different serotonergic reuptake inhibitors (including SSRIs vs SNRIs) (Bielski et al., 2005; Hidalgo et al., 2007). Trials have generally shown that all serotonergic reuptake inhibitors have similar degrees of efficacy so the choice of agent should be customized to the patient based on patient treatment history/preference or response, side effect profile, drug interactions (see Drug Interactions section), and/or cost.

SSRIS should initially be prescribed at half the normal starting dose for the treatment of depression, and the dose titrated upward into the normal antidepressant dose range as tolerated—though doses higher than typical antidepressant doses may be required for complete response. These serotonergic drugs are often activating (with increased anxiety, agitation, and sleep problems) and difficult to tolerate in early dosing. To avoid overstimulation and insomnia, doses may be given in the morning or at midday, except in patients reporting daytime sedation (Bandelow et al., 2008).

Time to onset of clinically meaningful action varies by patient, but response is usually seen within 6 weeks (Ballenger, 2004). The initial therapeutic dose should be continued for 4–6 weeks, and increased in 1- to 2-week increments until sufficient improvement is seen or the maximum recommended/highest tolerated doses is reached (Bystritsky, 2018). However, if there is no response (less than 25% reduction in symptoms from baseline), the patient may be switched to a different class of treatment (Davidson et al., 2010).

Panic Disorder

SSRIs are considered the first-line pharmacotherapy for panic disorder. SSRIs reduce the frequency of panic attacks, severity of anticipatory anxiety, and degree of phobic avoidance. There is no evidence of superior efficacy for some SSRIs over others (American Psychiatric Association, 2009); choice of agent is guided by the side effect profile, propensity for medication interactions, half-life, and/or availability of generic preparations.

As patients with panic disorder are unusually sensitive to overstimulating effects with antidepressants (Cowley et al., 1997), treatment should be started at low doses and gradually titrated 3–7 days after initiation and up to a therapeutic dose over 2–6 weeks. The dose can be increased if no clinical improvement is seen; however, increases should occur no faster than at 1- to 2-week intervals to minimize the risk of side effects. Higher doses of all drugs may be effective when standard doses have failed (National Institute for Health and Care Excellence, 2011).

Double-blind, placebo-controlled trials have found extended-release venlafaxine to be an efficacious treatment for patients with panic disorder (Bradwejn et al., 2005; Pollack et al., 2007). Like SSRIs, venlafaxine should be started at low doses (approximately half the starting dose given in depression). The immediate-release version of venlafaxine should not be used for panic disorder as it has a greater side effect burden and patient with panic disorder can have difficulty tolerating internal bodily sensations and somatic side effects (Bystritsky, 2018).

PTSD

Drug treatments for PTSD should not be used as a routine first-line treatment for adults in preference to trauma-focused psychological therapy. Where pharmacological treatment is required, such as when the individual has shown minimal or incomplete response to psychological therapy, SSRIs may be recommended as first-line pharmacotherapy for PTSD as they ameliorate all three PTSD symptom clusters (i.e., reexperiencing, avoidance/numbing, and hyperarousal). SSRIs are typically started at the low end of their therapeutic range and titrated up gradually until response. Although there is no clear evidence of a dose–response relationship for SSRIs in PTSD, it is not uncommon to push the dose to the very high end of the therapeutic range, as tolerated by the patient. A therapeutic trial of an SSRI should be a minimum of 6–8 weeks before concluding that a medication has failed (Stein, 2017). Paroxetine is the only drug that is approved for PTSD in the UK (National Institute for Health and Care Excellence, 2005b), while sertraline and paroxetine are approved for PTSD by the FDA (Jeffreys, 2017). No SSRIs are specifically approved for the treatment of PTSD in Australia and New Zealand (National Health Committee, 1998).

OCD

SSRIs are recommended as first-line treatment for OCD as there is greater support from randomized trials for SSRIs than for venlafaxine, and they have a superior side effect profile compared to TCAs (American Psychiatric Association, 2007). All SSRIs except citalopram have approval/authorization for use in OCD in the United States or United Kingdom (American Psychiatric Association, 2007; National Institute for Health and Care Excellence, 2005a). Neither venlafaxine nor duloxetine has been FDA-approved specifically for the treatment of OCD.

Most trials of serotonergic antidepressants in OCD suggest that higher doses are associated with greater response rates and/or greater mean rates of improvement, so the doses licensed in the treatment of OCD are higher than those licensed for the treatment of depression (Simpson, 2017). However, lower (standard antidepressant) doses may be effective, particularly for maintenance treatment. The initial response is usually slower to emerge than in depression (it can be up to 10–12 weeks), and guidelines suggest that patients who respond to an adequate trial of a serotonergic antidepressant should stay on that medication for at least 1 to 2 years (Simpson, 2017; Taylor et al., 2012).

Tricyclic Antidepressants

The efficacy of tricyclic antidepressants (TCAs) is predominantly related to the reuptake inhibition of serotonin. Imipramine and clomipramine have shown greater potency at SERT; therefore, they have proven efficacy in some anxiety disorders. Imipramine and clomipramine have been used in the treatment of panic disorder; imipramine has shown efficacy in GAD, and some studies suggest that clomipramine may have greater efficacy than SSRIs in OCD. However, SSRIs and SNRIs are generally preferred because they have a more favorable safety profile, particularly in terms of risk of Q_{Tc} prolongation and safety in overdose, as TCAs are highly toxic in overdose (Bystritsky, 2018; Roy-Byrne, 2017). Side effects of tricyclic antidepressant include anticholinergic effects e.g., dry mouth, blurred vision, urinary retention, antihistaminic effects, e.g., sedation and weight gain, and α_1-adrenergic blockade effects, e.g., postural hypotension. TCAs also interact with several medications—particularly those that inhibit CYP2D6 (Baldwin et al., 2014b).

Buspirone

Buspirone has well-established efficacy in GAD and anxiety symptoms in depression, but is ineffective for other anxiety disorders. It has similar efficacy to benzodiazepines but lacks addictive potential and is safe in overdose. However, when compared to benzodiazepines in GAD, the onset of anxiolytic effects is slower (more similar to that of antidepressants, on the order of 4–6 weeks) and appears to have a weaker anxiolytic effect (Bystritsky, 2018). Buspirone also has a relatively short half-life, which necessitates dosing two to three times per day, which can adversely affect adherence to treatment. These factors have limited its use in practice largely to augmentation of SSRIs in GAD, though it can be used as a monotherapy (in the absence of comorbid major depression). Buspirone is generally well tolerated; main side effects include dizziness, insomnia, agitation, and nausea on treatment initiation. These may be minimized by slow dose titration (Nutt, 2005).

Pregabalin

Pregabalin acts as a presynaptic modulator of several excitatory neurotransmitters and may also increase GABA synthesis (Pollack, 2009). Pregabalin should not be stopped abruptly as it may precipitate seizures.

Several large randomized controlled trials have demonstrated its efficacy and tolerability, with comparable speed of onset to benzodiazepines (Montgomery et al., 2006; Rickels et al., 2005). It is approved for the treatment of GAD in Europe; however, it is not approved for this indication by the US FDA.

Antipsychotic Medications

Given their efficacy in the treatment of mood disorders, the use of second-generation antipsychotics (SGAs) in the treatment of GAD has increased, particularly for patients who have not responded to other first-line treatments. However, use of SGAs in the treatment of GAD is currently considered off-label in the United States and Europe (Hershenberg et al., 2014).

There is some conflicting evidence as studies suggest that SGAs—quetiapine, aripiprazole, olanzapine, and risperidone—are effective in reducing symptoms of anxiety among individuals with primary diagnoses of GAD (Hershenberg et al., 2014). More specifically, the most evidence exists for the use of quetiapine in relatively low doses (150 mg/day XR) (Gao et al., 2011). Side effects associated with SGAs include sedation, extrapyramidal symptoms, tardive dyskinesia, weight gain, and elevation of glucose and lipid levels. Because of this, SGAs should only be considered for treatment-resistant GAD after better tolerated alternatives have been exhausted (Bystritsky, 2018).

β-Blockers

Beta-blockers were used historically because they reduce the peripheral physical symptoms of anxiety (palpitations, tachycardia) within 30–60 min; however, evidence from randomized controlled trials is lacking. They do have a role in performance anxiety where tremor is a problem (e.g., musicians) but they do not affect the cognitive and emotional symptoms of anxiety.

They are also associated with significant side effects e.g., negative chronotropic effects, increased airway resistance (so cannot be used in people with asthma), facilitation of hypoglycemia, hyperkalemia, and fatigue, and are toxic in overdose; therefore, they are not generally used in practice.

α-Blockers

There is some evidence for the efficacy of centrally acting α_1-adrenergic antagonist —prazosin—in PTSD (Miller, 2008; Raskind et al., 2003, 2007)—particularly to manage nightmares. Prazosin may counteract some of the excesses noradrenergic brain activity that contributes to PTSD-related trauma-content nightmares, and can decrease the occurrence of trauma-content nightmares in both combat veterans and patients with noncombat-related PTSD (Miller, 2008).

What is Coming Up in Pharmacological Management

There is much drug development focused on improving the efficacy and tolerability of existing anxiety medications; however, there are also efforts to identify novel molecular targets (Miller, 2010).

Novel Pharmacological Targets

Neuropeptides are short-chain amino acid neurotransmitters and neuromodulators implicated in anxiety, pain, and stress regulation (Belzung et al., 2006). Their activity is more discretely localized than antidepressants, suggesting a more favorable side effect profile (Madaan and Wilson, 2009).

Neuropeptide targets under investigation include substance P, neuropeptide Y, and vasopressin. However, trials have failed to show consistent evidence for efficacy and safety (Farach et al., 2012).

Other molecular targets, including agents that block the effects of glutamate or promote compensatory neurogenesis, are being actively pursued (Snyder et al., 2011). Blocking glutamate activity and stimulating N-methyl-D-aspartate (NMDA) receptors may reduce stress and anxiety, possibly by restoring neurogenesis. Preliminary studies with riluzole and ketamine—NMDA receptor antagonists—have been shown to reduce symptoms in patients with anxiety disorders (Pittenger et al., 2008; Rodriguez et al., 2011).

Psychedelic Drugs

Although most psychedelic drugs have been illegal or heavily regulated for several decades, some research has suggested that psychedelic drugs may be able to augment exposure-based treatment for anxiety disorders.

Among the psychedelic drugs, 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy") is thought to be the best candidate for exposure augmentation as traditional psychedelics (e.g., lysergic acid diethylamide, psilocybin) can impair cognitive functioning, visual perception, and emotional control. MDMA can support and enhance psychotherapy by increasing a patient's access to emotionally upsetting material, modulating the associated level of arousal, and strengthening the therapeutic alliance (Mithoefer et al., 2013). Placebo-controlled pilot studies have yielded promising results in PTSD; in one study, 85% of patients in the MDMA group (compared with 15% of patients in the placebo group) no longer met criteria for PTSD after three sessions of MDMA-assisted psychotherapy (Mithoefer et al., 2011). These results were sustained at over 3-year follow-up, with no further MDMA required and many patients stopping their regular psychiatric medications (Mithoefer et al., 2013). A subsequent study demonstrated substantial improvement in PTSD symptoms in patients with resistant, chronic PTSD (Chabrol, 2013). In late 2017, the US FDA granted Breakthrough Therapy Designation to MDMA for the treatment of PTSD, and also reached an agreement for the design of Phase 3 clinical trials for MDMA-assisted psychotherapy for patients with severe PTSD. This will allow further research to fully assess the potential of MDMA in PTSD.

In recent years, cannabidiol (CBD), a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ9-tetrahydrocannabinol (THC), has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. Preclinical evidence supports CBD as a treatment for GAD, panic disorder, OCD, and PTSD when administered acutely; however, few studies

have investigated chronic dosing (Blessing et al., 2015). Similarly, evidence supports an anxiolytic role for CBD, but studies are limited to acute dosing, uncontrolled studies/case reports, and few have been carried out in clinical populations (Greer et al., 2014; Passie et al., 2012). Further study is needed to understand the chronic and therapeutic effects of CBD in relevant clinical populations.

Digital Health Interventions

There has been a huge increase in the use of mobile health to target mental health through the use of "apps." It is estimated around 6% of the total number of apps available target people with mental health conditions. Advantages of apps include the improvement of treatment accessibility, real-time symptom and activity monitoring, tracking of treatment progress through ecological momentary assessment (EMA) and provision of personalized feedback and motivational support. However, there are disadvantages around the identification and timely management of crises, and risk of harm when integrating smartphone technology into health care (Donker et al., 2013).

Mobile health technologies will likely provide opportunities to deliver interventions to patients in their natural settings, and treatments such as CBT will become more affordable and accessible (Pramana et al., 2014).

Non-Pharmacological Management

There is good evidence to support the efficacy of some psychological interventions in anxiety disorders (Roberts et al., 2010). Occasionally, initial pharmacological therapy may be required to help the patient become more receptive to psychological input. Some studies suggest that optimal outcome is achieved by combining psychological and pharmacological therapies (National Institute for Health and Care Excellence, 2011); however, this is not always the case (Marcus et al., 2007; van Apeldoorn et al., 2008). For many patients, psychological therapies are an appropriate first-line treatment (National Institute for Health and Care Excellence, 2011).

Cognitive Behavioral Therapy

CBT is conceptualized as a short-term, skills-focused treatment aimed at altering maladaptive emotional responses by changing the patient's thoughts, behaviors, or both. Many diverse protocols have been created for providing CBT to patients with GAD, panic disorder, PTSD, OCD, as well as other anxiety conditions.

GAD

In CBT for GAD, patients are taught to become personal observers of their anxiety and worry. They learn to implement skills of cognitive restructuring to replace catastrophic appraisals with more evidence-based and coping oriented appraisals, and techniques of relaxation training to control excessive tension. Patients are encouraged to apply the cognitive and relaxation skills during exposures to images of feared negative events, and to anxiety-provoking situations, as they prevent themselves from engaging in overt and subtle avoidance behaviors.

Panic Disorder

In CBT for panic disorder, patients are taught to become personal observers of their panic, anxiety, and avoidance. They implement skills of cognitive restructuring to replace catastrophic appraisals with more evidence-based and coping oriented appraisals, and skills of breathing retraining or relaxation to control dysregulated physiology. Patients are encouraged to apply the cognitive and somatic skills during exposure to feared bodily sensations and situations. Through repeated exposure, patients learn that panic-related sensations are not harmful, that panic and anxiety can be managed or tolerated, and that they are able to accomplish tasks that were previously avoided.

PTSD

In CBT for PTSD, patients are assisted in thinking about the traumatic event and themselves more realistically. Socratic questioning is used to elicit information and challenge the patient's maladaptive beliefs. Exposure therapy assists patients in confronting their feared memories and situations in a therapeutic manner. Reexperiencing the trauma through exposure allows it to be emotionally processed so that it can become less painful.

Eye movement desensitization and reprocessing (EMDR) is a form of CBT that incorporates saccadic eye movements during exposure (Shapiro and Solomon, 1995). The technique involves the patient imagining a scene from the trauma, focusing on the accompanying cognition and arousal, while the therapist moves two fingers across the patient's visual field and instructs the patient to track the fingers. The sequence is repeated until anxiety decreases, at which point the patient is instructed to generate a more adaptive thought.

OCD

The most essential component of CBT for OCD is therapist-guided repeated and prolonged exposure to situations that provoke obsessional fear along with abstinence from compulsive behaviors (response prevention). This might occur in the form of

repeated actual confrontation with feared low-risk situations (i.e., in vivo exposure), or imaginal confrontation with the feared disastrous consequences of confronting the low-risk situations (imaginal exposure). Response prevention is a critical component because the performance of rituals to reduce obsessional anxiety would prematurely curtail exposure and rob the patient of learning that the obsessional situation is not truly dangerous, and that the anxiety would naturally subside. Effective exposure and response prevention requires that the patient remain in the exposure situation until the obsessional distress decreases spontaneously, without attempting to reduce the distress by withdrawing from the situation or by performing compulsive rituals or neutralizing strategies.

Psychodynamic Therapy

Psychodynamic therapy is based on the theories and principles of psychoanalysis, but is less focused on the patient–therapist relationship, as it is equally focused on the patient's relationship with his or her external world. In GAD, treatment focuses on core conflictual relationship themes, and emphasis is placed on a positive therapeutic alliance to provide a corrective emotional experience to offset insecure attachment. However, trials have found CBT to be more effective than psychodynamic therapy in GAD (Durham et al., 1999; Leichsenring et al., 2009). There is an absence of evidence for psychodynamic therapy in panic disorder, PTSD, and OCD (Fonagy, 2015).

Mindfulness and Acceptance and Commitment Therapy

Mindfulness involves the nonjudgmental observation of moment to moment experiences, while Acceptance and Commitment Therapy (ACT) combines mindfulness with acceptance of internal states and orientation of actions toward valued goals. Although there are some similarities between ACT and CBT (Arch and Craske, 2008), ACT does not involve any form of cognitive restructuring (i.e., identifying, challenging, and replacing negative thinking with more realistic thinking) or any attempt to change or correct somatic dysregulation (e.g., relaxation training). One meta-analysis suggested that mindfulness-based treatments are moderately effective in GAD (Hofmann et al., 2010); however, these approaches are less supported in other conditions e.g., panic disorder and PTSD.

Self-Help Techniques

The management of anxiety through self-help techniques undertaken individually or in groups has increased, partly driven by patient dissatisfaction with pharmacological treatment, and suboptimal effects of psychotropic and psychological interventions. The evidence behind these self-help interventions is limited but patients and their carers report considerable benefit. With the limited evidence base, one systematic review found that guided self-help had similar effectiveness compared to face-to-face psychotherapy (Cuijpers et al., 2010). Another systematic review concluded that Internet-based interventions have overall positive benefit in the management of anxiety but further investigations are required to determine the factors associated with beneficial outcomes (Griffiths et al., 2010). Self-help approaches such as the use of Internet-based educational resources have potential benefits in managing mild anxiety symptoms, but in some cases, patients may not benefit so keeping these patients under review is crucial so that alternative treatments can be initiated when warranted.

Role of the Pharmacist in Managing and Prescribing in Anxiety Disorders

Pharmacists are an integral part of the multidisciplinary team who can add value to the care of patients with anxiety disorders beyond medicines management and pharmaceutical care. The pharmacist can be involved in screening for anxiety disorders in primary care and identifying high-risk patients eligible for referral, optimizing treatment, and providing advice on complementary therapies where patients seek this approach. Pharmacists are well placed to support patients in making informed choices, thus in some ways, acting in a patient advocacy role.

Optimizing Treatment

Pharmacists can play a key role in optimizing pharmaceutical care—key aspects that are particularly relevant for anxiety are management of medication adverse effects, drug interactions, and benzodiazepine withdrawal.

Managing Adverse Effects of Pharmacological Treatment

Adverse effects with psychotropic medications can be distressing and can lead to patients stopping their medications. Adverse effects vary depending on the class of psychotropic; for example, SSRIs are commonly associated with sexual dysfunction, SNRIs with excessive perspiration, pregabalin and benzodiazepines with drowsiness, and antipsychotics with weight gain (see Pharmacological Management section). However, it is not only the adverse effect that may affect adherence but also the fear of developing tolerance or becoming dependent on medications contributes toward nonadherence. The pharmacist can play a key role in educating and providing information to patients, and correcting any misconceptions the patient has about their

Table 3 Groups of psychotropics used to manage anxiety disorders and most commonly reported adverse effects.

	SSRI	*SNRI*	*Pregabalin*	*Benzodiazepines*	*Antipsychotics*
Adverse effects	Sexual dysfunction, gastrointestinal (dose-related), increased risk of bleeding, dizziness, drowsiness	Hypertension, nausea, dry mouth, sexual dysfunction, increased risk of bleeding, drowsiness, insomnia	Increased appetite and weight gain, sexual dysfunction, gastrointestinal effects, euphoria, irritability, dizziness, somnolence	Drowsiness, decreased concentration, headaches, decreased libido, erectile dysfunction, paradoxical effects (talkativeness, excitement), tolerance and dependence	Extrapyramidal symptoms, weight gain, hyperprolactinemia, sedation, postural hypotension, dyslipidemia, impaired glucose tolerance, QT prolongation, anticholinergic effects

treatment. Pharmacists need to explore patient attitudes and concerns at the start of treatment, and periodically thereafter, allowing any issues to be addressed early on.

When starting antidepressant treatment, anxiety symptoms can worsen. Patients should be monitored closely for this and other adverse effects, as well as discontinuation symptoms (see Monitoring section) (**Table 3**).

Managing Drug Interactions

SSRIs

Some SSRIs are potent inhibitors of individual or multiple hepatic cytochrome P450 (CYP) pathways and the magnitude of these effects is dose related. For example, fluvoxamine is a potent inhibitor of CYP1A2, and fluoxetine and paroxetine are both potent inhibitors of CYP2D6. Care should be taken when prescribing escitalopram and citalopram alongside drugs that prolong the QT interval, due to the increased risk of torsade de pointes. The maximum daily doses have been restricted to escitalopram 20 mg and citalopram 40 mg daily in adults and in patients over the age of 65 years to escitalopram 10 mg and citalopram 20 mg daily, respectively.

Benzodiazepines

Benzodiazepines do not induce microsomal enzymes and so do not frequently precipitate pharmacokinetic interactions with other drugs. Most benzodiazepines are metabolized by CYP3A4 enzymes. Concomitant use of P450 inhibitors in a patient taking diazepam can result in increased serum levels of diazepam leading to increased effect; conversely, drugs that induce cytochrome P450 enzyme can accelerate hepatic elimination of diazepam and decrease its action. In practice, pharmacodynamic interactions (usually increased sedation) are common, for example, when benzodiazepines are administered alongside methadone, which can result in cardiopulmonary depression. The severity and impact of these interactions on patient safety need to be monitored for, and the pharmacist has an essential role in communicating these with the prescriber to manage their effects.

Management of Benzodiazepine Withdrawal

For most people in primary care, even minimal intervention, such as an information sheet or a single brief consultation, can be effective in reducing or stopping benzodiazepine use without adverse effects (Bashir et al., 1994). Although good quality evidence for this is lacking, withdrawing benzodiazepines gradually is recommended to allow a smooth, gradual fall in drug levels, thus minimizing withdrawal symptoms (Lader et al., 2009). Abrupt withdrawal can produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. This is more likely in people taking high doses, although seizures or psychosis may occur when other predisposing factors are present. The optimal speed or duration of dose reduction is unknown; drug withdrawal should be guided by individual choice and severity of withdrawal symptoms (Ashton, 2002). More detailed information on benzodiazepine withdrawal is outside the scope of this chapter, please refer to local specialist resources for further guidance.

Special Populations

Children and Adolescents

The evidence base for prescribing for the management of anxiety disorders of children and adolescents is relatively poor compared to adults (18–65 years old) with only a few randomized controlled studies (Ipser et al., 2010). It is recommended, where possible, to manage anxiety disorders in children and adolescents through the use of psychological interventions. Psychotropic treatment such as SSRIs should only be initiated where there has been no response to psychological interventions. If the decision has been made to initiate psychotropic treatment, then the same range of treatments for adults such as SSRIs should be considered, but done so very cautiously.

Women of Childbearing Age

Anxiety disorders are common in pregnancy and in the postpartum period, and in some cases, the symptoms may remit during these phases. As the evidence base for the use of psychotropics during pregnancy and breastfeeding is still growing, pharmacists have an important role in providing advice on a case-by-case basis. Key considerations include weighing up the risks of discontinuation when

stopping treatment, safety of the drug in pregnancy/breastfeeding, in addition to its effectiveness, tolerability, and adverse effects. When providing advice in relation to the appropriateness of a pharmacological agent during pregnancy, pharmacists should seek specialist advice from medicines information services. The decision to use any drug during pregnancy and breastfeeding should be done in collaboration with the patient who should be fully informed of all risks associated with taking or not taking a particular medication (Freeland and Shealy, 2013).

Older-aged Patients

Similar to the evidence base in children and adolescents, there are few randomized studies investigating the effectiveness and acceptability of psychotropics in the elderly population (>65 years old). Anxiety disorders in patients aged over 65 years are less common compared to the younger population (Oakley Browne et al., 2006). In elderly patients, the rate of clearance of drugs through the liver and/or kidneys is slower than adults, thus necessitating lower doses. The management of anxiety in elderly patients is not dissimilar compared to younger patients but the patient's full medical history (conditions) and any currently prescribed medications need to be carefully considered to mitigate possible drug interactions.

Monitoring Patients with Anxiety

Pharmacists have a key role in monitoring symptoms and treatment response and/or tolerance (Locke and Kamo, 2016). Patients who have started on an SSRI or SNRI should be seen every 2–4 weeks for the first 3 months, and if under the age of 30 years, should be reviewed within 1 week of initiation as these classes of drugs are associated with an increased risk of suicidal thinking and self-harm (Medicines and Healthcare Products Regulatory Agency, 2014).

Treatment should be continued for at least 12 months in patients diagnosed with OCD and PTSD, 6 months for social anxiety and panic disorder, and 18 months for GAD, to prevent relapse (Baldwin et al., 2014a). Patients should be monitored through this period to ensure continued benefit with treatment. The following should be reviewed:

- Monitor progress, considering factors including severity, duration of symptoms, degree of distress, and functional impairment. Consider using anxiety screening questionnaires such as GAD-7 to compare with previous scores.
- Check treatment adherence (either pharmacological or psychological interventions) and inquire about adverse effects.
    - If necessary, advise dose adjustment or a switch to a different drug, based on adverse effects and progress.
    - If a drug is effective, advise to continue taking it for at least a year as the likelihood of relapse is high if stopped earlier.
    - If there is no response to pharmacological treatment, offer an alternative medication (from the same or alternative medication class), or psychological intervention.
    - If there is no response to psychological intervention, consider offering a pharmacological treatment, if not previously on psychotropics.
- Assess for suicidal ideation and suicide risk, especially if the person has comorbid depression.

If the decision has been made to stop treatment, this should be done gradually over a minimum period of 3 months to avoid rebound symptoms and discontinuation symptoms, which may occur with abrupt cessation of treatment or missed doses. The drugs most implicated in causing discontinuation symptoms are the short half-life drugs such as venlafaxine or paroxetine (see Pharmacological Management section). Symptoms can be offset by switching to modified-release preparations to prolong drug release.

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Bipolar Affective Disorder

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Learning Objectives

- Describe the epidemiology and etiology of bipolar affective disorder (BPAD), including the different presentations and BPAD Types 1 and 2
- Briefly outline the signs and symptoms underlying different diagnostic criteria for BPAD
- Explain the pharmacological and nonpharmacological management options for BPAD
- Describe the first- and second-line treatment option for BPAD and what options can be considered when usual first-line treatments fail
- List the most common side effects and interactions associated with mood stabilizers, lithium, and antipsychotics
- Describe novel treatment options coming up in the management of BPAD
- Describe the role of the pharmacist in managing BPAD and where pharmacists can contribute to the pharmaceutical care

Take Home Messages

- Bipolar affective disorder (BPAD) is a serious mental health illness that can cause significant disruption to individuals, their families and carers, workplace, and society during an episode of mood disorder
- The presentation of BPAD can be heterogeneous with a variety of different symptoms and durations of onset
- Treatment varies depending on whether the presentation is primarily depression or mania during the acute stage, but should always include consideration of a mood stabilizer in the long term
- Lithium is generally considered the mainstay of treatment in terms of both acute and long-term maintenance treatment
- Second-generation antipsychotics or mood stabilizers can be considered for monotherapy management of the depressive phase of BPAD
- The use of antidepressants in people with BPAD remains contentious and its long-term efficacy unclear. Caution is advised due to risk of switching to mania
- Pharmacists are an integral part of the multidisciplinary team for BPAD management, partly due to the "neutral" position of pharmacists in terms of medication supervision and administration, thus may take on a patient advocacy role for optimization of treatment plans
- Key opportunities to optimize pharmaceutical care for patients include improving adherence through psychoeducation and maximizing efficacy or minimizing adverse effects of treatment

Introduction to Condition

Bipolar disorder, also known as manic depressive disorder or bipolar affective disorder (BPAD), is a serious mental illness. It is classified as a mood disorder, whereby mood disturbance is usually represented by episodes of depression or mania. Between acute episodes, patients may be in full remission, but in some cases, there can be residual symptoms between episodes. It usually presents in early adulthood with much heterogeneity as well as comorbidity, leading to poor mental and physical health and reduced quality of life (Gutierrez-Rojas et al., 2008). BPAD can cause significant disruption to individuals, their families, workplace, and society. Treatments not only involve medication but also psychoeducation to improve insight and support for the individual and family. When making a diagnosis, it is important to exclude potential physical disorders that could contribute to an altered mood state, e.g., thyroid disease, medications (e.g., steroids), or illicit drugs.

Brief History of BPAD

BPAD symptoms have been recognized for approximately 2000 years, and the condition has been known by other terms such as melancholia and manic depression. Melancholia is a term from ancient Greece that was used to describe someone in pre-Hippocratic times with depression. This is because their mood was thought to be related to the brain being affected by black bile, which was consistent with the theory of bodily humors at the time.

With regard to mania and depression being considered part of the spectrum of the same disease, the Greek physician Aretaeus of Cappadocia was the first to do so in the first century AD (Marneros, 2001). In the 1800s, BPAD was termed folie circulaire and folie à double forme by Jean-Pierre Falret and Jules Baillarger, respectively. Later, it was described by Emil Kraepelin in the early 1900s as "manic depressive psychosis" and subsequently as bipolar disorder by Karl Leonhard and colleagues.

Condition Information

Definition/Classification of BPAD

Mood can be conceptualized as a spectrum with major depressive disorder (MDD) at one end and mania at the opposite end.

Bipolar disorder I (BD I) is used to describe a clinical diagnosis of bipolar disorder with manic episodes, whereas bipolar II (BD II) is used to categorize bipolar disorder with hypomanic episodes in the absence of manic episodes (American Psychiatric Association, 2013). The ICD-10 diagnostic criteria do not include BD II as a separate diagnostic category (World Health Organization, 1992).

Cyclothymic disorder is a chronic mood disorder characterized by depressive or hypomanic symptoms, whereby these do not meet the threshold for a manic or depressive episode (American Psychiatric Association, 2013). The symptom duration is usually 2 years in adults, whereas the time criteria for adolescents are shorter at 1 year. Symptoms include mood swings and subthreshold low mood, and it is regarded as a milder form of BPAD.

Rapid cycling bipolar disorder is a term used to describe 4 or more discrete mood episodes (mania, hypomania, depression, or mixed) in an annual timeframe (Lee et al., 2010).

Depending on the diagnostic classification system used, for a diagnosis of BPAD to be made, an episode of mania is required (American Psychiatric Association, 2013), or two mood episodes whereby at least one is mania, see later in chapter for full diagnostic criteria (World Health Organization, 1992). With ICD-10, BPAD is classified as a mood disorder and can be found together with other mood disorders such as recurrent depressive disorder or persistent mood disorders (World Health Organization, 1992).

Epidemiology

The bipolar spectrum (which includes BD I, BD II, and subthreshold BPAD) has a lifetime prevalence of approximately 2.4% (Merikangas et al., 2011) and affects both genders equally (Leibenluft, 1996). The mean age of diagnosis is in the third decade although depressive symptoms or discrete episodes of depression occur earlier in life, typically in adolescence or early adulthood (Leboyer and Kupfer, 2010; Phillips and Kupfer, 2013), and there are often several episodes of depression before developing manic episodes (Leverich et al., 2007). The ratio of manic to depressive episodes is estimated to be 1:3 (Judd et al., 2003), and there are a number of associated comorbidities including anxiety, addiction, and other psychiatric disorders.

According to the Aesop study undertaken in the United Kingdom, BPAD was reported to be higher in Black and other minority ethnic groups compared to the White population (Lloyd et al., 2005). Studies have also shown that people of Afro-Caribbean background were more likely than White people to be hospitalized with BPAD, have a higher rate of attempted suicide, and more frequent psychotic episodes, which were more likely to be associated with substance or alcohol misuse (Bani-Fatemi et al., 2013; Snowden et al., 2009). Approximately 10% of people with BPAD have the rapid cycling form, which can cause significant functional and social disturbance and often associated with a poorer prognosis. Up to a quarter of those with BPAD have a lifetime history of self-harm, while rates of suicide are estimated to be 15 times higher than the general population (Angst et al., 2005; Goetz et al., 2007).

The quality of life impairments associated with BPAD are significant due to its chronic course, early onset and the loss of disability-adjusted life years (DALYs) which is more than all forms of cancer or major neurological conditions (Merikangas et al., 2011; World Health Organization, 2002). People with BPAD have an increased risk of cardiovascular disease and approximately 38% of people die from this, which is twice the expected mortality rate for the general population (18%) (Westman et al., 2013). People with BPAD also have an increased risk of chronic kidney disease, respiratory disease (such as chronic obstructive pulmonary disease (COPD)), and diabetes (Hsu et al., 2017; Smith et al., 2013).

Postpartum psychoses can occur in women with BPAD with the onset of symptoms following childbirth (Jones et al., 2014), and these are referred to as episodes with peripartum onset (American Psychiatric Association, 2013). Usually these episodes have a mood component (typically hypomanic or manic) but can be associated with depressive symptoms too. The symptoms often develop within 2 weeks after delivery and can include delusions, hallucinations, mood disorder symptoms, confusion, and perplexity (Jones et al.)

Etiology

BPAD is thought to have a strong genetic component and increased familial aggregation based on twin, adoption, and family studies (Cowen et al., 2012). A recent estimate of the heritability of bipolar disorder was quoted as 85%, and the lifetime risk for bipolar disorders in first-degree relatives is estimated to be about 10%. There also appears to be overlap of susceptibility between BPAD and schizophrenia with polygenic contribution from several individual risk alleles of small effect (Baum et al., 2008; Craddock and Sklar, 2013; Lichtenstein et al., 2009). As with many psychiatric disorders, there is an interplay between genetics, epigenetics, and environment.

For example, early childhood adversity has been suggested to contribute to the evolution of BPAD (Sugaya et al., 2012). Furthermore, rapid cycling and mixed affective episodes are more common in the context of substance use (Krishnan, 2005). There is recognition of substance- or medication-induced bipolar symptoms, which is termed bipolar and related disorder (American Psychiatric Association, 2013). It is not just illicit substances that can induce BPAD symptoms, but prescribed medication such as corticosteroid medication used for reducing inflammation has been associated with BPAD symptoms. Manic or hypomanic symptoms can additionally arise with other prescribed treatments such as levodopa, methylphenidate, and stimulants such as caffeine (Kiselev et al., 2015), cocaine, and amphetamines. However, should someone experience a hypomanic/manic state following the commencement of an antidepressant or course of electroconvulsive therapy, this is regarded as BPAD rather than a medication-induced bipolar and related disorder (Licht et al., 2008).

Bipolar and related disorder may also arise due to an underlying medical condition, which include endocrine disorders such as Cushing's disease and thyroid disorder. Dysfunction of the hypothalamic–pituitary–adrenal axis with abnormal secretion of cortisol has been implicated in depression and may contribute to BPAD (Daban et al., 2005; Fries et al., 2014). Neurodegenerative disorders such as multiple sclerosis, frontal lobe dementia, and HIV dementia can further contribute to BPAD presentations.

Diagnosis

Signs and Symptoms

People with BPAD usually present with episodes of depression earlier in their life, often in adolescence followed by manic episodes in adulthood. Sometimes the mood episodes, when severe, can be associated with psychotic symptoms. Up to half of the people diagnosed with BPAD experience psychotic symptoms such as hallucinations and delusions, which are regarded as distortions in reality (Vandeleur et al., 2014). When someone experiences mania and psychosis, the symptoms can be congruent with the mood state such as thinking they are famous or rich and can result in sexual indiscretions or overspending. Conversely, when depressed, they may have the belief that they are destitute and that there is no point living any longer.

BPAD has high comorbidity with other mental health disorders, personality disorders, and addictions. For example, conditions that are highly comorbid with BPAD include anxiety disorder, alcohol and substance misuse, gambling, and attention-deficit hyperactive disorder (ADHD) (Di Nicola et al., 2014; Malhi et al., 2015). There are increased rates of associated risks including self-harm and suicide, violent/nonviolent crime, and metabolic syndrome (Malhi et al., 2012; Schaffer et al., 2015a; Schaffer et al., 2015b).

Criteria for episodes of mania and hypomania are summarized in **Table 1**. Although manic episodes can occur acutely for the first time in adulthood, there are often warning signs for months and sometimes years prior to such episodes (Faedda et al., 2015). Symptoms can include irritability, lability, mood shifts, hyperactivity, and anxiety, and these symptoms may extend as far back as childhood or adolescence (Egeland et al., 2000; Merikangas et al., 2007; Shankman et al., 2009). The prodromal state may involve dysregulation of mood and energy; however, these symptoms are nonspecific and do not necessarily predict future development of BPAD (Skjelstad et al., 2010).

Treatment Considerations in BPAD

When managing BPAD, there should be consideration of not only the prevailing mood (e.g., depression or mania) but also the treatment phase, which would include mood prophylaxis/maintenance phase versus treatments that occur during an acute phase.

Indeed, when considering the best environment for BPAD to be managed, the severity and comorbidity of episodes affect the decision of managing someone as an inpatient or outpatient. With psychotic symptoms, suicidality, homicidality, catatonia, severe psychosocial disruption, vulnerability, impaired judgement/impulsivity, or substance addiction, inpatient management is preferred (Malhi et al., 2015). Apart from considering the most appropriate environment to manage BPAD, pharmacotherapy and non-pharmacotherapy are other important considerations; both should be used where appropriate.

Nonpharmacological Management

Optimum management of BPAD needs integration of pharmacotherapy with targeted psychotherapy. Common overall objectives of psychosocial interventions for BPAD include building a therapeutic alliance and education of patients (British Psychological Society, 2010), and where possible, caregivers, about strategies for the management of stress, the identification and intervention of early signs of recurrence, and how to maintain a regular lifestyle (e.g., sleep and exercise) habits (Miklowitz and Scott, 2009) and optimal metabolic control (Goodwin et al., 2016; Malhi et al., 2015).

Adjunctive Psychotherapy in the Acute Phase

There is a strong clinical consensus about the benefits of engaging with people even in acute mania, making all reasonable efforts to work in a genuinely collaborative and normalizing way. Unstructured supportive psychotherapy is likely to be useful for the patient and their family during acute mania. Acute settings also provide an opportunity to engage individuals for future psychological therapy.

Adjunctive Psychotherapy in the Maintenance Phase

Group and individual psychoeducation, detecting early warning signs, and family therapy can be used as adjunctive psychotherapies. These therapies are time limited, structured, and typically administered to euthymic patients during maintenance. Psychoeducation is a core element of adjunctive cognitive behavioral therapy, family therapy, and interpersonal and social rhythm therapy.

Table 1 Diagnostic criteria for BPAD with particular focus on features of manic and hypomanic episodes (American Psychiatric Association, 2013)

Diagnostic Criteria

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (e.g., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (e.g., purposeless nongoal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.
   - **Note:** A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (e.g., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.
   - **Note:** A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, or necessarily indicative of a bipolar diathesis.

Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Some topics covered in psychoeducation include illness awareness, medication options and adherence, identifying prodromal signs of recurrent episodes, and regulating habits. Other topics may include triggers, avoiding substance abuse, pregnancy and heritability, and stress management (Geddes and Miklowitz, 2013).

Pharmacotherapy Treatment Options

Pharmacotherapy can be used for all stages of BPAD, with the aim of reducing morbidity and mortality (Harrison et al., 2016). The desired outcome of treatment is to prevent acute manic, hypomanic, or depressive episodes, resulting in improved functioning to premorbid level, and reducing further episodes of mania and depression (American Psychiatric Association, 2002). Treatment of

BPAD must be individualized depending on the clinical presentation, severity, and frequency of episodes. Once the acute presentation has been managed, maintenance pharmacotherapy is recommended with observational studies demonstrating that initiation of maintenance early in the course of illness is associated with better long-term outcomes (Kessing et al., 2014).

Acute Mania and Hypomania

Despite clinical differences between acute manic and hypomanic episodes, for the purposes of treatment, they are considered to be similar and thus treated with the same medication (Grunze et al., 2009; Wong, 2011; Yatham et al., 2013). The goal of treatment is remission, defined as "resolution of mood symptoms or improvement to the point that only one or two symptoms of mild intensity persist. If psychotic features (delusions or hallucinations) are also present, resolution of the psychosis is required for remission" (Grunze et al., 2009).

Based on randomized trials, the medication classes commonly used to treat acute mania or hypomania include lithium, anticonvulsants, and antipsychotics used in combination or as monotherapy, depending on severity of symptoms. Benzodiazepines are primarily used as adjunctive treatment for insomnia, agitation, or anxiety.

Lithium

Lithium monotherapy is effective in the treatment of moderate to severe mania, depression, and mixed episodes. The main indication for lithium is the prophylaxis of BPAD, where it reduces both the number and severity of relapses (Tondo et al., 2010); however, lithium is more effective at preventing manic than depressive relapses. The National Institute for Health and Care Excellence (NICE) in the United Kingdom supports the use of lithium as a first-line mood stabilizer (National Institute for Health and Care Excellence, 2014a).

Before initiating lithium, renal, thyroid, and cardiac function should be checked. Thyroid dysfunction should be corrected before treatment is commenced. An electrocardiogram (ECG) is recommended in patients with risk factors for, or existing, cardiovascular disease. A baseline weight is also appropriate.

Lithium dosing depends on the patient's age and weight, tolerance to adverse effects, and the acuity of the illness. Plasma levels should be measured 12 h postdose, 1 week after starting lithium, and 1 week after every dose change, and weekly until the levels are stable (National Institute for Health and Care Excellence, 2014a). Standardized 12-h lithium (trough) levels have become the accepted mode of monitoring. A systematic review of the relationship between plasma levels and response determined that the optimal range is 0.6–0.75 mmol/L (Severus et al., 2008).

Once the desired therapeutic reference range for lithium levels has been achieved, levels should be measured every 3 months. More frequent tests may be necessary in those who are prescribed interacting medications such as anti-inflammatory or angiotensin-converting enzyme drugs, and in elderly, people at risk of impaired renal or thyroid function, or people who have poor symptom control or adherence. Body weight (or body mass index) and tests for urea, electrolytes, estimated glomerular filtration rate (eGFR), and thyroid function should be measured every 6 months (National Institute for Health and Care Excellence, 2014a).

Most side effects associated with lithium treatment are dose related and, therefore, plasma level related. These include mild gastrointestinal upset, fine tremor, polyuria, and polydipsia (Taylor et al., 2015). Long-term use increases the risk of hypothyroidism (Frye et al., 2009), which can be managed with thyroxine. Thyroid levels can also normalize with lithium cessation; however, this is often not practical if lithium is pivotal to a treatment. There is also increased risk of hyperparathyroidism; calcium levels should be monitored every 6 months, or more often if there is impaired renal function. For a review of the toxicity profile of lithium, see McKnight et al. (2012).

Toxic effects of lithium occur at levels >1.5 mmol/L but also have known to occur at normal plasma levels and usually consist of gastrointestinal effects (anorexia, nausea, and diarrhea) and central nervous system effects (muscle weakness, drowsiness, ataxia, coarse tremor, and muscle twitching). At levels above 2.0 mmol/L, increased disorientation and seizures occur, which can progress to coma, and ultimately death. When lithium treatment is initiated, patients should always be given information relating to the symptoms of toxicity and common risk factors (Gerrett et al., 2010). When lithium toxicity is suspected, an urgent lithium level should be done and, because there is no antidote to lithium, supportive measures should be put in place and lithium levels checked every 6–12 h to ensure they are falling. When considering stopping lithium, abrupt discontinuation should be avoided as this is associated with increased risk of relapse to mania. When discontinuing long-term treatment, doses should be gradually tapered over at least 4 weeks and preferably over 3 months. Patients should be monitored for signs of relapse, emerging symptoms, mood, and mental state while discontinuing treatment, and for up to 2 years after treatment has stopped.

Valproate

Valproate is often prescribed as a mood-stabilizing agent and commonly used in the maintenance phase of treatment. It's mechanism of action is not fully understood. Valproate is available in three formulations: valproic acid (widely used for BPAD in the United States, but only licensed for the treatment epilepsy in the United Kingdom), sodium valproate, and semi-sodium valproate. Both sodium valproate and semi-sodium valproate formulations are metabolized to valproic acid, which is responsible for the pharmacological activity. Doses of sodium valproate and semi-sodium valproate are not equivalent; a slightly higher dose (approximately 10%) is required to allow for extra sodium content when sodium valproate is used (Fisher and Broderick, 2003).

Randomized controlled trials have shown valproate to be effective in the treatment of mania, with a response rate of 50% (Nasrallah et al., 2006). It may be considered a first-line option for acute episodes and for prophylaxis. It can also be used in

combination with antidepressants for acute episodes of depression (National Institute for Health and Care Excellence, 2014a). Valproate may also be preferred over lithium for mixed episodes (American Psychiatric Association, 2002).

Before initiating valproate therapy, baseline full blood count, liver function tests, and weight or BMI should be measured. Full blood counts, weight/BMI, and liver tests should be repeated after 6 months and annually thereafter.

Common dose-related side effects include gastrointestinal distress, hyperammonemia, sedation, and hair loss with curly regrowth (Segura-Bruna et al., 2006). Rare, idiosyncratic, but potentially fatal adverse events include irreversible hepatic dysfunction, hemorrhagic pancreatitis, and agranulocytosis (American Psychiatric Association, 2002). Lethargy and confusion can occasionally occur with starting doses above 750 mg/day; therefore, treatment should start with low divided doses to minimize side effects, then titrated accordingly. Weight gain can be significant and up to a quarter of patients may develop postural tremor (Zadikoff et al., 2007), which is reversible upon valproate cessation. If stopping valproate, the dose should be slowly reduced over at least 4 weeks to minimize the risk of relapse (National Institute for Health and Care Excellence, 2014a). Valproate is associated with an increased prevalence of polycystic ovary syndrome (Bilo and Meo, 2008); it should not be offered to female children/adolescents, women of childbearing potential, or pregnant women without specialist advice (National Institute for Health and Care Excellence, 2014a).

Carbamazepine

Randomized studies have suggested that carbamazepine monotherapy is effective in bipolar depression (Dilsaver et al., 1996); however, it is generally thought to be less effective than lithium in the prophylaxis of mania (Nasrallah et al., 2006), and is considered to be a third-line agent for this purpose (National Institute for Health and Care Excellence, 2014a).

Before initiating carbamazepine, baseline full blood count, liver function tests, and renal function tests should be done. Serum electrolytes can also be obtained, especially in the elderly, who may be at higher risk of hyponatremia. A baseline measure of weight is also desirable (American Psychiatric Association, 2002; National Institute for Health and Care Excellence, 2014a).

The main side effects associated with carbamazepine are dizziness, diplopia, drowsiness, ataxia, and headaches. This can sometimes be avoided by starting with a low dose and increasing slowly. Carbamazepine commonly causes chronic low white blood cell count and treatment should be discontinued if the patient develops leucopenia that is severe, progressive, or accompanied by clinical manifestations, e.g., fever or sore throat. Rare, idiosyncratic, but serious side effects include agranulocytosis, aplastic anemia, hepatic failure, exfoliative dermatitis (e.g., Stevens–Johnson syndrome), and pancreatitis. Carbamazepine is a hepatic enzyme inducer that induces its own metabolism as well as that of other drugs. It is, therefore, advisable to check plasma levels to ensure levels are within the therapeutic range or if noncompliance is suspected. Plasma levels should be checked 2–4 weeks after dosage increases to ensure that desired levels (of at least 7 mg/L) are still being obtained to ensure efficacy of treatment (Taylor et al., 2015).

Antipsychotics

Individual antipsychotics possess sedative, anxiolytic, anti-manic, mood-stabilizing, and antidepressant properties; some (quetiapine and olanzapine) show all of these.

First-generation antipsychotics (FGAs) have long been used in that treatment of mania; however, until recently, there was a paucity of published evidence on their role in the treatment of mania. Recent studies have demonstrated clear efficacy of haloperidol for this indication (Smulevich et al., 2005). However, the long-term use of FGAs is limited by the increased risk of extrapyramidal side effects and tardive dyskinesia (Tohen and Vieta, 2009). The efficacy of second-generation antipsychotics (SGAs) aripiprazole, clozapine, olanzapine, quetiapine, and risperidone has been more robustly evaluated. Comparison among different SGAs is difficult as there are no conclusive head-to-head studies; the choice often depends upon the difference in side effects. In the United Kingdom, NICE recommends a therapeutic trial of either haloperidol, olanzapine, quetiapine, or risperidone in the management of the acute phase of mania and, if the first antipsychotic is not effective or tolerated, a second antipsychotic from the four options is offered. Metabolic problems such as weight gain, glucose intolerance, and hyperlipidemia are most likely to occur with olanzapine, followed by quetiapine and risperidone.

Asenapine is newly approved in the United States and the United Kingdom for the acute treatment of manic or mixed episodes with or without psychotic features. Trials have demonstrated that it is well-tolerated and may be less likely than olanzapine to cause clinically significant weight gain (McIntyre et al., 2009, 2010).

Before starting antipsychotic medication, weight or BMI, pulse, fasting blood glucose, and blood lipid profile should be measured. Pulse and blood pressure should be monitored after each dose change, weight/BMI should be monitored weekly for the first 6 weeks and then at 12 weeks, and blood glucose and lipid profile should be measured at 12 weeks. ECG should be done before initiation of an antipsychotic, especially if using haloperidol, and subsequently after dose changes. Prolactin levels should be measured 6 months after starting treatment, and liver function tests completed every 12 months. Response to treatment, adherence, and side effects should also be monitored regularly throughout treatment (National Institute for Health and Care Excellence, 2014a).

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) may be considered for patients with severe or treatment-resistant mania. In addition, ECT is a potential treatment for patients experiencing mixed episodes or for patients experiencing severe mania during pregnancy (American Psychiatric Association, 2002).

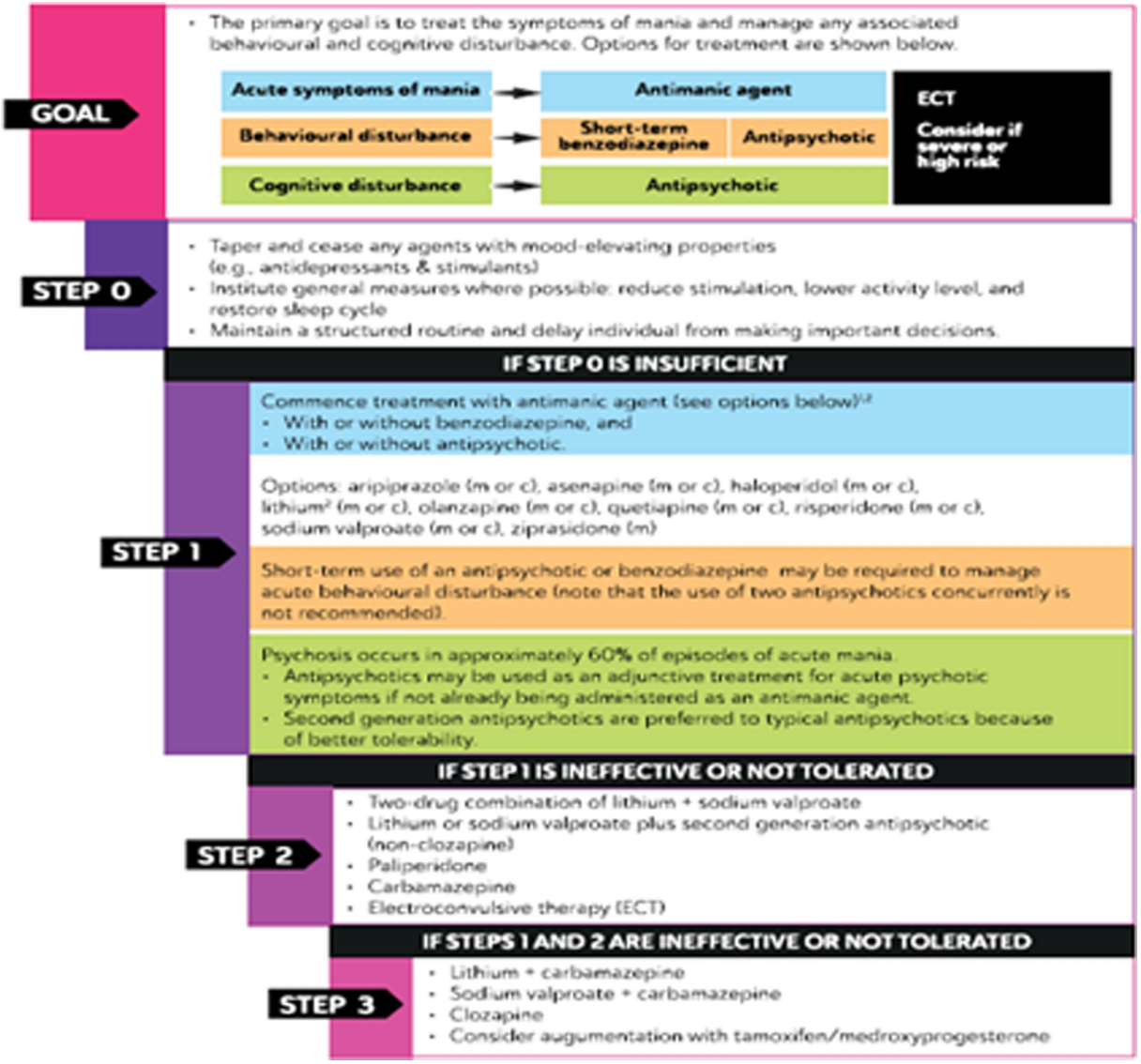

Figure 1 The management of mania is illustrated as a series of steps. The primary targets of treatment are "ABC": Acute symptoms of mania, behaviour disturbance, and cognitive disturbance. Taken from the Australian and New Zealand College of Psychiatrists clinical practice guidelines. m, monotherapy; c, combination.

Fig. 1 nicely illustrates a step-wise approach in managing patients with mania, which is used in Australia and New Zealand. However, it is important to note the pharmacological approach used to manage patients with mania may be different depending on the country and clinical guidelines used.

Acute Depression

Bipolar depression is the predominant and most disabling component of BPAD (Judd et al., 2003). Patients can present with either de novo or breakthrough episodes while on maintenance therapy (Malhi et al., 2015).

Monotherapy

Monotherapy has demonstrated efficacy in bipolar depression and comprises two groups of medications SGAs and mood-stabilizing agents. The use of adjunctive antidepressants remains contentious, and the long-term efficacy is unclear. There is a growing consensus that antidepressant monotherapy should be avoided if possible due to the risk of switching to mania.

SGAs include quetiapine (at doses of 300–600 mg), lurasidone, and olanzapine; the latter being least favored as it has the greatest likelihood of causing metabolic syndrome. Mood-stabilizing agents such a lithium, lamotrigine, and valproate can also be prescribed (Malhi et al., 2015).

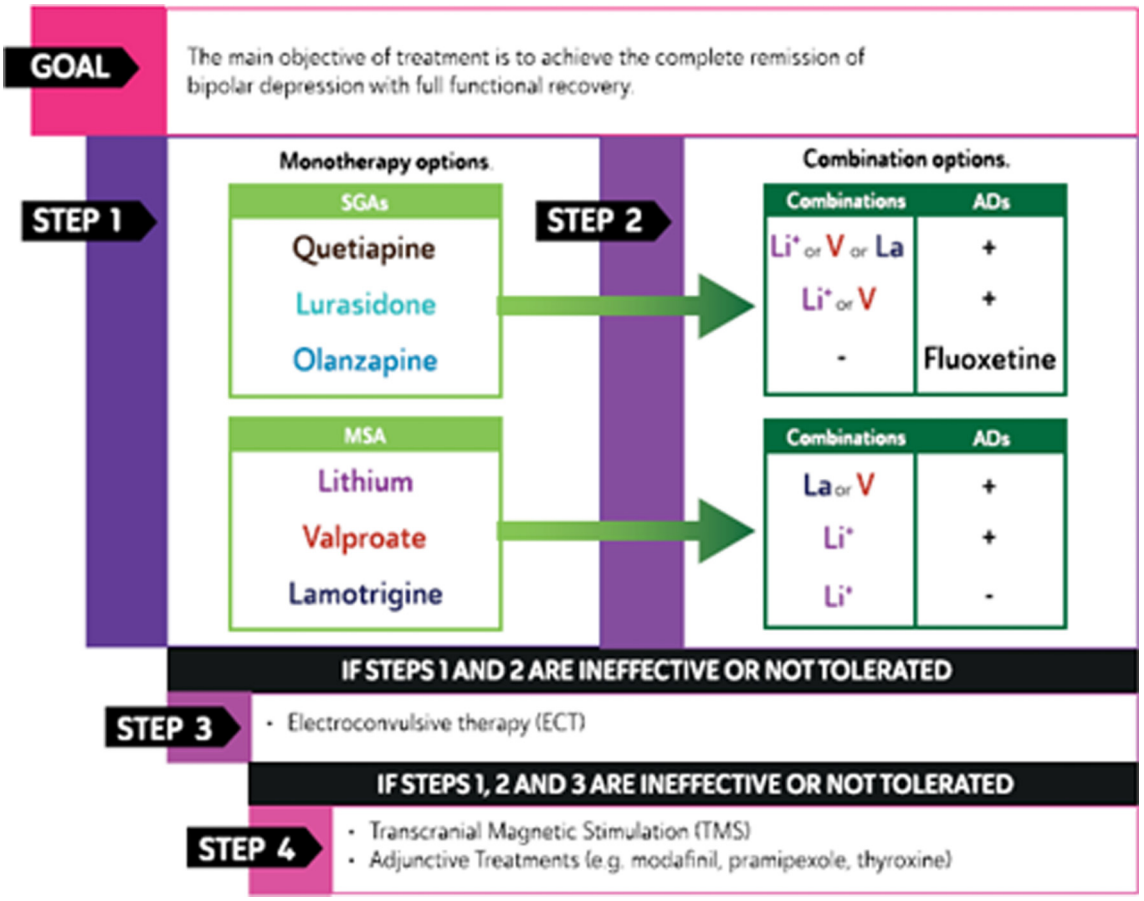

Figure 2 Treatment pathway illustrating the step-wise pharmacological management of bipolar depression. Taken from the Australian and New Zealand College of Psychiatrists clinical practice guidelines.

Combination Therapy

While monotherapy is ideal, patients frequently require combinations of medicines. The SGAs can be added to either mood-stabilizing agents or antidepressants. Lithium and valproate can be combined with all other monotherapy options. However, caution is advised when valproate is combined with lamotrigine, as valproate inhibits the clearance of lamotrigine by 30%–50% (Kanner, 2004). Therefore, lower dose of lamotrigine should be used to reduce the risk of the interaction and avoid side effects. Lamotrigine is associated with causing hypersensitivity reactions and rare life-threatening skin rashes and requires slow dosage titration (American Psychiatric Association, 2002). Antidepressants can be added to all effective monotherapy options, with the exception of lamotrigine, but the benefits of this strategy remain unclear (Malhi et al., 2015). However, there is specific clinical trial evidence for the combination of olanzapine and fluoxetine (Selle et al., 2014). It is important to note here that management of bipolar depression may vary from country to country with certain drug choices being considered first line and combination of drugs favored over others. Fig. 2 is an example of managing a patient with bipolar depression in Australia and New Zealand.

The diagram illustrates the potential binary combinations between second-generation antipsychotics (SGAs), mood-stabilizing agents (MSAs), and antidepressants (ADs) when considered appropriate. Lithium (Li+) and ADs can be added to all agents, but each has one exception: olanzapine and lamotrigine (La), respectively. The combination of SGAs with each other has no confirmed benefits in efficacy, but MSAs may usefully be combined, provided one is lithium. The combination of lithium and lamotrigine carries the complication of increased blood levels of both medications, making close monitoring critically important. "+" means that agent can be added, "−" means that it should not be added.

Switching

The occurrence of mania and hypomania in people receiving antidepressant therapy may be an adverse effect of treatment with tricyclic antidepressants and dual-action agents, e.g., venlafaxine, which carry a greater risk than single-action drugs (Gijsman et al., 2004; Tondo et al., 2010). Risk is higher with tricyclic antidepressants compared to SSRIs.

Choosing Maintenance

Following remission of an episode, patients generally require maintenance treatment to delay or prevent another episode. Successful long-term management requires both pharmacological and psychological interventions. In long-term treatment, the first decision point occurs at the transition from acute to continuation treatment (up to 6 months after). Antidepressants should also only be used in the short term and continued if the risk of severe depressive relapse is high. In the long-term management of BD I antidepressants should be combined with a mood stabilizer.

The second decision point occurs at the transition from continuation to maintenance treatment. At this point, efficacy of treatment should be assessed. The gold standard of maintenance is monotherapy; however, this is often an elusive goal. Most individuals require more than one medication long-term to maintain mood stability. Generally, maintenance pharmacotherapy consists of the same regimen that successfully treated the acute episode (National Institute for Health and Care Excellence, 2014a; Yatham et al., 2013). Options for maintenance therapy include lithium, valproate, olanzapine, quetiapine, lamotrigine, risperidone, and aripiprazole.

What's Coming Up in Pharmacological Management

Overall, advances in drug treatment for BPAD remain quite modest. Advances in pharmacological treatment have come mainly from the repurposing of drugs used in other neuropsychiatric disorders and do not target the mood instability that characterizes the disorder.

Cariprazine is a potent D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors. Cariprazine appears promising for the treatment of acute mania—it is approved in Europe for schizophrenia and has demonstrated efficacy in manic and mixed/manic states in BPAD I in Phase III clinical trials (Sachs et al., 2015) but has not yet been approved by Canadian or US regulatory agencies. It is also being evaluated in Phase II trials for bipolar depression (Durgam et al., 2016).

Novel or Experimental Agents

Preliminary data are available to support novel treatments not previously investigated in patients with bipolar depression, including ketamine and armodafinil. Patients receiving a single ketamine infusion experience rapid reduction of depressive symptoms and suicidal ideation (within 40 min), with the improvement remaining significant through day 3 (Diazgranados et al., 2010; Zarate et al., 2012). Adjunctive armodafinil— the longer-lasting R-enantiomer of modafinil – has been associated with an improvement in depressive symptoms according to some, but not all, measures (Calabrese et al., 2010). While ketamine is more widely accepted as a rapid antidepressant treatment, armodafinil is still regarded as experimental and both agents require further study in the context of BPAD.

Monitoring and Measuring

Regular contact with health professionals is essential for appropriate management, but the frequency of visits can vary considerably, and rapid access for additional consultations when early warning signs are emerging, should be allowed for. The frequency of contact is usually not less than biannual visits once long-term stability is achieved. Follow-up is more frequent depending upon the history of the illness and time since the last mood episode.

People with bipolar disorder are at increased risk of morbidity and mortality because of mental health complications (such as increased suicide risk) as well as physical complications such as type 2 diabetes, obesity, and cardiovascular disease. It is also important to monitor the adverse effects of antipsychotics and antidepressant medication as these can lead to the person stopping medication and relapsing. More frequent reviews are recommended if the person has sleep disturbance or following stressful life events on the basis that both may trigger an acute episode, and sleep disturbance is an early symptom of a depressive or hypomanic/manic episode.

Treatment Nonresponse

It is important to assess the patient's symptoms through self-report, observation, and corroboration from family in order to understand the patient's entire disease process. Observation by health professionals is an essential source, and an overall pattern of subtle core manic signs and symptoms may only be apparent when assessed continuously over hours or days and even weeks. Furthermore, the nature of nonresponse might extend beyond the persistence of core manic symptoms to comorbidity, such as substance abuse and lack of compliance with treatment.

Routine investigations should be repeated, e.g., full blood count, electrolyte levels, renal, liver, and thyroid function tests along with (if indicated) neuroimaging and urine screen for substances to determine whether there are rare organic reasons for nonresponse.

Strategies to address nonresponse may include (Malhi et al., 2015) the following:

- Addressing adherence: medication administration and blood levels should be checked when available (this is covered more in the "Role of the Pharmacist" section).

- Changing medication: switching to a different anti-manic or SGA can be effective. However, prior to switching, doses of existing agents should be maximized in case of "pharmacokinetic" treatment resistance and should not be abruptly stopped but tapered down over a period of 4 weeks.
- Combination therapy: combining an SGA with lithium or valproate is a common strategy. Conventional treatments have also been combined with hormonal therapies, e.g., tamoxifen, hormone-replacement therapies, in the treatment of mania.
- ECT: can be highly effective in refractory mania and can be useful in the management of treatment-resistant mania where there is direct threat to the person's life.

Ongoing subsyndromal depressive symptoms are common in BPAD, as is a high rate of treatment nonresponse. Data suggest that the absence of early improvement (2–3 weeks) may be a reliable predictor of eventual nonresponse, suggesting that these patients may benefit from a change in therapy (Kemp et al., 2011).

Role of the Pharmacist in Managing and Prescribing in BPAD

Pharmacists are an integral part of the multidisciplinary team who can add value to patient care beyond medicines management and pharmaceutical care. Many patients seek the views of a pharmacist for an unbiased "neutral" opinion of medication since the pharmacist is not involved in direct medication supervision and administration of medicines. Pharmacists are well-placed to support patients in making informed choices about their treatment, thus in some ways, acting in a patient advocacy role.

The Pharmacist in the Multidisciplinary Team

Pharmacists are considered experts in medicines and bring a unique skill set that complements those in the multidisciplinary team (Rubio-Valera et al., 2014). While there are differences in the role of a pharmacist depending on the health-care setting; in general, pharmacists provide (Harms et al., 2017; McMillan et al., 2017) pharmaceutical input broadly in two key areas:

- Improving adherence and facilitating informed consent (through *education* and addressing barriers to *adherence*)
- Optimizing pharmaceutical care (through *maximizing efficacy* and *reducing or managing adverse effects* of treatment and ensuring medication safety)

These aspects will be discussed in further detail below.

In a hospital setting, pharmacists are routinely involved in reconciling medicines on admission, confirming previous treatments trialed and ensuring the most appropriate treatment for managing the acute presentation. This may include optimizing treatments to achieve control of mania and depression, managing any acute behavioral disturbance, and advice around the use of parenteral medication to manage the acute presentation. In the short- to medium-term, the pharmaceutical goals will shift toward stabilization of the patients' medication(s) before discharge. Key points for pharmacists to consider include optimizing medication formulation and regimen to encourage adherence, therapeutic drug monitoring, reviewing funding and supply of medication on discharge, discharge medicines reconciliation, psychoeducation, and liaison with the community care team (including the pharmacy team in community) to ensure continuity of care.

Improving Adherence and Facilitating Informed Consent

Education—Shared care/decision-making

Receiving and understanding information about the medicines prescribed is an essential part where the pharmacist can add value. Despite the availability of various medication information, patients often report not receiving sufficient information and express a desire for more (Bowskill et al., 2007); one study found patients with BPAD were significantly less satisfied with information about their medication than people prescribed medication for HIV (Bowskill et al., 2007).

In order to achieve treatment goals, patients should be involved in shared decision making, which can increase patient satisfaction, adherence, and improve therapeutic relationships (Younas et al., 2016). Purely educational interventions have been shown to be ineffective in changing patient behavior and modifying adherence (Dolder et al., 2003). A shared decision-making approach is recommended by international treatment guidelines in BPAD, which state that patients should have the opportunity to make informed decisions about their care and treatment in partnership with their health-care professionals (Hasan et al., 2013; Malhi et al., 2015; National Institute for Health and Care Excellence, 2014a, 2014b).

Medication education delivered by pharmacists is in collaboration with psychiatrists, in an outpatient setting, can have a significant impact on improving adherence and quality of life (Mishra et al., 2017). Education should deliver information about their medication and BPAD and give personalized advice on adherence that is tailored to the patient's reasons for nonadherence.

One example of an education model that has demonstrated effectiveness for improving adherence, symptom-management, and risk of relapse are medication education or psychotherapy groups (Swartz and Swanson, 2014) (see **Box 1**).

Box 1 Medication education groups in mental health

Medication education or psychotherapy groups have been run in community and inpatient settings by pharmacists. A format for these groups have been proposed by the United Kingdom Psychiatric Pharmacy Group (UKPPG) guidelines—the education sessions involve discussion of the neuropharmacological basis of various mental health conditions and how psychotropics (including antipsychotics, antidepressants, mood stabilizers, and benzodiazepines) are thought to work (explanation of neurotransmitters and associated imbalances), the how and why of side effects, the need for long-term treatment adherence, and issues of dependence and tolerance. A recent pilot study investigating the effectiveness of these groups found a positive impact on patient understanding of the purpose and side effects of their medication, and their perceptions of involvement in decisions about their medicines (White et al., 2017). The positive effects demonstrated support the implementation of these pharmacist-led education groups as part of pharmaceutical care of patients.

Improving Adherence

Medication nonadherence is a major issue in patients with BPAD (Bates et al., 2010) with over a third of patients missing at least one dose of medication in a 10-day period (Baldessarini et al., 2008). While there have been many studies that have considered factors predicting nonadherence in BPAD, such as gender or ethnicity, no single sociodemographic factor or group of factors have been consistently shown to be predictive of nonadherence (Bates et al., 2010). Medication nonadherence is driven by patient-centered experiences such as their satisfaction with treatment (Bates et al., 2010), experiences of side effects (Johnson et al., 2007), and their beliefs about the treatment (Clatworthy et al., 2007), as well as practical adherence barriers (White et al., 2017). Effective pharmacist adherence interventions and education should target both practical and perceptual adherence barriers (White et al., 2017).

Addressing Practical Barriers

Pharmacists have expert knowledge of different formulations and dosing, which can be a key in simplifying dosing regimens and facilitating informed choice to improve adherence. An example is lithium or antipsychotics; rather than prescribing as twice daily they can be prescribed once daily (Malhi and Tanious, 2011).

Building a routine around medication taking can be helpful—for example, linking medication taking to particular habits such as placing the morning medication near the toothbrush. "Interpersonal and social rhythm therapy," which focuses on maintaining regular daily rhythms in activities such as sleeping, waking, eating, and exercise, can also have positive impacts on quality of life, symptoms and adherence, suggesting that having a structured routine may be helpful (Frank et al., 2005).

External reminders such as alarms and medication organizers can increase the ease of medication taking and improve adherence by reducing some of the cognitive effort of needing to take a medication regularly (Depp et al., 2008).

Addressing Perceptual Barriers

Many patients with BPAD have elements of both unintentional and intentional nonadherence (Clatworthy et al., 2007). In unintentional nonadherence, the patient inadvertently does not take medication as prescribed. In intentional nonadherence, the patient deliberately does not adhere; this could be due to lack of insight about their condition and views about treatment (treatment beliefs), perception of the illness, and attitude toward medication (side effect burden) (Clifford et al., 2008).

Pharmacists should consider these beliefs when addressing adherence (Lingam and Scott, 2002; Petrie and Weinman, 2012; Scott and Pope, 2002). These beliefs may be influenced by social networks (Sajatovic et al., 2011); establishing an effective therapeutic alliance may combat some of the negative effects of such social networks and help foster more positive beliefs and perceptions (Chakrabarti, 2016; Lingam and Scott, 2002; Strauss and Johnson, 2006).

Optimizing Pharmaceutical Care

Optimizing Treatment Efficacy

Beyond education and improving adherence, pharmacists can optimize patient treatment efficacy through addressing stigma, or minimizing system-related factors that prevent access to optimal treatment (Chakrabarti, 2016).

Pharmacists can help ensure continuity of care by acting as a point of liaison between primary care, hospital, and psychiatrists around medication-related issues. This can include handing over treatment and monitoring plans, sharing decisions made by the previous treating team around medication choices to prevent duplication of any ineffective treatment trials and/or poorly tolerated treatments, and ensuring adequate supply of medication that may be difficult to source or afford.

Over adherence, where patients take more medication than prescribed, can occur in BPAD, particularly in those patients at risk of substance abuse or addiction (Weiss et al., 1998). Benzodiazepines, neuroleptics, such as quetiapine, and tricyclic antidepressants are considered high-risk medicines. Facilitating communication between the different health-care professionals involved in the patient's care can minimize this risk.

Deprescribing and addressing polypharmacy in BPAD or more broadly mental health patients (Gupta and Cahill, 2016) is also key. Many medications are started in the acute setting to achieve remission and manage acute behavioral disturbance. These medications are at risk of being continued beyond the required period of treatment, partly due to the reluctance of community and primary care teams changing what appears to be a stable regime. Pharmacists can facilitate liaison between primary care and hospital teams, providing education and advice around safe deprescribing of unnecessary medication. Deprescribing within

Table 2 Deprescribing psychotropic medications

Step 1: Choose the right time
Step 2: Compile a list of all the patient's medications (medication reconciliation)
Step 3: Initiate the discussion with the patient
Step 4: Introduce deprescribing to the patient
Step 5: Identify which medication would be most appropriate for a taper
Step 6: Develop a plan
Step 7: Monitor and adapt, if necessary

Source: Adapted from Gupta and Cahill (2016)

psychiatry itself is a relatively new area, and Gupta et al. have proposed some guidelines, which describe steps to deprescribing (**Table 2**).

Patients on multiple medications have increased risk of medication interactions, which can be particularly problematic in BPAD as many BPAD treatments are considered high risk for interactions, partly because of the narrow therapeutic index. Checking for interactions whenever a new medication is started, and deprescribing, can minimize harm.

Side Effect Management

Managing side effects is a key to ensuring ongoing adherence, relapse prevention, patient satisfaction, and quality of life. Patients are more likely to be dissatisfied with treatments that cause weight gain, extrapyramidal side effects, sexual dysfunction, and cognitive side effects (Johnson et al., 2007; Zarate, 2000), but are more likely to take medication, which can help reduce the severity of depressive episodes (Johnson et al., 2007). The pharmacist is well-placed to advise on side effect profiles and may often be the first person to see side effects or be aware that a patient's presentation is related to medication use. The pharmacist can help with discussing treatment options with the patient, facilitating informed choice, and negotiating treatment options with the clinical team to ensure the best treatment options, which ensure both clinical efficacy, and patient satisfaction and long-term adherence to treatment.

Special Populations

Children and Adolescents

Due to limited studies in youth, most of the treatment recommendations for BPAD are derived from the adult literature. Evidence supporting the efficacy of these medications is increasing; however, significant gaps remain.

The mainstay of treatment of BPAD in children and adolescents is pharmacotherapy. Aripiprazole is first-line treatment because it is licensed in adolescents (over 13 years) with BPAD. There is some research that other SGAs, valproate, and lithium are efficacious in adolescents (Goodwin et al., 2016). Although patients may respond to monotherapy, combination pharmacotherapy is necessary for some patients (McClellan et al., 2007). When offering treatment to young people, their cognitive ability, emotional maturity, developmental level, their capacity to consent to treatment, the severity of their bipolar disorder, and risk of suicide or self-harm or any other risk must be taken into account (National Institute for Health and Care Excellence, 2014a).

Adjunctive psychotherapy is generally regarded as essential to provide families with an understanding of symptoms, course, and treatment, teach youth and parents methods for coping with symptoms, and prevent relapse (Fristad and MacPherson, 2014).

Women of Childbearing Age

For women planning to conceive, an integrated care plan should be developed. Where possible, this should involve the individual, their partner/family/carer, primary and secondary care teams (obstetrics, psychiatry), pharmacists, and midwives and outline the care and treatment during pregnancy and the postnatal period (National Institute for Health and Care Excellence, 2017).

Valproate and carbamazepine have established teratogenic effects in humans—known as fetal valproate syndrome or fetal carbamazepine syndrome, respectively. Valproate should not be offered to women of childbearing potential, or pregnant women without specialist advice (National Institute for Health and Care Excellence, 2014a). If valproate treatment cannot be avoided, adequate contraception should be ensured. The patient should be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate and carbamazepine, and prophylactic folic acid should be prescribed to reduce the incidence of neural tube defects (Drug Safety Update, 2015).

Approximately 20%−−50% of women with BPAD relapse postpartum; therefore, prophylactic treatment is recommended immediately postpartum to decrease the risk of relapse (Viguera et al., 2002). Prophylactic medications such as lithium or valproate can prevent postpartum episodes in women with BPAD (American Psychiatric Association, 2002). When lithium is used during pregnancy, it should be tapered to the lowest effective dose necessary to decrease the risk of relapse.

If the woman would like to breastfeed and is taking medications to treat BPAD, specialist's help and advice should be sought. Lithium is present in significant amounts in breast milk; most experts therefore recommend against lithium use in breastfeeding (American Academy of Pediatrics Committee on Drugs, 2000; American Psychiatric Association, 2002; Ernst and Goldberg, 2002).

Valproate has been used widely in mothers who breastfeed; reports of toxicity in infants from ingestion of valproate in breast milk are rare (Dodd and Berk, 2004). Evidence suggests that the exposure of infants to valproate by breastfeeding is low (Tsuru

et al., 1988), and that, in most cases, the benefits of breastfeeding outweigh the risks; however, vigilance against hematological adverse events in the infant is required.

Carbamazepine and its active metabolite are poorly excreted into breastmilk, partly due to plasma protein binding. The serum level in infants is usually low, and it is considered compatible with breastfeeding (American Academy of Pediatrics Committee on Drugs, 2001).

Older-aged Patients

General principles for managing mania in older patients are similar to those for younger patients. Older patients will generally require lower doses, since aging is associated with reduced renal clearance and volumes of distribution (Sproule et al., 2000). Concomitant medications and other medical conditions may also alter the pharmacokinetics (Young and Klerman, 1992); older patients may also be more sensitive to side effects. Many elderly patients may respond to low serum levels of lithium (0.4–0.6 mmol/L) (Van Gerpen et al., 1999).

Older patients may be more likely to develop cognitive impairment with medications such as lithium and benzodiazepines (Van Gerpen et al., 1999). They may also have difficulty tolerating antipsychotic medications and are more prone to extrapyramidal side effects and tardive dyskinesia than younger patients (Caligiuri et al., 2000). Furthermore, due to age-related changes in pharmacokinetics and pharmacodynamics, there is an increased risk of cardiovascular and cerebrovascular accidents (Gareri et al., 2014).

Summary

The medicines expertise of pharmacists is invaluable in optimizing patient pharmaceutical care and improving quality of life. The importance of the pharmacist in managing BPAD is clear from the literature. Benefits are seen throughout all aspects of the patient's treatment journey, from the acute presentation to longer-term care. The pharmacist is a key part of the patient's multidisciplinary team and can add value to the therapeutic alliance by providing impartial medicines information to support informed consent and choice.

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Major Depressive Disorder

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Learning Objectives

- Describe the incidence, prevalence, epidemiology, and etiology of major depressive disorder (MDD).
- Briefly outline the signs and symptoms of MDD.
- Explain the pharmacological and nonpharmacological management options for MDD.
- Describe the first- and second-line treatment options for MDD and what options can be considered when usual first-line treatments fail.
- List the most common side effects and interactions associated with antidepressants and how to manage these.
- Describe the role of the pharmacist in managing MDD and give examples where pharmacists can contribute to the pharmaceutical care.

Take-Home Messages

- Major depressive disorder (MDD) is a common mental health disorder, which can cause significant disruption to individuals, their families and carers, workplace, and society.
- The use of antidepressant medicines in people with MDD remains the mainstay of therapy, alongside behavioral therapy.
- Pharmacists play an integral role in the multidisciplinary team for MDD management.

- Key opportunities to optimize pharmaceutical care for patients include improving medication adherence, and advice on switching, tapering, and discontinuation of medicines.
- In the future, pharmacists may be routinely involved in targeted screening services for depression in primary care; however, this would need to be coupled with training, the use of validated screening tools and resources, including private areas to conduct this screening, time, and up-to-date information. More research needs to be conducted on this avenue.

Introduction to the Condition

Major depressive disorder (MDD) is one of the most prevalent mental health disorders. According to the World Health Organization, it is the leading cause of ill health and disability (World Health Organization, 2017a, 2018). The proportion of the global population living with depression is estimated to be 322 million people—4.4% of the world's population (World Health Organization, 2017b). The number of people living with depression has increased by 18.4% between 2005 and 2015, and depressive disorders were the single largest contributor to nonfatal health loss globally in 2015. At its worst, depression can lead to suicide. Close to 800,000 people die due to suicide every year (World Health Organization, 2012).

MDD is characterized by: "a depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration" (World Health Organization, 2012). Symptoms should be present for at least 2 weeks and at sufficient severity for most of every day. MDD has an enormous impact on the individual and their family. Emotional and physical well-being can be affected, in addition to social functioning and the economic burden caused by the condition. The economic impact of MDD on patients and society has been reported to be 4.2 times higher than a nondepressed patient (Simon et al., 2001; World Health Organization, 2003). The overall economic burden (medical costs, suicide-related mortality costs, and workplace costs) was estimated to be $US 83 billion in the United States in 2000. This cost was comprised of direct medical costs, suicide-related mortality costs, and workplace costs (Greenberg et al., 2003).

Despite the huge impact that depression has on every aspect of the person and society, many people do not seek help. It is reported that men are less likely to ask for help than women, and only 25% of men who suffer from anxiety or depression actually access treatment (Beyond Blue, 2008).

This chapter will provide an overview of the current thinking around treatment on MDD for pharmacists, beginning with an overview of diagnosis and presentation of the condition, followed by a discussion of treatment options and the role of pharmacists and how they can contribute to the management MDD.

Epidemiology of MDD

MDD is highly prevalent through the world and the prevalence has increased over time (Andrade et al., 2003). A survey of epidemiological data in 14 countries in the World Health Organization (WHO) World Mental Health Survey Initiative estimated the lifetime prevalence of major depression and persistent depressive disorder (dysthymia) in adults to be 12% (Kessler et al., 2011).

The prevalence of MDD is approximately two times greater in females compared with males (Pedersen et al., 2014), and higher in high-income versus low/middle-income countries (Kessler and Bromet, 2013). Prevalence rates also vary by age, peaking in older adulthood (above 7.5% in females aged 55–74 years, and above 5.5% in males aged 55–74 years). Depression also occurs in children and adolescents below the age of 15, but at a lower level than older age groups (World Health Organization, 2017b).

Etiology of MDD

Despite advances in the understanding of the neurobiology of MDD, currently no established mechanism can explain all aspects of the disorder; it is multifactorial and complex. There is thought to be an interaction between individual vulnerability and environmental stressors (New Zealand Guidelines Group, 2008). This may explain the wide variation in clinical presentation and response to treatment.

Various mechanisms, theories, and hypotheses have been proposed to help explain the pathophysiological basis of depression, including (Jesulola et al., 2018; Otte et al., 2016):

- The biogenic amine hypothesis: monoaminergic systems (noradrenergic, serotonergic, and dopaminergic) are instrumental to many behavioral symptoms of depression, such as low mood, reduced motivation, fatigue, and psychomotor agitation or retardation. They are responsible for many fundamental brain functions and the "monoamine hypothesis" proposes that the reduced availability of these neurotransmitters may contribute to MDD.
- Neuroendocrine dysfunction: several endocrine system abnormalities have been identified as possible contributors to the etiology of MDD. These include altered growth hormone levels, thyroid abnormalities, and hypothalamus-pituitary-adrenal axis dysfunction.
- Environmental and genetic factors: heritability for MDD has been quantified as approximately 35%. Other relevant genetic variants can also confer risk or protection; a "stress vulnerability" model has been described whereby stressful situations may

trigger depression in vulnerable or susceptible individuals, but not in others who display protective traits. These situations, or life events, may include, for example, work stress, loss of employment, relationship loss, or grief.

There are many other contributors including neurogenesis, neuroinflammation, elevated levels of corticotrophin-releasing factor, and abnormalities of second messenger systems. Full discussion of these factors—and the combinations and linkages between them—is beyond the scope of this chapter; for a comprehensive review, please see Jesulola et al. (2018).

Diagnosis of MDD

The essential features of depression are depressed mood (dysphoria) and/or loss of pleasure in most activities (anhedonia). Severity of the disorder is determined by the number and severity of symptoms, as well as the extent of functional impairment.

Definition/Classification of MDD

Depression is a heterogeneous disorder in which a number of underlying presentations may share a common phenomenology. A number of classification systems/subgroupings have been used; two frequently used classification systems are the International Classification of Diseases (ICD) 10th edition and Diagnostic and Statistical Manual for Mental Disorders (DSM) 5th edition. The ICD and DSM are both operational diagnostic systems that classify behavioral and psychological disorders (American Psychiatric Association, 2013; World Health Organization, 1992).

The ICD has been endorsed by the WHO as a standard diagnostic tool for epidemiology, health management, and clinical purposes of all diseases and other health problems. It classifies "mood disorders" as part of "mental and behavioral disorders." Within the cluster of mood disorders, depression is mentioned as a "depressive episode" or a "recurrent depressive disorder," defined as (Cesar and Chavoushi, 2013):

- *Depressive episode:* In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day-to-day, is unresponsive to circumstances, and may be accompanied by so-called somatic symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate, or severe.
- *Recurrent depressive disorder:* A disorder characterized by repeated episodes of depression as described for depressive episode (see above), without any history of independent episodes of mood elevation and increased energy (mania). There may, however, be brief episodes of mild mood elevation and over-activity (hypomania) immediately after a depressive episode, sometimes precipitated by antidepressant treatment. The more severe forms of recurrent depressive disorder have much in common with earlier concepts such as manic-depressive depression, melancholia, vital depression, and endogenous depression. The first episode may occur at any age from childhood to old age, the onset may be either acute or insidious, and the duration varies from a few weeks to many months. The risk that a patient with recurrent depressive disorder will have an episode of mania never disappears completely; however, many depressive episodes have been experienced. If such an episode does occur, the diagnosis should be changed to bipolar affective disorder.

Unlike the ICD, the DSM only classifies mental disorders. Within the cluster of "mood disorders," depressive disorders are further specified as a "single major depressive disorder," "recurrent major depressive disorder," "dysthymia," or as a "depressive disorder not otherwise specified" (Cesar and Chavoushi, 2013).

Signs and Symptoms

A formal diagnosis using the ICD-10 classification system requires at least 4 out of 10 depressive symptoms, whereas the DSM-V system requires at least five out of nine (**Table 1**). Symptoms should be present for at least 2 weeks, and each symptom should be present at sufficient severity for most of every day. Both diagnostic systems require at least one (DSM) or two (ICD) key symptoms to be present: low mood/loss of interest or pleasure (both ICD and DSM) and loss of energy (ICD only).

It is being increasingly recognized that depressive symptoms below the DSM and ICD threshold criteria can be distressing and disabling if persistent. Therefore, the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence, 2016) guidelines cover "subthreshold depressive symptoms," and are defined as at least one key symptom of depression but with insufficient other symptoms and/or functional impairment to meet the criteria for full diagnosis.

Treatment of MDD

In the management of MDD, there are two main initial treatment options: psychotherapy and pharmacotherapy. The goal of treatment in those diagnosed with depression is to achieve remission of symptoms and prevent relapse. Interventions for MDD comprise a range of therapies, including exercise and self-management, psychological therapies, pharmacological treatments, and

Table 1 Definition of MDD according to DSM-5

- An individual will show five (or more) of the following symptoms, which should be present during the same 2-week period nearly every day and should represent a change from previous functioning:
  - Depressed mood[a]
  - Markedly diminished interest or pleasure in all, or almost all, activities[a]
  - Considerable weight loss when not dieting, weight gain, or decrease or increase in appetite
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue or loss of energy
  - Feelings of worthlessness, or excessive or inappropriate guilt, which might be delusional; that is, not merely self-reproach or guilt about being sick
  - Diminished ability to concentrate, or indecisiveness
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan; the individual has made a suicide attempt or a specific plan for committing suicide
- The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
- The episode is not attributable to the physiological effects of a substance or to another medical condition
- The occurrence of the episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other psychotic disorders
- The individual has never had a manic episode or hypomanic episode

[a]Depressed mood and/or diminished interest or pleasure must be evidence for a diagnosis.

Table 2 The stepped-care model

Focus of the intervention	*Nature of the intervention*
Step 1 All known and suspected presentations of depression	Assessment, support, psychoeducation, active monitoring, and referral for further assessment and interventions
Step 2 Persistent subthreshold depressive symptoms; mild-to-moderate depression	Low-intensity psychological interventions, psychological interventions, medication, and referral for further assessment and interventions
Step 3 Persistent subthreshold depressive symptoms or mild-to-moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high-intensity psychological interventions, combined treatments, collaborative care, and referral for further assessment and interventions
Step 4 Severe and complex depression; risk to life; severe self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional, and inpatient care

Source: Adapted from National Institute for Health and Care Excellence, 2016. Depression in adults: recognition and management

intensive interdisciplinary interventions (New Zealand Guidelines Group, 2008). The consensus among different guidelines is that individuals with moderate-to-severe MDD should be treated with medication or with a combination of medication and psychotherapy (National Institute for Health and Care Excellence, 2016; Cleare et al., 2015; Gelenberg, 2010). In contrast, a mild depressive episode may be treated with psychotherapy alone (Otte et al., 2016). However, when deciding on the clinical management, individual preferences and prior treatment history should be taken into consideration.

Stepped Care

The stepped care model provides a framework in which to organize the provision of interventions. Under this model, the least intrusive, most effective intervention is provided first; if a person does not benefit from, or declines, the initial intervention, he or she is offered an alternative intervention from the next step (**Table 2**).

Pharmacological Treatment

Although trial data support some differences in the efficacy and tolerability between antidepressant medicines, their effectiveness is generally considered comparable between and within classes of medications, although individual response may vary markedly (Cipriani et al., 2018). Therefore, the choice of antidepressant will largely be based on:

- Individual preference
- Nature of prior response to medications
- Safety, tolerability, and anticipated side effects

- Concomitant psychiatric or general medical conditions
- Pharmacological properties of the medication, for example, half-life, actions on cytochrome P450 enzymes, other drug interactions
- Cost and availability of formulations

First-Line Therapy

Selective serotonin reuptake inhibitors

For most indications, selective serotonin reuptake inhibitors (SSRIs) are considered first-line, as they are generally well tolerated and have a wider safety margin than other classes of antidepressant medicines. However, SSRIs do have some potentially troublesome side effects, including initial nervousness, insomnia, nausea, sexual dysfunction, and weight gain (Gartlehner et al., 2011; Serretti and Chiesa, 2009; Sinclair et al., 2009). These are particularly troublesome when first starting treatment but tolerance to these effects usually occurs after 4–6 weeks of treatment.

The principal agents within the SSRI class have the same major pharmacologic feature: selective and potent inhibition of the serotonin transporter (SERT). However, each SSRI has secondary pharmacologic actions other than SERT blockade, and no two SSRIs have identical secondary characteristics (Stahl, 2013):

- Fluoxetine has additional $5HT_{2C}$ antagonist actions, which disinhibits the release of noradrenaline and dopamine. This may contribute not only to its therapeutic action but also to its tolerability profile.
- Sertraline has dopamine reuptake inhibition and sigma-1 receptor binding properties. Its sigma-1 binding properties may contribute to its anxiolytic actions. The clinical relevance of dopamine reuptake inhibition to anxiolytic effects is unknown; however, it is possible that dopaminergic action is associated with lower risk of sexual side effects and hyperprolactinemia, compared to other SSRIs (Park, 2017).
- Paroxetine has muscarinic anticholinergic properties as well as noradrenaline reuptake inhibition. This SSRI is preferred by many clinicians for patients with anxiety symptoms; it tends to be more calming early in treatment compared to fluoxetine and sertraline. However, of the SSRIs, paroxetine is most associated with serotonin syndrome and discontinuation syndrome due to its very short half-life.
- Fluvoxamine binds to sigma-1 receptors but its action is more potent compared to sertraline, which may contribute additional anxiolytic effects. Of the SSRIs, it is one of the weakest inhibitors of dopamine and norepinephrine reuptake (Ordacgi et al., 2009). However, it is associated with higher incidence of adverse effects than other SSRIs, particularly gastrointestinal effects, and has the potential for P450-mediated drug interactions (Irons, 2005).
- Citalopram is comprised of two enantiomers, *R* and *S*, one of which is the mirror image of the other. The racemic mixture has mild antihistaminic properties attributed to the *R*-enantiomer. This may be responsible for some of its sedating properties. It is generally one of the better-tolerated SSRIs; however, there is potential for Q_{Tc} prolongation at high doses. Removing the *R*-enantiomer from the mixture leaves the pure active *S*-enantiomer, known as escitalopram. Escitalopram lacks antihistaminic properties and, while the risk of Q_{Tc} prolongation appears to be similar to citalopram, the magnitude of this side effect in practice is less than citalopram. See drug interactions section for additional detail about this effect.

Some improvement is usually evident within 2 weeks of treatment with an antidepressant medicine at a therapeutic dose. If there is a partial response after 3–4 weeks of treatment, the dose of medication can be increased (Trangle et al., 2016). If the individual does not respond to treatment, that is, report a significant level of improvement by 4–6 weeks, the treatment plan should be reviewed with the individual. Options include increasing the dose, changing the medicine, changing to a psychological therapy, or adding a psychological therapy (Irish College of General Practitioners, 2006; National Institute for Health and Care Excellence, 2016; New Zealand Guidelines Group, 2008).

If the individual opts to change to a different antidepressant medicine, either a second SSRI, another class of serotonergic reuptake inhibitor or a tricyclic antidepressant (TCA) is suitable as a second-line option.

Second-Line Therapies

Serotonin–noradrenaline reuptake inhibitor

Serotonin–noradrenaline reuptake inhibitors (SNRIs) primarily act upon serotonergic and noradrenergic neurons and are often referred to as "dual action agents." SNRIs differ in their affinity for the serotonin and noradrenergic transporter. Venlafaxine and duloxetine are more potent inhibitors of serotonin reuptake than noradrenaline; however, this can depend on the dose administered. For example, venlafaxine is essentially an SSRI at 75 mg/day (Spina et al., 2012) but at higher doses, such as >150 mg/day, it has significant effects on the noradrenaline transporter (Debonnel et al., 2007). SNRIs have little or no effect on α_1-adrenergic, cholinergic, dopaminergic, or histaminergic receptors (Spina et al., 2012).

TCAs

SSRIs have generally replaced TCAs as first-line agents, not because of established differences in efficacy, but rather due to a generally more favorable side effect and safety profile. The TCAs are "broad spectrum" in that they interact with many neurotransmitter systems, which is the basis for their efficacy as well as side effects (Hirsch and Birnbaum, 2018a). TCAs block muscarinic M1,

histamine H1, and α_1-adrenergic receptors and can cause cardiac effects, anticholinergic effects, antihistaminic effects, decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor. TCAs are extremely dangerous in overdose; unlike SSRIs, TCAs can be fatal in doses as little as 10 times the daily dose (Schatzberg and Nemeroff, 2017). They are also cardiotoxic and should be avoided in susceptible individuals with heart disease. These factors generally make TCAs less tolerable compared with SSRIs and other newer antidepressants (Anderson et al., 2008). Nevertheless, many individuals use TCAs safely and effectively.

Other Treatments

Mirtazapine

Mirtazapine, an "atypical antidepressant," can be used as a second-line therapy when there is an inadequate response or an intolerable side effect with first-line medications. Mirtazapine is not a reuptake inhibitor; instead, it antagonizes presynaptic α_2-adrenergic receptors and postsynaptic $5HT_2$ and $5HT_3$ receptors, thereby increasing release of noradrenaline and serotonin. Additionally, mirtazapine also has high affinity for histamine H1 receptors (which may account for its sedative properties), and low affinity for cholinergic, α_1-adrenergic, and dopaminergic receptors (Hirsch and Birnbaum, 2018b). Mirtazapine can also be an appropriate choice for an individual with anxiety-predominant depression, and in elderly patients who have low body weight as it can help promote weight gain (Alam et al., 2013).

Bupropion

Bupropion is classified as a dopamine–noradrenaline reuptake inhibitor and is structurally related to amphetamine (Labbate et al., 2010). It inhibits presynaptic reuptake of dopamine and noradrenaline (with a greater effect upon dopamine). The drug has little effect upon other neurotransmitters, and little to no affinity for postsynaptic receptors. Bupropion appears to be associated with less risk of weight gain and sexual dysfunction compared to SSRIs, and can be mildly stimulating in some individuals (Hirsch and Birnbaum, 2018b).

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are now rarely used because of their relatively extensive side-effect profile, drug–drug interactions leading to severe adverse effects such as hypertensive crisis and serotonin syndrome. These potential side effects necessitate dietary restrictions and caution regarding drug–drug interactions. Many of the traditional "MAOI diets," which remain standard at numerous hospitals, are unnecessarily restrictive (Sullivan and Shulman, 1984), and many of the foods once thought to be dangerous for individuals taking MAOIs are now considered to be safe. However, foods containing high amounts of tyramine should be restricted, for example, aged cheeses and meats, sauerkraut, soybean products (including soy sauce), and tap beer. Health care professionals should monitor and advise on any recommended dietary restrictions (Sweet et al., 1995).

MAOIs have potent hypotensive effects, which is particularly important when treating elderly patients as they may be more sensitive to hypotensive effects and more likely to fall and sustain fractures (Hirsch and Birnbaum, 2018c).

Several compounds with selective MAO-a and MAO-b inhibiting properties have been developed, as well as reversible MAOIs, for example, moclobemide. These agents have less potential for interaction than irreversible agents such as phenelzine and tranylcypromine; however, MAOIs should only be initiated by psychiatrists familiar with their use (Hirsch and Birnbaum, 2018c).

Other antidepressant medicines

Some antidepressant medicines are distant from the other classes mentioned previously; they are often used in individuals who have inadequate responses or intolerable side effects to first-line treatments. Although there is some evidence for their use, additional comparative studies are need to better compare efficacy and safety with traditional agents and determine the best place in practice.

- Agomelatine is a synthetic analogue of melatonin and antagonizes $5HT_{2C}$ receptors; its effects appear to be marginally better than placebo is contraindicated in individuals with liver disease (Hirsch and Birnbaum, 2018b).
- Reboxetine was the first selective noradrenaline reuptake inhibitor used in the treatment of MDD; however, in a meta-analysis of active controlled trials, reboxetine was significantly less effective than other newer antidepressant medicines and had the highest dropout rates (Cipriani et al., 2018). A further meta-analysis showed that reboxetine showed no benefit over placebo and was inferior to other SSRIs for remission and response rates (Eyding et al., 2010).
- Vortioxetine is a serotonin modulator that acts as an antagonist at several subtypes postsynaptic serotonin receptors to inhibit the reuptake of serotonin (Hirsch and Birnbaum, 2018d). The downstream pharmacodynamic effects include increased levels of serotonin, acetylcholine, dopamine, and norepinephrine in specific areas of the brain (Sanchez et al., 2015). The safety and efficacy of vortioxetine have only been assessed in three published trials (D'Agostino et al., 2015); therefore, additional studies are needed to better compare with more traditional therapies.

Complementary and alternative medicine (CAM) therapies

There is increasing interest in the use of complementary and alternative medicine (CAM) therapies to treat depression. A recent study found that 40% of adults with depressed mood used CAM therapies, and most did not tell their physicians (Freeman, 2009). It is becoming more important for health professionals to proactively ask patients about use of CAM therapies.

St John's wort is an extract of *Hypericum perforatum* and it has been commonly used to treat depression since the 1980s. Its exact mechanism of action is unclear; however, it appears to inhibit serotonin reuptake and alter levels of dopamine, norepinephrine, and other neurotransmitters (Shelton, 2009). The efficacy and safety of St John's wort have been well established; short-term use of St John's wort is as effective as antidepressant medicines for mild to moderate depression (Linde et al., 2008). However, it is not recommended as a first-line treatment due to drug–drug interactions and varying levels of potency across different preparations (Cleare et al., 2015). St John's wort should not be combined with other antidepressant medicines, such as SSRIs, TCAs, or MAOIs, as this will increase the risk of drug-induced side effects such as serotonin toxicity. It also induces cytochrome P450 3A4 enzymes and intestinal P glycoprotein, and, therefore, interacts with many other medicines, including cyclosporine, warfarin, and HIV treatments (Izzo, 2004).

Limited evidence exists to support the use of other CAM therapies in depression, including omega-3 fatty acids, S-adenosyl methionine, folate, or L-methylfolate; therefore, they are not recommended as monotherapy treatment for MDD (Cleare et al., 2015; Nahas and Sheikh, 2011).

Antidepressant Prophylaxis

A single episode of depression should be treated for at least 6–9 months following full remission of symptoms (Anderson et al., 2008). If antidepressant therapy is stopped immediately on recovery, approximately 50% of individuals experience a return of their depressive symptoms within 3–6 months (Anderson et al., 2008; Reimherr et al., 1998). Of the individuals who have one episode of major depression, 50%–85% will go on to have a second episode, and 80%–90%, of those who have a second episode, will go on to have a third (Bauer et al., 2017). Therefore, NICE recommends that individuals who have had two or more episodes of depressions in the recent past, and who have experienced significant functional impairment during those episodes, should be advised to continue antidepressants for at least 2 years (National Institute for Health and Care Excellence, 2016). Doses for prophylaxis are the same as used for acute treatment (Anderson et al., 2008).

Refractory Depression

Refractory, or treatment-resistant, depression is difficult to treat successfully and outcomes are poor (Dunner et al., 2006). However, the evidence base has been substantially improved by the publication of the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) program. STAR-D was a pragmatic effectiveness study in which participants received first citalopram; participants who failed to remit were then entered into the continued study of sequential treatments (Fava et al., 2006; McGrath et al., 2006; Nierenberg et al., 2006; Rush et al., 2006; Trivedi et al., 2006). The results of STAR-D showed that treatment of refractory depression requires a flexible approach and that response to a particular treatment is not readily predicted by pharmacology or previous treatments. The program established bupropion and buspirone augmentation as worthwhile options, as well as T_3 augmentation and the use of nortriptyline.

Augmentation of antidepressant treatment with low-dose antipsychotics is also well supported by published literature. For example, quetiapine (300–600 mg/day) added to SSRI/SNRI (Anderson et al., 2009; Sagud et al., 2006), risperidone (0.5–2 mg/day) added to antidepressant (Mahmoud et al., 2007; Rapaport et al., 2006; Yoshimura et al., 2008), or aripiprazole (5–20 mg/day) added to antidepressant (Hellerstein et al., 2008; Marcus et al., 2008).

Switching Antidepressants

There are a number of strategies for switching between antidepressants (Jefferson, 2008; Luft, 2013; Taylor and Kapur, 2015). Close clinical observation and caution is required with all approaches, and individual patient factors and illness factors may require modification of a switching strategy.

- Conservative switch: the first antidepressant is gradually reduced and stopped. It is followed by a drug-free washout interval of five half-lives of the first drug before the new antidepressant is started according to its dose regimen. This strategy is most appropriate for primary care; the risk of drug–drug interactions is very low; however, there is a high risk of relapse as there is a prolonged period where the individual is without medication. Therefore, this method is not appropriate for high-risk individuals, and close monitoring is required.
- Moderate switch: the first antidepressant is gradually reduced and stopped. It is followed by a drug-free washout interval of 2–4 days before the new antidepressant is started at a low dose. This strategy may also be used in general practice; the risk of drug interactions is reduced, depending on the half-life of the first antidepressant.
- Direct switch: the first antidepressant is stopped and the second antidepressant is started the next day at the usual therapeutic dose. This strategy is quick; however, discontinuation symptoms may occur, depending on the pharmacological profile of the first antidepressant medicine. Moreover, there is a high risk of pharmacodynamic interactions, as both antidepressant medicines may affect similar neurotransmitter systems. This method requires clinical expertise and is only feasible in certain circumstances, for example, switching from one short half-life SSRI to another or in acute hospital settings where more intensive monitoring is possible.
- Cross-taper switch: the first antidepressant is gradually reduced and stopped while the second antidepressant is introduced at a low dose at some stage during the reduction of the first. The patient will be taking both antidepressants simultaneously; the dose of the second antidepressant is increased to the therapeutic dose when the first antidepressant has been stopped. This strategy is frequently used in patients with high risk of illness relapse; however, there is risk of drug–drug interactions and increased adverse effects from both medicines.

Withdrawing Antidepressants

Antidepressants should normally be withdrawn gradually over a 4-week period, although some individuals may require a longer period, particularly with drugs with shorter half-lives (e.g., paroxetine and venlafaxine). This is generally not required with fluoxetine because of its long half-life. Patients should be warned that they may experience withdrawal symptoms; however, these are usually mild and self-limiting. Common withdrawal symptoms for SSRIs are flu-like symptoms, "shock-like" sensations, dizziness, excessive dreaming, insomnia, and tearfulness. Withdrawal of TCAs can cause flu-like symptoms and insomnia. If discontinuation symptoms are severe, the patient may need to resume taking the original antidepressant medicine and taper the dose more gradually while monitoring symptoms (National Institute for Health and Care Excellence, 2016; New Zealand Guidelines Group, 2008).

Nonpharmacological Treatment

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) may be considered when all other treatments have failed or in life-threatening situations. ECT should only be considered a first-line treatment in MDD for urgent and emergency situations such as catatonia, high risk of suicide, or extreme levels of distress (Cleare et al., 2015; Otte et al., 2016). It requires hospitalization needs to be administered by specialists and usually requires hospital attendance. Although ECT is considered a safe treatment, it is associated with side effects, including effects on cognition, especially anterograde and retrograde amnesia, and heart rhythm disturbances.

Psychotherapy

There are many different forms of psychotherapy for MDD; each paradigm relies on different conceptual models and prescribed techniques that vary in their focus and methods. The most common forms include cognitive behavioral therapy (CBT), behavioral activation therapy, psychodynamic therapy, problem-solving therapy, interpersonal psychotherapy, and mindfulness therapy. In severe depression, there often needs to be pharmacological treatment to help an individual to a stage where he or she is able to engage with psychotherapy.

Emerging Treatments in MDD

There are numerous new approaches to the treatment of MDD including –

- Transcranial magnetic stimulation (TMS): a method of delivering brain stimulation using an electromagnetic coil. It is thought to activate regions of the brain that have decreased activity in MDD. A recent review of studies of standard repetitive TMS (rTMS) concluded that, for patients with MDD that failed treatment with at least two antidepressant medicines, rTMS is a reasonable and effective consideration (Gaynes et al., 2014). Although is it not associated with seizures and other risks and side effects of ECT, it is inferior with regard to efficacy (Ren et al., 2014). In contrast to rTMS, deep TMS (dTMS) modulates neuronal activity in deeper regions of the brain. One review concluded that, in patients with treatment-resistant depression, dTMS is effective as a monotherapy and as adjunctive treatment to other pharmacotherapy (Bersani et al., 2013).
- Glutamatergic drugs: a novel pharmacologic approach involves parenteral or intranasal delivery of ketamine or esketamine, which are *N*-methyl-D-aspartate (NMDA) receptor antagonists. A meta-analysis of 21 studies showed that a single intravenous infusion of ketamine can elicit a significant antidepressant effect from 4 h to 7 days in patients with MDD (Coyle and Laws, 2015). Another study using esketamine, which has a threefold to fourfold higher affinity of NMDA receptors, reported similar rapid onset of antidepressant effects (Singh et al., 2016). However, this treatment remains experimental as more adequately controlled studies are necessary.

Role of the Pharmacist

The goals of treatment in those diagnosed with depression are to achieve remission of symptoms and prevent relapse (Best Practice Advocacy Centre New Zealand, 2009a). Antidepressant medicines are often prescribed to individuals with moderate to severe depression (Best Practice Advocacy Centre New Zealand, 2009a, 2009b). Many patients are nonadherent to antidepressant medicines. Studies have reported that one-third of individuals discontinue their antidepressant treatment in the first month (Lin et al., 1995) and 50%–75% discontinue within 6 months of treatment initiation (Chong et al., 2011). Whilst this poor adherence may be due to the efficacy of the antidepressants, or the stigma that surrounds mental health, it also may be due to side effect and concerns that individuals have about treatment. Hu et al. (2004) studied a group of 401 patients who were prescribed an SSRI. They reported that 86% of patients experienced a side effect and over half of patients found at least one of their side effects bothersome (Hu et al., 2004).

Pharmacists, across different practice settings (e.g., community pharmacy, hospitals), are in the ideal position to discuss and provide support to patients, especially those who are initiating antidepressant therapy, swapping, or discontinuing medicines (Anderson, 2014; Rubio-Valera et al., 2014). Furthermore, it has been suggested by Boudreau, Capoccia (Boudreau et al., 2002) that effective drug management in patients with depression includes the provision of a group of services that can be effectively supplied

by a pharmacist; these services include: "patient education, medication selection, and appropriate dosing, enhancing medication compliance, monitoring treatment effectiveness, and identifying and managing of adverse effects" (Boudreau et al., 2002). Two randomized controlled trials focused on pharmaceutical care interventions in depression. Clinical outcomes measuring clinical severity in the intervention groups led to mixed results. One study found a significant difference in clinical measures (Marques et al., 2013), whereas the other did not (Rubio-Valera et al., 2013). The latter study, however, led to significant changes in quality of life, but not clinical severity.

In addition, evidence has indicated that the behavior of health-care professionals, including pharmacists, has the potential to have a substantial impact on antidepressant adherence (Chong et al., 2011). The majority of the studies have focused on the impact on adherence. Bultman and Svarstad (2002) interviewed individuals with depression regarding their interactions with pharmacists. While 75% reported that the pharmacist had asked if they had questions, only 54% said the pharmacist listened to their concerns. There is scope for pharmacists to advise individuals about potential side effects and what action to take and to advise clinicians about when antidepressants need to be tapered and switched; however, studies that have evaluated the effect of the pharmacist in these roles are scant.

Adherence

Nonadherence to medicines can be further divided into two categories: discontinuation or inconsistent administration (Chong et al., 2011). In regard to the latter, treatment with antidepressants requires consistent daily dosing, and some patients do not take their medication regularly. Nonadherence is a significant barrier to the success of the treatment (Chong et al., 2011).

Pharmacist involvement in patient education has resulted in improvements in patient satisfaction, adherence, and clinical outcomes. A systematic review, conducted by Chong and Aslani (Chong et al., 2011), evaluated pharmacist adherence interventions specific to individuals with depression. The interventions that were identified in the review were classified as educational, behavioral, and multifaceted interventions (i.e., that employed combinations of educational, behavioral, affective, and provider-targeted strategies). Forty-three percent of the interventions were successful at significantly improving outcomes, and these interventions were mostly multifaceted and involved mental health care specialists (Chong et al., 2011). The authors suggest that these findings highlight the need to target all dimensions affecting medication adherence problems—the patient, the healthcare provider, and the health care system to show benefit to patients (Chong et al., 2011). In another systematic review, Srimongkon et al. have reported on the psychometric properties of tools used to evaluate medication adherence in consumers with depression, using the ABC adherence framework, which conceptualizes adherence into initiation, implementation, and discontinuation phases. Specifically, this review points to the use of specific tools to measure adherence depending on the phase of adherence (Srimongkon et al., 2019).

Management of Side Effects

Antidepressant effect can be slow to onset; while some patients may feel some treatment response in the first 2 weeks, others may take up to 4–6 weeks to have an effect (Best Practice Advocacy Centre New Zealand, 2009b), and therefore many patients may experience side effects before treatment response. As mentioned, side effects can have a negative impact on individuals and cause a significant burden (Kelly et al., 2008). Talking to patients about expectations surrounding treatment response/effect is of utmost importance, since the occurrence of side effects can have a large impact on adherence (particularly leading to early discontinuation), quality of life, and treatment response. Each patient may view side effects differently, with some assigning greater importance to some side effects than others (Kelly et al., 2008). In addition, patients may have preconceived ideas about what side effects are, how they relate to treatment response (Uzun and Kozumplik, 2009), and the relationship between the side effects and medication efficacy. It is important therefore to understand the patient's thoughts and beliefs around side effects and offer reassurance about any preconceived notions. Factored in to suitability of an antidepressant is the treatment response that the patient is experiencing, as both response to treatment and side effects can differ between individuals (Best Practice Advocacy Centre New Zealand, 2009a, 2009b).

The type, frequency, and likelihood of when a side effect could emerge should be discussed. It is also important to discuss which side effects require prompt action versus those which are more than likely self-limiting. Written advice tends to be beneficial so that patients have something to refer to if side effects do occur. Discussion of potential side effects has not been associated with higher discontinuation rates (Hu et al., 2004); a study by Bull et al. (2002) reported that discussing adverse effects with patients is associated with less or equal rates of premature discontinuation and a higher rate of switching of medicines, which can be considered a favorable outcome if use of a different medication is associated with greater treatment continuation and symptom improvement (Bull et al., 2002; Kelly et al., 2008).

Pharmacists must be aware of an individual's ability to tolerate side effects; if a patient considers a side effect intolerable, they may discontinue treatment or reduce their dose of their own accord (Hu et al., 2004; Uzun and Kozumplik, 2009). *Patients must be advised not to do either of these without their health professional's advice*; symptoms of depression may return and withdrawal-like side effects may also occur (Kelly et al., 2008). It is imperative to ensure that patients are aware of potential side effects (both common and more rare but serious), and how to manage these, including when to seek help from their doctor (Kelly et al., 2008; Uzun and Kozumplik, 2009).

For specific antidepressant side effects, please consult individual drug monographs and the data sheets for prevalence. All recommendations concerning medications should be discussed with the patient's prescriber.

Nausea may occur with any antidepressant but it is most often associated with venlafaxine and SSRIs (Sienaert, 2014). Taking the medication with food can help alleviate nausea (MayoClinic, 2016; NPS MedicineWise, 2012; Sienaert, 2014). Other ways to reduce nausea include eater smaller meals more often, drinking plenty of fluids, sucking on sugar-free sweets (MayoClinic, 2016), and consuming ginger-containing food or beverages (Kelly et al., 2008).

Some antidepressants may cause fatigue and drowsiness, especially at the start of treatment, or longer in some individuals (Hu et al., 2004; Kelly et al., 2008). Discussion with the prescriber regarding drowsiness is advised; careful management of dosing and monitoring of sleep patterns is important. For example, timing dose administration at bedtime for some medications may help (Best Practice Advocacy Centre New Zealand, 2009b; Kelly et al., 2008; Bostwick, 2010). Sleep hygiene is important; encourage the patient to take part in physical exercise and avoiding napping during the day (Kelly et al., 2008; MayoClinic, 2016). If a patient is drowsy or is fatigued, it is important to ensure that he or she understands not to drive or operate machinery (MayoClinic, 2016; NPS MedicineWise, 2012).

Furthermore, individuals with depression can have altered sleeping patterns, including difficulty getting to sleep or staying asleep (Bostwick, 2010). This can be due to the depression itself, or may be a side effect of the antidepressants (Bostwick, 2010; Ferguson, 2001; Kelly et al., 2008). For some antidepressants, ways to reduce insomnia include avoiding caffeinated foods and drinks, engaging in regular exercise, or recommendations on sleep hygiene measures (Kelly et al., 2008).

Weight loss can occur during the initial period of antidepressant use; however, this is often regained and then increased with long-term use (Ferguson, 2001; Sienaert, 2014). The majority of antidepressants cause only slight weight gain, except for mirtazapine, amitriptyline, and paroxetine (Sienaert, 2014). To limit weight gain, patients can be advised to make healthy choices with eating—reducing the consumption of sugary foods and beverages and increasing fruit and vegetables, keeping a food diary and partaking in regular physical activity (Kelly et al., 2008).

Depression itself can cause sexual dysfunction, and sexual side effects can also be due to some antidepressants. Paroxetine has been reported to be the antidepressant most likely to cause sexual dysfunction (Kelly et al., 2008). Dysfunction can include reduced sexual drive and difficulty reaching orgasm (Ferguson, 2001; Kelly et al., 2008). If the medication is being taken only once daily, patients could try to time sexual activity prior to dosing; if this is not successful, the patient should be advised to discuss further with his or her health professional (Kelly et al., 2008). There is a clear role for the pharmacist in managing side effects discussing with their doctor and/or care team. Other courses of action may include additional medication to be prescribed, if appropriate, or may consider lowering the antidepressant dose or switching antidepressant depending on the individual (Kelly et al., 2008; MayoClinic, 2016; NPS MedicineWise, 2012).

SSRIs have been associated with suicide and suicidal thoughts (US Food and Drug Administration, 2016). Suicidal thoughts and behaviors are more prevalent in children and young adults (US Food and Drug Administration, 2016). If any of these symptoms emerge, then patients should be advised to seek assistance straight away. Information on after hour's crisis services is something that could also be given to all patients.

Advice to Prescribers

As many individuals will may have to try more than one antidepressant medicine before finding the one that is most appropriate for them (Best Practice Advocacy Centre New Zealand, 2009b), the pharmacist has an integral role in advising on tapering and switching of antidepressants to clinicians. More specifically, the pharmacist is in an ideal position to advise when switching medications on the need for washout periods, cross-tapering, potential drug interactions and their management, and the management of discontinuation syndrome (Best Practice Advocacy Centre New Zealand, 2009a; Shepherd and Parker, 2017). Factors that will need to be considered include the individual pharmacokinetics of the medications and the existence of active metabolites (Best Practice Advocacy Centre New Zealand, 2009b).

Advice on the potential for serotonin toxicity is also particularly important. Serotonin toxicity, although rare, is an extremely serious and potentially life-threatening condition that can occur if a medication that affects serotonin is given in high doses or if it is coadministered with other medicines with serotonergic activity (Medsafe, 2015). The pharmacist should be checking interactions with prescribed antidepressant medicines (including natural and complementary medications, such as St John's wort) and advising the prescriber accordingly while bearing in mind the washout periods for the medications (Medsafe, 2015).

Self-Management and Promotion of Support Networks

As discussed earlier, self-management is something that can be encouraged and promoted as part of the overall management of people with depression. In addition, giving clear information about the appropriate online resources that the patients can use, and which local groups are available for the support of people with depression (Shepherd and Parker, 2017).

Challenges

There are challenges that need to be surmounted by pharmacists to cement their role in the ongoing care of patients with depression. These include time, privacy, lack of pharmacist training, remuneration for the service, and lack of liaison between the pharmacist and other health-care professionals (Liekens et al., 2013).

Appropriate education of pharmacists in this area is paramount. A lack of education in mental health has been described as the main barrier to successful pharmaceutical care for people with depression (Scheerder et al., 2008). A study by Crockett and Taylor (2009) conducted an intervention study with rural pharmacists. Pharmacists allocated to the intervention group were given training in depression and asked to dispense medication with extra advice and support. By the conclusion of the study, pharmacists were more likely to initiate conversation, discuss medication and its side effects, point out the importance of remaining on the medication, provide ongoing follow-up, and encourage patients to talk with their GPs and pharmacists (Crockett and Taylor, 2009). In addition, the pharmacists who were in the intervention group were more likely to initiate conversation on dispensing a repeat prescription and to discuss extended support. A key element highlighted by the pharmacists in this study was that a major barrier to care was the "fear of saying the wrong thing." This is echoed by other studies, such as Liekens et al. (2012) and Scheerder et al. (2008), where a lack of education in mental health was perceived as a barrier to depression care. Specialized training for pharmacists in this field could potentially lead to more confidence in initiating conversations with patients with depression. To support this notion, Liekens et al. (2014) assessed the impact of an educational training day on pharmacists in a cluster randomized controlled trial. Mystery shopper interactions were assessed to measure outcomes, evaluating pharmacists' communication with individuals starting a new antidepressant therapy. The authors reported that pharmacist training can positively affect the quality of care in patients with depression (Liekens et al., 2014).

Understanding roles of other healthcare professions in the holistic approach to mental health care is also an important challenge. This was also identified by Crockett and Taylor (2009), with the suggestion that this training should be implemented during undergraduate training of all medical and health professionals. Subsequently, this should lead to improved understanding of the various roles of health professionals in mental health and facilitate interprofessional teamwork (Crockett and Taylor, 2009).

These barriers are not isolated to the community setting. Desplenter et al. (2011) described the perceptions and challenges of counseling patients at discharge from hospital in Belgium. Whilst pharmacists were perceived as a reliable healthcare professional and a key person in the team, the authors reported barriers to care included the acceptance of the broadening role and new competencies of the pharmacist in the team, interdisciplinary communication, timing of discharge, and lack of medical information (Desplenter et al., 2011).

Future Potential Roles

In many countries worldwide, the role of the pharmacist is continuing to evolve (Liekens et al., 2013). Collaborative care models have been proposed between clinic-based pharmacists and clinicians to support the management of patients with major depression (Kehoe, 2002). In an ongoing study by Boudreau et al. (2002), a pragmatic randomized control trial, was conducted. Patients were randomized to receive either standard care or enhanced care. Enhanced care included the role of the pharmacist in the team, and there was ongoing follow-up with the patient from the pharmacist or PharmD resident. At each follow-up contact, depression score was assessed. If no significant improvement in symptoms were seen after 8–10 weeks, then the pharmacist referred the patient back to the psychiatrist. The authors report that this study, albeit ongoing, demonstrated that pharmacists working as members of teams could "positively affect patient outcomes, satisfaction with face to face contact, quality of prescribing and the delivery of care."

This result was also reflected in a separate study by Finley et al. (2002). Patient satisfaction, outcomes, medication adherence, and visits to their primary care providers were all improved in those patients in the intervention group (Finley et al., 2002). A further randomized control trial using the same collaborative care model found improvements in adherence and patient satisfaction; clinical improvement was seen in both groups, but difference was not statistically significant (Finley et al., 2003).

Depression screening has the potential to increase early identification of signs and symptoms and allow for referral to the most appropriate medical professional. Pharmacists are in a unique position, being the most accessible health-care professional in the community setting (O'Reilly et al., 2015) and held in high regard by the public (Roy Morgan News Poll, 2014). Screening services within community pharmacies have evaluated by several studies and have the potential to be a beneficial. A feasibility study in Australia evaluated the potential of community pharmacists to provide screening services for depression (O'Reilly et al., 2015). Results showed that pharmacists were capable of providing this service and making the appropriate referrals when necessary. In addition, in a separate study by Rosser et al. (2013), a screening service was developed and implemented over 32 locations, which also demonstrated that pharmacists had the ability to effectively screen patients using a validated tool, and follow-up showed that these patients had initiated or modified treatment. Through this screening, individuals at risk of suicide were also identified and referred, highlighting the value of the pharmacist in this role and unmet need of patients (Rosser et al., 2013). However, if pharmacists are to engage in this type of screening service, it is imperative to have appropriate training in depression and using a recognized and validated tool to conduct this service, with resources available to refer patients to the most appropriate health care professional.

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Management of Mental Health Disorders and the Pharmacist's Role: Schizophrenia

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Introduction

Schizophrenia is a serious mental health condition, characterized by relapsing episodes of delusions, hallucinations and diminished emotional expression, persistent cognitive dysfunction, and a number of other disruptive symptoms. The disorder most commonly emerges during adolescents or early adulthood and is a leading cause of disability in individuals aged between 15 and 44 years (Rössler et al., 2005, 2013). Pharmacological intervention is the most effective means for controlling the positive symptoms associated with schizophrenia and is effective in many cases (Matheson et al., 2014); however, there remains a small proportion of individuals whose symptoms persist despite best practice.

The current definition of schizophrenia, as set out in the Diagnostic and Statistical Manual of mental disorders (DSM-5) (American Psychiatric Association, 2013) and International Classification of Diseases (ICD-10) (WHO, 2016), is a culmination of several influential theories described over the past century. Many noteworthy developments have occurred in the history of the disorder but particular importance should be placed on:

1. Emil Kraepelin's popularization of the term "dementia praecox" (premature dementia or precocious madness) to describe the chronic, deteriorating nature of this psychotic illness,
2. Eugen Bleuler's emphasis of the splitting of psychic functioning and renaming of the disorder to "schizophrenia,"
3. Karl Jasper's elegant description of the symptoms of schizophrenia in philosophical and psychological terms in this book Allgemeine psychopathologie (General Psycholopathology, 1913),
4. The discovery of chlorpromazine for the treatment of schizophrenia in the early 1950s.

A complete history of schizophrenia is outside the remit of this encyclopedia; however, many excellent resources are available should readers wish to learn more about the subject.

Schizophrenia within the International Criteria for Diagnosis-10 (ICD-10) and the proposed changes for ICD-11

Within the framework of the ICD-10 (WHO, 2016), schizophrenia is grouped with schizotypal and delusional disorders as well as a larger group of acute and transient psychotic disorders. The Diagnostics and Statistics Manual-5 (DSM-5) (American Psychiatric Association, 2013) adopts a similar arrangement, grouping schizophrenia spectrum and other psychotic disorders together. Both diagnostic tools demand that a diagnosis of schizophrenia be made only in the absence of extensive depressive or manic symptoms, unless schizophrenic symptoms antedate the affective disturbance. Likewise, a diagnosis of schizophrenia should not be made in the presence of overt brain disease or during states of intoxication or withdrawal.

Although the ICD-10 (and DSM-IV) (American Psychiatric Association, 1994) categorizes schizophrenia based on clinical features (simple, hebephrenic, catatonic, paranoid, undifferentiated, schizoaffective, childhood, and chronic), low stability, poor inter-rater reliability, minimal clinical utility, and limited validity of these subtypes have resulted in their proposed exclusion from ICD-11 (not yet released). These changes have already been implemented in the DSM-5 (American Psychiatric Association, 2013). Suggested replacements to the traditional subtyping include using ratings of individual symptom domains (Keeley and Gaebel, 2017), clinical staging (McGorry et al., 2006), and response to treatment (Farooq et al., 2013). Each strategy possesses

its own strengths and weaknesses, some providing benefits surrounding a diagnosis (symptom ratings or clinical staging) and others surrounding treatment (response subtyping).

Estimates suggest that from as few as 5% to as many as 60% of the population affected with schizophrenia are resistant to first-line treatment (Brenner et al., 1990; Elkis, 2007; Essock et al., 1996; Juarez-Reyes et al., 1995; Kane, 1995; Lehman et al., 2004). Treatment-resistance accounts for some of the highest rates of hospitalization and impaired functioning in mental health (Iasevoli et al., 2016; Lieberman and Murray, 2012). The atypical antipsychotic, clozapine is effective for treating between 30% and 70% of individuals who are deemed treatment resistant because it provides relief for their most debilitating symptoms (Elkis, 2007; Essali et al., 2009; Kane and Correll, 2016; Kane et al., 1988b; Meltzer, 2010). However, the serious and potentially life-threatening side effects associated with clozapine limit its use so it is reserved for treatment-resistant patients only. Unfortunately, a significant number of patients do not respond to clozapine either (Howes et al., 2016).

Epidemiology/Burden of Disease

During 2013, the Global Burden of Disease Study estimated that 23 million people, worldwide, were living with schizophrenia (Vos et al., 2015). This disorder accounts for between 0.01% and 0.7% of the total population but is a leading cause of years lived with disability and accounts for 3.7% of the global burden of disease (McGrath et al., 2008; Vos et al., 2015). Individuals with schizophrenia experience a standardized mortality ratio 2.6 times that of the general population (McGrath et al., 2008). The incidence of suicide in those with schizophrenia is also particularly high (12.9 times that of the general population) (McGrath et al., 2008). A high incidence of premature cardiovascular disease has also been reported. The annual national cost of schizophrenia is estimated to range between US$ 92 million and US$ 102 billion, with indirect costs making up between 50% and 85% of this amount (Chong et al., 2016). Resistance to first-line antipsychotic therapy is estimated to require US$ 34 billion per annum in direct health-care costs in the United States alone (Kennedy et al., 2014).

Etiology of Schizophrenia

Evidence supports both genetic and environmental influences in the etiology of schizophrenia, as well as purported gene–-environment interactions.

The estimated heritability of schizophrenia from a recent study was ~80% (Hilker et al., 2018), which emphasizes a substantial genetic risk for those with affected parents and siblings. The genetic risk is conferred by a large number of alleles, with over 100 loci associated with the disorder (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Of major interest are polymorphisms associated with the dopamine (D2) receptor gene DRD2 and the genes involved in glutamatergic neurotransmission (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Despite high heritability, however, concordance rates from monozygotic and dizygotic twins are only 33% and 7%, respectively, implying that vulnerability is not solely attributable to genetic factors (Hilker et al., 2018).

Substantial evidence also implicates environmental factors such as urban upbringing (Krabbendam and van Os, 2005), childhood adversity (Longden and Read, 2016), cannabis use (Arseneault et al., 2002), and maternal influenza infection (Adams et al., 1993) in the development of schizophrenia. These factors in combination with genetic influences are thought to increase the risk of developing schizophrenia via gene–environment interactions, whereby the effect of an individual's genotype depends on environmental exposure and vice versa (European Network of National Networks studying Gene-Environment Interactions in et al., 2014).

In neurochemical terms, schizophrenia has been linked to disrupted striatal and prefrontal dopamine regulation (Howes and Kapur, 2009), which is possibly the result of underlying disturbances in N-methyl-D-aspartate (NMDA) receptor modulation (Stephan et al., 2009). All currently licenced antipsychotic drugs block dopamine D2 receptors (whether via antagonism, inverse agonism, or partial agonism) (Howes et al., 2015), which reinforces the hypothesis that dopamine plays a critical role in the manifestation of the symptoms associated with schizophrenia. Variability in the responsiveness of individual patients to these drugs (Agid et al., 2011), however, indicates that in some cases, the disorder is at least partly attributable to other neurochemical mechanisms.

Clinical Presentation of the Positive, Negative, and Cognitive Symptoms

Three main types of symptom contribute to the overall diagnosis of schizophrenia, i.e., the positive, negative, and cognitive symptoms.

Bleuler described positive symptoms as features of schizophrenia supplementary to a healthy psyche. They consist of delusions and hallucinations among other excessive functions (Stahl, 2013); positive symptoms are listed in **Table 1**.

Karl Jaspers defined delusions as "*pathologically falsified judgements*" of reality, describing them as transformations in one's total awareness of, and impairment in one's ability to judge, reality (Jaspers et al., 1997). This is in accordance with modern interpretations which describe delusions as "*involving a misinterpretation of perceptions or experiences*" (Stahl, 2013). Delusions themselves can take on many forms; Jaspers expressed that it is not the content of the delusion that is important, however, but the original experience

Table 1 Positive symptoms of schizophrenia

Positive symptoms
Delusions
Hallucinations
Distortions or exaggerations in language and communication
Disorganized speech
Disorganized behavior
Catatonic behavior
Agitation

Table 2 Negative symptoms and their descriptions

Negative symptoms of schizophrenia	
Avolition	A reduction in desire, motivation, or persistence, restricting the initiation of goal-directed behavior. May reduce one's ability to undertake or complete everyday tasks, including personal hygiene.
Blunted affect	Restriction in the range or intensity of emotional perception, experience, and expression. A person may report feeling "numb" or "empty inside."
Asociality	Reduced social drive and interaction—diminished sexual interest, few friends, or little interest in spending time with friends. May be a consequence of limited social interactions or an association of avolition.
Anhedonia	A reduction in the ability to experience pleasure or recount pleasurable experiences. Previous hobbies or interests may become less pleasurable.
Alogia	Restriction in the fluency and productivity of thought and speech—Conversation is stunted; an affected individual will offer few words and fail to elaborate without prompting.

that leads to this content (Jaspers et al., 1997). This experience, arising as a sensation, feeling, mood, or altered awareness, signals to the individual that there has been some subtle change in the environment (Jaspers et al., 1997). Kapur suggested that these impressions of altered atmosphere stem from an increase in aberrant salience that causes misattribution of significance to normally nonsalient stimuli (Kapur, 2003). Individuals reporting their experiences during the prodromal phase of schizophrenia recount that they *"became fascinated by the little insignificant things around [them]"* (Bowers and Freedman, 1966) that something in the world around them is changing, leaving them confused and looking for explanations (Kapur, 2003). Though Jaspers purported that these delusional ideas develop through essentially normal cognitive processes (Stanghellini et al., 2013), others suggest that a defect in probabilistic reasoning (i.e., jumping to conclusions) may be involved (Maj, 2013; Menon et al., 2008).

Like delusions, hallucinations may also be attributed to abnormal salience, this time of the mental impressions of sensory experiences and memories (Kapur, 2003). Auditory and visual hallucinations are most common, although tactile and gustatory hallucinations can also occur.

Disorganized thinking refers to substantially impaired communication resulting from frequent derailment of or incoherent speech (2013). Speech may become so disorganized as to resemble receptive aphasia, restricting an individual's ability to express him/herself meaningfully through language and resulting in complete incoherence or "word salad" (2013). Distortions or exaggerations in language and communication may also occur (Stahl, 2013).

In some cases, motor behavior may be affected in schizophrenia, hindering goal-directed behavior and activities of daily living (2013). "Child-like silliness" and unpredictable agitation are hallmarks of this disorganized or abnormal motor behavior (2013). In more severe cases, a marked decrease in reactivity to the environment, known as catatonia, may occur (2013). Catatonic behavior may manifest in a number of different ways, some of which are presented in **Table 2**.

Negative symptoms contribute substantially to the morbidity associated with schizophrenia and are strong determinants of poor social functioning and outcome (2013, Rabinowitz et al., 2012). They generally represent deteriorations in normal function and though less dramatic than positive symptoms, their presence is often associated with long periods of hospitalization, trouble maintaining stable social relationships and employment, and a decreased ability to live independently (Stahl, 2013).

The most prominent negative symptoms of schizophrenia are avolition and blunted affect, described, along with the remaining negative symptoms, in **Table 2**.

The cognitive symptoms of schizophrenia present early in the course of the disorder and are largely resistant to current antipsychotic drug therapy. They may appear prior to the development of psychosis in some individuals and are more highly correlated with measurable brain dysfunction that other aspects of the disorder (Keefe and Fenton, 2007). Cognitive symptoms affect mental processes necessary for day-to-day function and future planning and include deficits in attention, working memory, explicit memory, problem solving, and executive function. Social cognitive deficits may also be present. These include deficits in the ability to infer the intentions of others (theory of mind) and may lead to the generation of explanatory delusions.

Although recognized as an associated feature of schizophrenia in the DSM-5, cognitive symptoms are not explicitly included in the diagnostic criteria for the disorder. Instead, guidelines emphasize the importance of cognitive assessment for making critical distinctions between the various schizophrenia spectrum and other psychotic disorders.

Diagnosis of Schizophrenia

The DSM-5 requires that a diagnosis of schizophrenia be made if an individual presents with delusions, hallucinations, or disorganized speech, either in combination with each other or with grossly disorganized or catatonic behavior, diminished emotional expression, or avolition. The DSM-5 diagnostic criteria for schizophrenia (American Psychiatric Association, 2013) are summarized below.

1. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (a), (b), or (c):
    a. Delusions.
    b. Hallucinations.
    c. Disorganized speech (e.g., frequent derailment or incoherence).
    d. Grossly disorganized or catatonic behavior.
    e. Negative symptoms (i.e., diminished emotional expression or avolition).
2. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
3. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
4. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
5. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
6. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Treatment Options

Early treatment options included bloodletting and emesis that was thought to remove poisons from the body, or for example spinning the patient until they lost consciousness, which was believed to rearrange the content of the brain. Insulin coma therapy was also used and very popular in the 1930s, but it was not until the serendipitous discovery of chlorpromazine (which was being tested as a sedative antihistamine) during the early 1950s that an effective treatment for schizophrenia was developed.

Treatment options now include oral or intramuscular injections of antipsychotic medication in conjunction with psychological interventions (family intervention and individual Cognitive Behavioural Therapy). Generally, there are two and some argue three classes of oral antipsychotic available. These include the first-generation antipsychotics (FGA) like chlorpromazine, first synthesized in 1950 by Paul Charpentier. During the subsequent two decades, increasingly selective D2 antagonists such as haloperidol were synthesized and tested with the aim of improving their efficacy. Ultimately this approach was unsuccessful, but a range of drugs became available with varying degrees of adverse effects such as sedation. For example, chlorpromazine and levomepromazine are very sedative and haloperidol is far less so. The primary pharmacological effect of the FGA is attributed to their antagonism of dopamine receptors (D2). The ability to block D2 receptors in the mesolimbic pathway is largely responsible for reducing the positive symptoms of schizophrenia and also unfortunately inducing Parkinsonian-like or extrapyramidal side-effects (EPSEs), which they are so well known for (Stahl, 2013).

The second-generation antipsychotics (SGA) include risperidone, olanzapine, quetiapine, and amisulpride. The defining pharmacological property that separates SGAs from FGAs is their antagonism of serotonin ($5HT_{2A}$) receptors, in addition to D2 receptor antagonism (Sykes et al., 2017). The decreased incidence of EPSEs during a patient's first exposure to a SGA in contrast to the FGA's has led to their recommendation as drugs of choice within clinical treatment guidelines for antipsychotic use. The side effect profile is also different from that of the FGAs. The more common side effects induced by this group include weight gain and symptoms associated with the metabolic syndrome, i.e., high cholesterol, diabetes, and cardiovascular disease. Like the FGAs some are also very sedative and some are not.

Third-generation antipsychotics currently include aripiprazole and brexpiprazole (Fleischhacker et al., 2017; Forbes et al., 2018; Shirley and Perry, 2014). Both drugs differ from the other antipsychotics in that they are partial agonists of D_2 and 5-HT_{1A} receptors rather than antagonists. They also act as antagonists of serotonin 5-HT2A and noradrenaline α1B/2C receptors. They are not

generally sedative and not associated with increasing prolactin levels or weight gain so they are becoming more widely used. However, akathisia can be a problematic side effect.

For the purposes of this encyclopedia, we will refer to only two classes of antipsychotic, i.e., FGA and SGAs including aripiprazole and brexpiprazole.

Clozapine appeared in Vienna in 1966 and for most of the last three decades remains the drug of choice for treatment-resistant schizophrenia. It is considered a SGA and the only drug shown to reduce the rate of suicide and hospitalization in those with schizophrenia (Meltzer, 2010; Modestin et al., 2005; Tiihonen et al., 2009).

All antipsychotics have their own specific properties and are effectively used in the acute and long-term treatment of schizophrenia. Tandon et al. (2008) state that there is no convincing evidence to support the preferential use of SGAs over FGAs especially if the EPSEs can be minimized (Tandon et al., 2008). With the exception of clozapine, a number of Cochrane reviews across heterogeneous populations have not provided any evidence that any particular antipsychotic is more effective than another (Asenjo Lobos et al., 2010; Asmal et al., 2013; Khanna et al., 2014; Komossa et al., 2009; Komossa et al., 2010a; Komossa et al., 2010b; Komossa et al., 2011; Leucht et al., 2012a). However, there is clear evidence of differing adverse effects of clinical significance between specific antipsychotics (Bazire, 2016). For example, although both olanzapine and amisulpride are SGAs, their side effect profiles are quite different. In practice, olanzapine causes marked sedation and weight gain, likely due to its antagonist effects at histamine (H1), muscarinic (M1), and adrenergic (α1) receptors (Leucht et al., 2013). In contrast, amisulpride can cause a marked elevation in prolactin leading to amenorrhea, galactorrhea, sexual dysfunction, and possibly over time osteoporosis (Bazire, 2016). However, amisulpride is not very sedative and less likely to induce weight gain when compared to olanzapine.

Interestingly, a meta-analysis conducted by Leucht et al. (2013) showed there may be small advantages in symptom resolution when using olanzapine, amisulpride, and risperidone in contrast to other antipsychotics with the exception of clozapine (Leucht et al., 2013). Aripiprazole may be somewhat less effective than olanzapine, but more tolerable because it has a lower incidence of adverse metabolic effects and is less sedative. Aripiprazole is also less likely to induce EPSE's than risperidone or the majority of FGA's (Leucht et al., 2013).

Of particular importance, a report published by the World Health Organization during 2003 stated that adherence rates in developed countries average only about 50% (World Health Organisation, 2003) for all drugs. Consequently, ensuring long-term adherence is fundamental to treating people who suffer from schizophrenia (Kovacs et al., 2018). The desired outcomes of treatment are to prevent acute psychotic episodes, reduce hospital admissions, minimize drug-induced adverse effects, and maintain a reasonable quality of life for the patient.

For those with a diagnosis of schizophrenia, long-term use of an antipsychotic is crucial in conjunction with psychological and psychosocial interventions (Leucht et al., 2012a). To increase adherence, prescriber's might also utilize depot antipsychotics, which guarantee medication delivery and in turn help to improve treatment outcomes. Antipsychotics taken regularly, protect against the short-, medium-, and long-term risk of relapse (Leucht et al., 2012b). By preventing relapse, the risk of developing treatment-resistance is also decreased (Kane, 2013).

A number of country-specific guidelines such as the National Institute for Clinical Excellence (NICE) from the United Kingdom (UK) and the Royal Australian and New Zealand College of Psychiatrists recommend that after 4–6 weeks of treatment at an optimal antipsychotic dose, a change in antipsychotic should be considered (McGorry, 2005; NICE, 2009). These guidelines also recommend that where there is partial response, the patient should be reassessed after 8 weeks unless there are significant adverse effects. If a patient does not respond to treatment with two different antipsychotics (one of which should be a SGA), then treatment with clozapine is recommended (McGorry, 2005; NICE, 2009).

Importantly, treatment of schizophrenia must be individualized and tailored to the clinical presentation, comorbidities, concurrent medication, the use of recreational drugs, severity and frequency of episodes, and should include both pharmacological and nonpharmacological strategies (McGorry, 2005; NICE, 2009).

Pharmacological and Nonpharmacological Management

The choice of antipsychotic should be well informed and discussed with the patient and include where possible support from family members or carers. A multidisciplinary team (MDT) caring for a patient will typically include some of the following:

- Responsible clinician, i.e., consultant psychiatrist
- Registrar
- House or senior house officer
- Nurse looking after the patient
- Pharmacist
- Social worker
- Psychologist
- Occupational therapist

The pharmacist needs to be actively involved in facilitating an open, impartial, considered decision about which antipsychotic is the most appropriate for an individual. There are many useful reputable sources of information available to both health-care professionals and service users, for example, the Psychotropic Drug Directory (Bazire, 2016), which provides

considerable detail about the condition and treatment options. Pharmacists need to provide an appropriate level of information and be prepared to discuss the benefits and possible adverse effects of each drug with members of the MDT and patient or carer. Adverse effects may include:

- Metabolic disturbances (including weight gain and diabetes)
- Extrapyramidal side effects (including akathisia, dyskinesia, and dystonia)
- Cardiovascular side effects (including QT prolongation)
- Hormonal (including increasing plasma prolactin)
- Others such as sedation, constipation, dry mouth, and dry eyes

Pharmacological options include a choice of first- or second-generation antipsychotics. Some examples of FGAs include chlorpromazine, flupentixol, haloperidol, zuclopenthixol, and fluphenazine. Examples of the SGAs include olanzapine, amisulpride, quetiapine, risperidone, paliperidone, and ziprasidone. As mentioned previously, with the exception of clozapine, the difference between the two classes is essentially due to differing side effects. Clozapine has superior efficacy in those experiencing resistant symptoms but its serious adverse effects profile means it is reserved for those who are treatment resistant (Kane et al., 1988a; Leucht et al., 2013).

Treatment guidelines typically follow the same algorithm for first-episode psychosis, please see Fig. 1. Choice should be based on the potential of the drugs offered to induce metabolic and extrapyramidal side effects. On first exposure to an antipsychotic, the likelihood of EPSEs occurring is also greater than subsequent exposures, depending on the drug chosen. Metabolic side effects are not immediate, but careful monitoring of body weight, blood glucose, and lipid profiles is important in the short term, i.e., weeks and over longer time periods. If the patient has a history of cardiac disease or the drug is likely to induce QT-prolongation, an ECG should also be carried out both before and after beginning treatment.

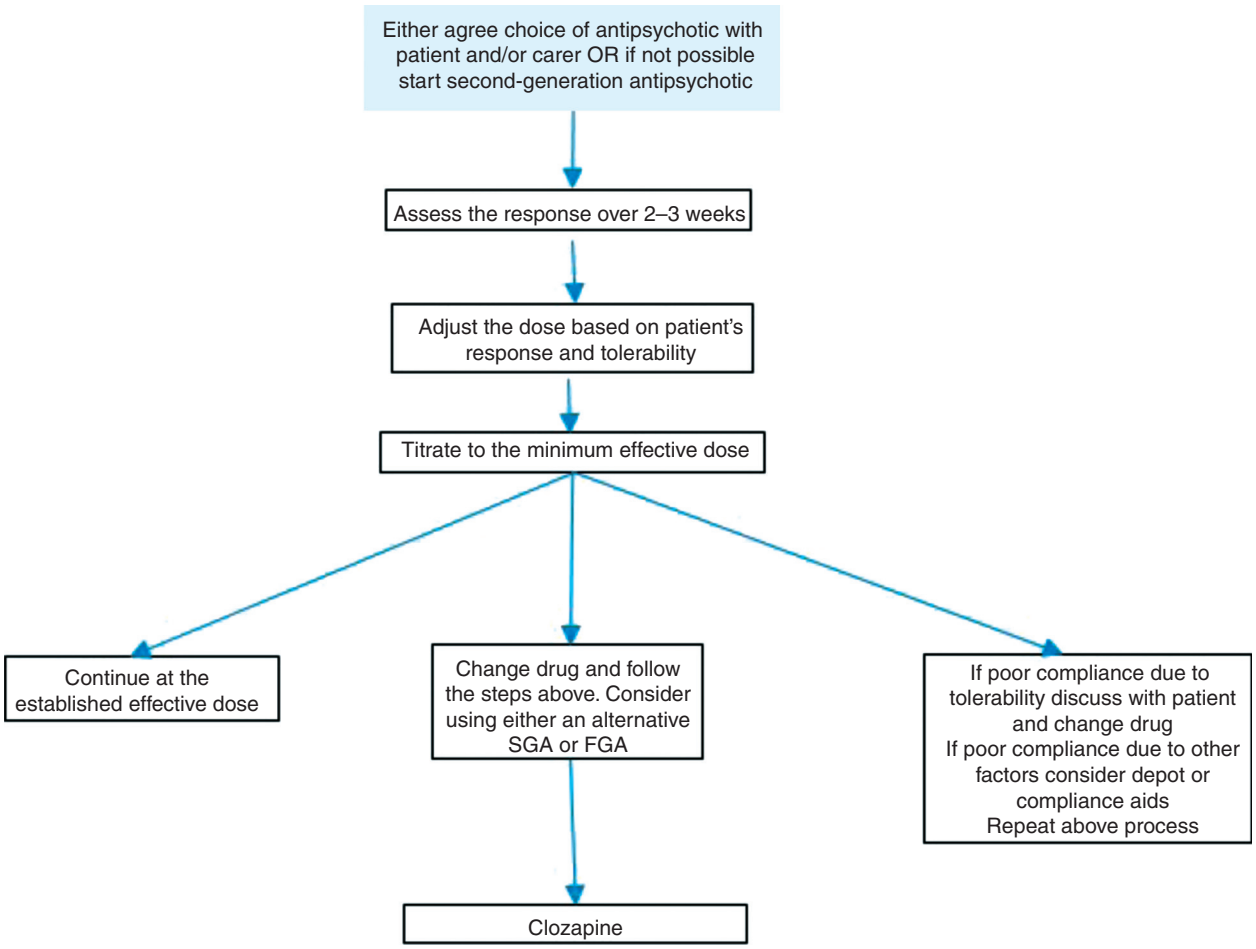

Figure 1 Treatment of first-episode psychosis. Improvements subsequent to beginning an antipsychotic are usually apparent within 2–3 weeks of reaching an effective dose, although a full response can often take 6 weeks or longer. Generally, if there is no improvement at all within the first few weeks of treatment it is unlikely there be a response. If there are no improvements within this period, consider changing the drug/dose.

Whether or not SGAs have an advantage over the FGAs for the treatment of schizophrenia remains uncertain (Naber and Lambert, 2009). During the last two decades, there have been two significant trials undertaken to determine whether there any significant advantages associated with the use of SGAs in contrast to FGAs. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS) trials have proven to be landmark, independent, pragmatic clinical trials with no industry sponsorship. Both trials used broad inclusion criteria and a long follow-up period to mimic routine practice. The CATIE trial recruited 1493 patients and observed them for 18-months as a double-blind trial comparing the SGAs olanzapine, quetiapine, risperidone, and ziprasidone with the FGA perphenazine (Stroup et al., 2003; Swartz et al., 2003). The CUtLASS trial (n = 277) was an open label, multisite, randomized controlled trial of FGA (chlorpromazine, flupenthixol, haloperidol, loxapine, methotrimeprazine, sulpiride, trifluoperazine, zuclopenthixol, and the depots fluphenazine decanoate, flupentixol decanoate, haloperidol decanoate, pipothiazine palmitate, and zuclopenthixol decanoate), and SGAs (risperidone, olanzapine, amisulpride, zotepine, and quetiapine) with blind assessments at 12, 26, and 56 weeks using an intention-to-treat analysis (Jones et al., 2006). In both studies, there was no clear separation in the quality of life or patient responses between FGA and SGA. Consequently, there is no single antipsychotic that is best for each patient because individual responses differ considerably. For successfully individualized treatment, a multitude of antipsychotic options are needed (Leucht et al., 2013).

A more recent study (n = 69 taking FGA and n = 80 taking SGA for 24 weeks) suggested that patient-reported quality of life is significantly higher in those given SGAs in contrast to those given FGAs when treatment selection was individualized (Grunder et al., 2016). However, their advantage still needs to be weighed against the potential metabolic adverse effects of some SGAs, which do not always become apparent within that time frame.

The British Association for Psychopharmacology (BAP) guidelines recommend identification and treatment of schizophrenia spectrum disorders as early as possible to prevent the development of negative symptoms (Barnes and Schizophrenia Consensus Group of British Association for, 2011).

Maintenance pharmacotherapy is generally recommended for every patient; however, there has been debate about the use of long-term prophylactic antipsychotics in those who have had an acute psychotic episode, especially if they are diagnosed with schizophrenia (Murray et al., 2016). As with all medical practices, there are advantages and disadvantages to treating or not treating. There is also concern over the cumulative effects of antipsychotics on physical health and brain structure (Murray et al., 2016). The pharmacist should regularly review the benefits of continuing prophylactic antipsychotics against the risks associated with side-effects for each patient. Psychiatrists should also work with their patients to slowly reduce the antipsychotic to the lowest practical dose that prevents the return of distressing symptoms. While there is uncertainty about how long to continue antipsychotics, it is also well known that there is an approximately 80% rate of relapse into psychosis during the 1st year following the discontinuation of antipsychotics, which increases to >90% before the end of second year (Leucht et al., 2012a).

Combining antipsychotics should be avoided, as there is little evidence to support this practice and ample evidence to support the potential for harm (Porcelli et al., 2011). However, there is also some evidence to support the addition of a second antipsychotic as an adjunct to treatment with clozapine to provide relief from residual symptoms. In practice, the most commonly prescribed drugs used as adjunctive treatments are amisulpride (Barnes et al., 2017) and aripiprazole (Muscatello et al., 2011).

Some antiepileptic drugs have also been used as adjuncts (Zheng et al., 2017). In particular, lamotrigine, a drug which inhibits glutamate release, has been utilized as an adjunctive treatment for schizophrenia but with mixed results (Ohnuma et al., 2013; Vayisoglu et al., 2013).

Psychological and psychosocial interventions also increase the chance of staying well and avoiding a relapse (NICE, 2009). The NICE guidelines suggest individual cognitive behavioral therapy (CBT) with or without family intervention. CBT should be delivered on a one-to-one basis over at least 16 planned sessions (McGorry, 2005; NICE, 2009).

Where practical, family interventions should include the person with psychosis or schizophrenia and be carried out for between 3 months and 1 year, including at least 10 planned sessions. These sessions should take account of the relationship between the main carer and the person with psychosis or schizophrenia and have a specific supportive, educational or treatment function including negotiated problem solving or crisis management (McGorry, 2005; NICE, 2009).

A care plan should also be developed that includes activities that promote physical health and social inclusion, especially education, but also employment, volunteering, and other occupations such as leisure activities. Provide support to help the person and their family or carers realize the plan and agree on a suitable time to review it (McGorry, 2005; NICE, 2009).

For children and young people with first episode psychosis who are unable to attend mainstream school or college, facilitate alternative educational input in line with their capacity to engage with educational activities and according to their individual needs, with an ultimate goal of returning to mainstream education, training, or employment (McGorry, 2005; NICE, 2009).

New Developments

The current focus remains on improving the use of the dopamine antagonists currently prescribed with an emphasis on reducing their adverse effects, rather than developing entirely new classes of drugs (Taylor et al., 2015).

However, there are also efforts being made to develop new treatments, which target specific symptoms such as thought blocking and cognitive decline. For example, blonanserin that acts as a mixed 5HT2A and D2 receptor antagonist but unfortunately has yet to exhibit any significant advantages over existing antipsychotics (Kishi et al., 2018).

New methods of drug delivery are also being developed, for example, inhaled loxapine, a new 3-monthly paliperidone depot injection and the 2-monthly aripiprazole depot (Frampton, 2017).

Depot injections are useful preparations because they help to ensure adherence by supporting ongoing contact with services without significantly disrupting day to day living. The arrival of a clozapine IM injection is also being followed with great interest by acute service providers. The aim of using an IM injection of clozapine is as a short-term intervention to initiate patients who refuse medication, with a view to convert to oral clozapine as soon as possible (Trust, 2017).

The evidence for abnormalities in glutamatergic neuronal function in schizophrenia has also been increasing and provides support for the development of novel antipsychotic agents which target this system (Howes et al., 2015). These drugs have a completely different side-effect profile to D2 antagonists and to date have no propensity to extrapyramidal side effects, prolactinaemia, or weight gain. It has been hypothesized that glutamatergic drugs may be of benefit to the 20%–30% of individuals with schizophrenia who fail to show any response to dopaminergic agents and may be particularly useful in the early stages of the illness, where they may be disease-modifying. A number of glutamatergic compounds have been reported as having promising results in phase II drug trials. If these reach the clinic, they will represent the first truly novel approach to pharmacotherapy in schizophrenia for more than 50 years (Stansley and Conn, 2018).

The antibiotic minocycline has somewhat unexpectedly been shown to inhibit the effects of NMDA receptor antagonism and appears to be an effective adjunctive treatment option for schizophrenia. Moreover, minocycline has an acceptable safety and tolerability profile (Solmi et al., 2017; Xiang et al., 2017). However, more methodologically sound and larger RCTs remain necessary to confirm and extend these results (Solmi et al., 2017).

Monitoring and Measuring—How do we Know That Treatment is Working?

It is vital that patients, carers, and key workers are aware of the early signs of relapse and how to access help (Bazire, 2016; Taylor et al., 2015).

Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial and continued at optimum dosage for a specified period of time. If during treatment, the service user continues to have symptoms, impaired functioning, or is distressed, then consider increasing the dose of the drug (if possible) or changing to another antipsychotic by cross-titrating.

However, there is some variation within treatment guidelines about the minimum length of time required before deciding whether a patient has shown a satisfactory response to the first antipsychotic selected. For example, the Maudsley Guidelines suggest the first antipsychotic need only be used for 2–3 weeks before considering a change in the absence of a significant response. This would be followed by a 6-week period for the second antipsychotic selected before considering any further changes or the use of clozapine (Taylor et al., 2015). In contrast, the American Psychiatric Association guidelines suggest that the first antipsychotic selected should be used for ≥6 weeks before deciding whether there has been a satisfactory response. If not, a second antipsychotic could be trialled for at least another 6 weeks.

A recent publication in the American Journal of Psychiatry by experts within the field from around the world has a convenient summary of treatment guidelines and made practical suggestions about the diagnosis of treatment-resistant schizophrenia (Howes et al., 2016).

The Psychotropic Drug Directory by Stephen Bazire also has clear, practical advice about how to switch treatment from one antipsychotic to another using a variety of methods (Bazire, 2016). These include drug-free intervals (safest), no intervals (generally preferred), abrupt switching (risks discontinuation symptoms), partial overlap (usually acceptable), overlap (risks—neuroleptic malignant syndrome, serotonin syndrome, and combined adverse drug reactions), and full overlap (as with overlap).

Adherence must also be considered as a possible reason for treatment failure. There are a variety of methods to check/aid adherence, which include monitoring plasma concentrations and side-effects, speaking to family members or carers, and simply changing from oral medication to a depot formulation. Clear documentation of any action taken and the rationale for change in dose/drug must be recorded in the medical notes; this is incredibly useful if the patient needs a medication history to consider future treatment options. The frequency and duration of monitoring should be determined by the severity and frequency of symptoms/behavior (using a validated assessment tool), level of impairment and/or distress, and the degree of family disruption or concern (NICE, 2009).

Schizophrenia is thought to be caused by a combination of biological, psychological, and environmental factors, which may be impossible to avoid. So preventing the development of the illness appears unlikely. Heavy cannabis use has been associated with onset of psychotic illness (Colizzi and Murray, 2018); however, it is not clear whether risk of psychosis increases with use of cannabis or those at high risk are more likely to use the drug. A definitive cause has yet to be discovered (Nielsen et al., 2017).

Patients may be at an increased risk of relapse or developing psychosis for a variety of reasons. The NICE guidelines suggest that early identification and referral are helpful if a person is distressed, has a decline in social function, and exhibits transient or attenuated psychotic symptoms, or other experiences or behavior suggestive of possible psychosis or a first-degree relative with psychosis or schizophrenia.

Role of a Mental Health Pharmacist

The role of a pharmacist in the MDT is contextual in nature and can differ in focus and scope between primary and secondary care and between specialisms (Quinlan and Robertson, 2010). In general, hospital pharmacists' participate in regular MDT meetings.

Their role is often clearly defined, where they work directly with other health-care professionals (HCPs) focusing on a specialist clinical area. By way of a general example, every morning the psychiatric intensive care unit would have a MDT meeting, but the eating disorders unit might only have weekly MDT meetings. In community settings, pharmacists often work in isolation or remotely from other clinical colleagues and may not always have a specific team to contact (Quinlan and Robertson, 2010).

Pharmacists have been involved in MDT meetings for many years (time frame of involvement varies from country-to-country and region-to-region). Their position in the clinical team is integral. A key determinant of a successful MDT meeting includes good quality, unambiguous communication, which allows full involvement of all team members. Mutual recognition of clinical experience and influence, collegial respect, knowledge of differing MDT skills, and an ability to build rapport are important components of building and sustaining trust between colleagues in the MDT and patients. Quinlan and Robertson (2010) suggested understanding the role and responsibility of other team members increases efficiency and productivity by reducing repetition and allowing experts in their field to state their views. Not only that, having clear team objectives, shared goals and roles clearly defined (in other words, who does what and when) help to ensure a more effective team.

The MDT meeting is recognized as a platform for pharmacists to demonstrate a variety of their specialist skills, including but not limited to:

Interventions. Identification of drug/drug interactions. For example, clozapine and carbamazepine; or altering drug doses/formulations (i.e., a switch from oral to depot or from tablets to liquid). Pharmacists can also offer advice on rapid tranquilization, if required.

Request monitoring and follow-up. For example, monitoring weight gain with olanzapine or blood pressure with quetiapine. Follow-up—ensuring that the drug is working as intended, whereby symptoms are well controlled and any associated side effects are not problematic for the patient. It is very important that the Pharmacist documents baseline measurements as a benchmark, which can include weight and height; waist and hip circumference; pulse and blood pressure; blood tests such as liver function tests (LFTs), thyroid function tests (TFTs), urea and electrolytes (U&Es), full blood count (FBC), HbA1c, lipid profiles, creatine kinase (CK), and prolactin levels; and assessment of movement disorders.

Aid adherence—service users who are identified as needing advice are referred. Pharmacists provide counseling about drug-induced adverse effects and try to engage those who are struggling with for example: sedation while prescribed clozapine, galactorrhea while prescribed risperidone, or muscle stiffness while taking haloperidol. Pharmacists can also provide general lifestyle advice, such as improvements to diet and/or exercise regimes, smoking cessation, alcohol-related issues, and/or illicit substance cessation.

Monitoring outcomes is a key component of a Pharmacist's role. *Is the drug prescribed actually doing what we want it to do*? More generally, being able to engage with service users is a vital skill.

Discuss future recommendations—if the current drug is not seen as efficacious or the side effects are intolerable, a Pharmacist will form a view about the next reasonable step(s) to pursue.

Aiding a smooth transition from secondary to primary care—Ensuring clear, concise communication of medication that a service user has ceased, commenced, or altered during their admission, which is done in order to try to prevent errors and potential readmission as a result.

Education—Pharmacists have a role in educating the MDT about any new drugs available, safety alerts, new or changes in policies and procedures that require adherence, and performing or giving feedback on audits undertaken in their service/practice.

When a Pharmacist participates in the review of a service user, they will critically analyze the need for each individual medication and from experience and evidenced-based medicine form a clinical view about whether or not the medication is working as intended and/or is superfluous to requirements. A Pharmacist will also listen to feedback from MDT members or patients and critically assess whether there has been a reasonable reduction in a patient's symptoms. Confirming any troublesome adverse effects experienced by patients—and discussing how to resolve any problems identified—is an important element of a Pharmacists role. Often two or more antipsychotics can be prescribed in an acute setting (both regularly and "as required"), which can continue long term if not highlighted and reviewed within the MDT meeting by the pharmacist. A Pharmacist will help ensure service users are counseled about their medication at discharge to alleviate any concerns they have and aid adherence. They also monitor blood results to ensure that the drug is not affecting the liver, kidneys, thyroid, prolactin, cholesterol, glucose levels, or ability to fight infection for example. If any of these results are concerning, suggestions for mitigating their effects will be offered to the team. Pharmacists also play an important role in assisting nursing staff with pragmatic solutions to problems as they arise—for example, issues with drug formulation where the patient has swallowing difficulties may be required. Funding issues, crisis planning, and seamless discharge planning fall under the umbrella of the Pharmacist's remit and are also addressed in the MDT meeting.

Independent Prescribing for the Pharmacist

Doctors will continue to be responsible for the diagnosis of psychotic illnesses, but pharmacists are ideally placed to undertake the prescribing and monitoring of medication for that particular condition (within their scope of expertise). Pharmacists are capable of managing the prescribing of high-risk medications—for example, clozapine, including continual monitoring clinical performance and any adverse effects induced by the medicine. Not only that, pharmacists can interpret plasma levels, alter doses to optimize a drug's safe and effective use (pharmacovigilance), and advising patients about lifestyle changes to achieve maximum benefit and increase adherence. Treating and monitoring patients with long-term conditions (LTCs) require a good working rapport and clear communication with other health-care professionals. Pharmacists will need to continue to actively engage and collaboratively work with General Practitioners to add value to current services.

In their current role, pharmacists can play a critical, positive role in helping to minimize the risk of prescribing errors reaching patients (Baqir et al., 2015).

Case Studies

The following examples illustrate differing degrees of complexity.

1. A 20-year-old female with a family history of schizophrenia has become socially withdrawn while studying at university. She is paranoid and believes that her housemates can read her mind and that the television is talking to her.
   She has no allergies or comorbidities and does not drink or smoke.
   This person is exhibiting prodromal negative symptoms associated with schizophrenia (social withdrawal). She is also showing some positive symptoms, which include paranoia, thought broadcasting, and ideas of reference (thinks the TV is talking to her).
   Treatment choice involving the patient will ultimately aid adherence. In practice, a Pharmacist might consider a website such as "choice and medication" http://www.choiceandmedication.org/ (Limited, 2018) to assist decision making. The NICE guidelines emphasize the importance of patient choice, especially for first-line treatment (NICE, 2009). Generally all treatment guidelines suggest that a SGA is used first line.
   Fortunately antipsychotics are effective in both the acute and maintenance treatment of schizophrenia and other psychotic disorders. They all differ in their pharmacodynamics, pharmacokinetics, overall efficacy/effectiveness, and tolerability, but perhaps more importantly, response and tolerability differ between patients. Unfortunately, the variability of individual response suggests that there is no clear first-line antipsychotic suitable for all (Taylor et al., 2015).
   This person may choose any of the antipsychotics available, either typical or atypical. In practice, the choice is usually based on the likelihood of inducing minimal acceptable side-effects. Arguably young women do not tend to choose drugs that cause marked increase in weight such as olanzapine or quetiapine. The patient will generally choose to continue using a drug that has already been prescribed while acutely unwell if it is efficacious and tolerable.
2. A 51-year-old male with a family history of schizophrenia is recalled to hospital again for shouting at traffic on the side of a busy motorway. At times he experiences marked positive and negative symptoms. He has taken both typical and atypical antipsychotics in the past.
   As recommended by the SIGN and NICE guidelines, this person is a candidate for clozapine because he has had more than two antipsychotics, one of them has been an atypical (NICE, 2009; Taylor et al., 2015). It is important to start treatment at a low dose, increase the dose slowly to minimize adverse effects, and increase it to the lowest effective dose (Taylor et al., 2015). The pharmacists' role in the MDT for this person would include:
   Ensuring registration with the appropriate monitoring service, checking whether the MDT is aware of the requirements for monitoring FBC when prescribing clozapine. These requirements vary in different parts of the world. For example, in the United Kingdom, the requirements are a weekly FBC for the first 18 weeks that clozapine is taken then bi-weekly for up to 1 year and then 4-weekly FBCs.
   Counsel the patient and family/carer if possible about clozapine—ensuring that the patient has some insight or capacity to understand, i.e., not while floridly psychotic. In practice, this is not always possible. The key to the potential success of clozapine is to ensure adherence, which is often the greatest challenge.
   Discuss any nonprescribed therapies the patient might wish to use (including complementary therapies) with the patient and carer if appropriate (NICE, 2009).
   Managing a switch from the current prescribed antipsychotic to clozapine, this can be more difficult if the previous antipsychotic was a depot formulation.
   Listening to the patient once established on clozapine and attempting to resolve any issues with adverse effects. For example, hypersalivation can be successfully treated with 300 μg hyoscine hydrobromide (Kwells) taken up to three times daily with monitoring and follow-up to ensure effectiveness. Desmopressin nasal spray (10–20 μg nocte) is also an effective way to treat nocturnal enuresis if lifestyle changes are ineffective. Nocturnal enuresis can occur at any time while taking clozapine and is very distressing, which can affect adherence. There are strict rules about monitoring FBCs to prevent agranulocytosis. There are now more deaths from gastrointestinal stenosis and obstruction than from clozapine-induced dyscrasias (Shirazi et al., 2016). Ensuring that a patient is not constipated can be difficult because many people do not like discussing their bowel habit or may be unaware they are constipated. The Porirua protocol is now widely considered to be a useful guideline and was introduced in New Zealand following a fatality during 2017 (Every-Palmer et al., 2017).

   Checking there are no drug/drug interactions.
   Chemotherapy—due the neutropenia caused secondary to bone marrow suppression.
   Care needs to be taken with concurrently prescribed medications that prolong the QTc interval.
   When relevant smoking status should be discussed because the effects of cigarette smoke can alter clozapine levels by up to 70% (Lowe and Ackman, 2010).
   Illicit drug use—cannabis cessation can cause clozapine intoxication by stopping the induction of CYP1A2 (Zullino et al., 2002).

Consider future potential comorbidities, e.g., family history of myocardial infarction, diabetes mellitus—may need baseline ECG or HbA1c, respectively.

Education about the differences between FBC and clozapine plasma levels. Requesting the latter should be undertaken if poor adherence is suspected, change in smoking status, constipation, or other side effects that have changed significantly. Once clozapine and norclozapine levels are received, the MDT might need support when interpreting the results and then alter the clozapine dose accordingly if required.

Ensuring that the GP and community pharmacy are kept up-to-date with medication prescribed in the hospital (especially clozapine).

Organizing the smooth transfer of clozapine prescribing from an inpatient setting to a community setting or vice versa.

Conclusion

The aims of the chapter are to give an overview of schizophrenia, its treatments (including side effects), and how pharmacists play an essential role within the multidisciplinary team, using case study examples. Schizophrenia is a long-term, serious mental health condition caused by a combination of genetic and environmental factors.

The condition most commonly emerges during adolescence or early adulthood and is a leading cause of disability in individuals aged between 15 and 44 years (Rössler et al., 2005, 2013). Three main types of symptom contribute to the diagnosis of schizophrenia, i.e., positive, negative, and cognitive symptoms.

Numerous antipsychotics have been developed, each with their own side effects. However, FGAs tend to cause EPSEs on first exposure, whereas SGAs are more often associated with weight gain and diabetes. Tandon et al. (2008) state that there is no convincing evidence to support the preferential use of SGAs over FGAs, especially if the EPSEs can be minimized. In both the CATIE and CUtLASS trials, there was no clear separation in the quality of life or patient responses between FGA and SGA.

Clozapine is the gold standard antipsychotic used for treatment-resistant schizophrenia and is the only medicine shown to reduce the rate of suicide and hospitalization (Meltzer, 2010; Modestin et al., 2005; Tiihonen et al., 2009).

Pharmacists are actively involved in facilitating open, impartial, considered decision-making about which antipsychotic is the most appropriate for an individual. Choice of antipsychotic should be well informed and discussed with the patient and include where possible support from family members or carers, which will in turn aid adherence.

Pharmacists have been involved in MDTs for many years and demonstrate a variety of specialist skills, including but not limited to, making interventions; monitoring outcomes and follow-up, aiding adherence; discussing future recommendations; aiding a smooth transition from secondary to primary care; and educating staff, patients, and families/carers.

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Acne Vulgaris

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Learning Objectives

To Understand in Acne vulgaris:

- Pathophysiology
- Psychosocial burden
- Indications for acne treatment
- Topical and systemic treatments
- Common adverse effects of acne treatments
- Pharmacists role in the multidisciplinary care of patients with acne vulgaris

Key Points

- A global disease.
- Not confined only to adolescence but also seen in children and especially post adolescence (>25 years old) age groups.
- Psychosocial burden is significant and does not always correlate with the severity of the disease.
- Patients need reassurance that effective treatments exist for acne vulgaris.
- Treatments need to be targeted to specific patient circumstances.
- Do not use topical or systemic antibiotics as monotherapy.
- With effective early intervention permanent acne scarring can be minimised.
- Pharmacists can treat mild, non-scarring, predominantly comedonal acne.

- Pharmacists should not treat extensive inflammatory acne, scarring acne or acne with a significant psychosocial component.
- Pharmacists can reinforce key messages about acne treatments as part of the healthcare team.

Epidemiology

Acne vulgaris (henceforth referred to as acne) is a common disorder ranking 8th in the most prevalent global diseases (Hay et al., 2014). It is a common and possibly universal disease of adolescence and early adulthood with an 85% prevalence rate recorded in 12–24 year olds in North America (White, 1998). In other locations prevalence rates recorded in students and institutions are: Far East (9.8%–91.3%), Europe (0.10%–82%), Australasia (14%–91%), Africa (0.2%–36%), Middle East (13%–93.2%), and South America (3%–42%) (Tan and Bhate, 2015).

Although acne is commonly considered a disease of adolescence and early adulthood, it can affect a wide age range including young and older patients. Neonatal acne may be inflammatory due to maternal hormones (Henderson et al., 2000) with 20% having an acneiform eruption commonly settling by 3 months (Mancini et al., 2011) as the maternal hormonal influence wanes, infants may develop non-inflammatory comedonal acne. In males, acne prevalence and severity correlates with advancing pubertal maturation with acne lesions identified in 9 year olds (Lucky et al., 1991). In females acne lesions can also be identified in 9 year olds with early development of comedones associated with more severe disease (Lucky et al., 1997). Acne prevalence in an older European population was reported at 64% in 20–29 year olds, 43.5% in 30–39 year old, 24.3% in 40–49 years old 9.1% in 50–59 years old and 12.7% in those greater than 59 years (Schafer et al., 2001).

Adult acne becomes more prevalent with age in females compared to men both in Europe and Asia (Goulden et al., 1999; Shen et al., 2012). Three types of female acne are identified; "Continuous" where acne never settles from teenage years to adulthood, "Late Start" occurring after the age of 25 years and "Relapse" having had the disease in adolescent years which settles but only to recur in adulthood (Preneau and Dreno, 2012).

There are many different scoring systems for the grade of acne, which makes the epidemiology of the severity of the disease difficult. Generally, acne improves with increasing age (Goulden et al., 1999; Perkins et al., 2012). The risk for acne increases after 11 years of age to a prevalence of 12.1% at 17 years of age in a North American population, more prevalent in boys aged 16–17 years and higher socio-economic groups (Silverberg and Silverberg, 2014). Using objective grading, adult female acne usually is less severe (Goulden et al., 1999; Perkins et al., 2012).

Information on the differences in the epidemiology of acne between ethnicities is limited. In North American acne was found in Asian, African-American, Caucasian and Hispanic women and this study also found acne in women from the UK (Caucasian and Indian), Italy (Caucasian) and Japan (Asian) (Perkins et al., 2011). Severe acne was more prevalent in those of white skin compared with African–American/black, Asian and multiracial groups (Silverberg and Silverberg, 2014). In Peru, Peruvian Indians have significantly less acne than Peruvian whites or Mestizos (Freyre et al., 1998). Interestingly, no cases of active acne were observed on the Kitavan Islanders of Papua New Guinea or the Aché hunter gatherers of eastern Paraguay (Cordain et al., 2002).

Pathophysiology

The pathogenesis of acne is not completely understood, particularly the correct sequence of events leading to comedo formation and then rupture. The clinically diagnostic hall mark lesion of acne is the macrocomedo (>1 mm in diameter) which can be open ("blackhead") or closed ("whitehead") (**Figs. 1** and **2**). The development of a comedo is a complex interaction between occlusion of

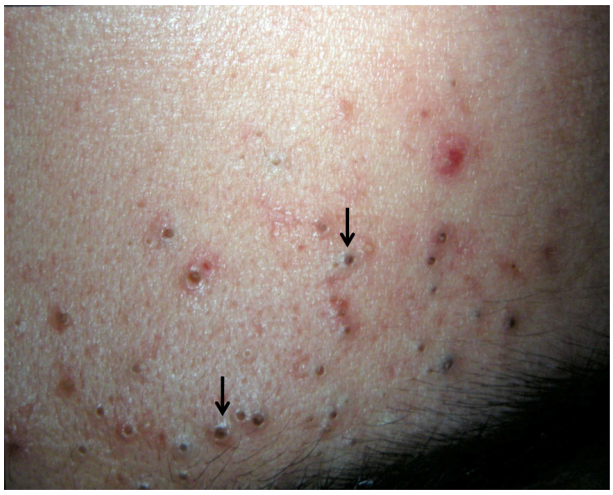

Figure 1 Open comedones "Blackheads" (examples indicated by *arrows*). *Source: Courtesy of DermNet New Zealand.*

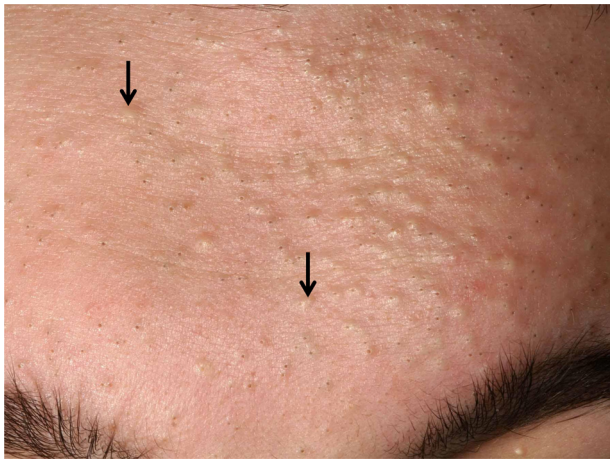

Figure 2 Closed comedones "Whiteheads" (Examples indicated by *arrows*). *Source: Courtesy of DermNet New Zealand.*

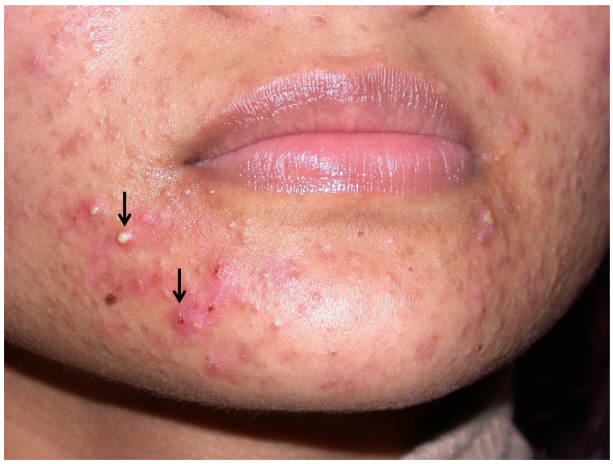

Figure 3 Inflammatory papules and pustules (examples indicated by *arrows*). *Source: Courtesy of DermNet New Zealand.*

the pilosebaceous duct due to cornification, increased sebum production and the bacterium *Propionibacterium acnes*. An inflammatory response centered around the comedo produces the clinical papule or pustule (Fig. 3) which may resolve by fibrosis causing scarring (Figs. 4–6).

The sebaceous gland is a lobular structure with a duct communicating with a hair follicle. The duct is lined by stratified squamous epithelium. Ductal hyperproliferation in acne has been confirmed by immunohistochemistry (Knaggs et al., 1994). Hyperproliferation causes ductal hypercornification with subsequent retention of ductal corneocytes and blockage of the duct lumen. This process forms the basis of microcomedo formation but with sebum and keratinocyte debris accumulating until the larger clinically visible macrocomedo is formed (Gollnick, 2015).

Sebum production is derived from the sebaceous gland, which is under the control of androgens. Testosterone and 5α dihydrotestosterone stimulate the proliferation of facial sebocytes in a dose dependent manner (Akamatsu et al., 1992). Sebocyte activity is also controlled by a number of other factors including growth hormone, insulin-like growth factor and melanocortins (Schneider and Paus, 2010).

P. acnes is an oxygen tolerant, anaerobic bacterium which colonises the pilosebaceous duct (Gollnick, 2015). The exact role of this organism in the pathogenesis of acne is uncertain. *P. acnes* is associated with inflammation through a variety of mechanisms including secreted inflammatory mediators and both the innate and cellular immunity pathways (Beylot et al., 2014). Acne affected follicles show a higher prevalence of *P. acnes* colonisation (Jahns et al., 2012). Although *P. acnes* is found in both affected and unaffected skin, an examination of the skin microbiome reveals that different strains are implicated in acne patients (Fitz-Gibbon et al., 2013).

The inflammatory response is complex and occurs at the early stages of the comedone formation with expression of interleukin 1 (Dreno et al., 2015a; Jeremy et al., 2003). Interleukin 1α has been shown in vitro to promote infundibular cornification (Guy and Kealey, 1998) and interleukin 1β has been demonstrated to drive inflammatory responses to *P. acnes* (Kistowska et al., 2014).

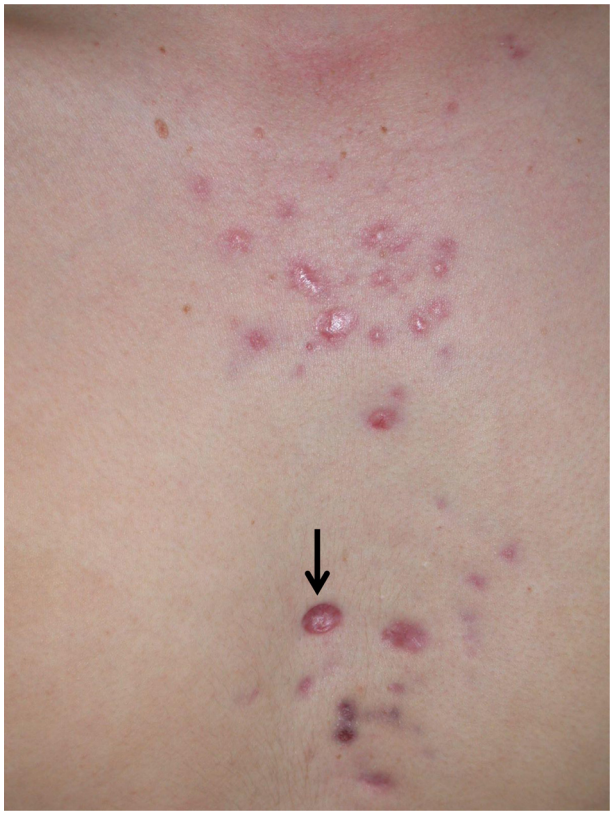

Figure 4 Atrophic acne scarring central chest (example indicated by *arrow*). *Source: Courtesy of DermNet New Zealand.*

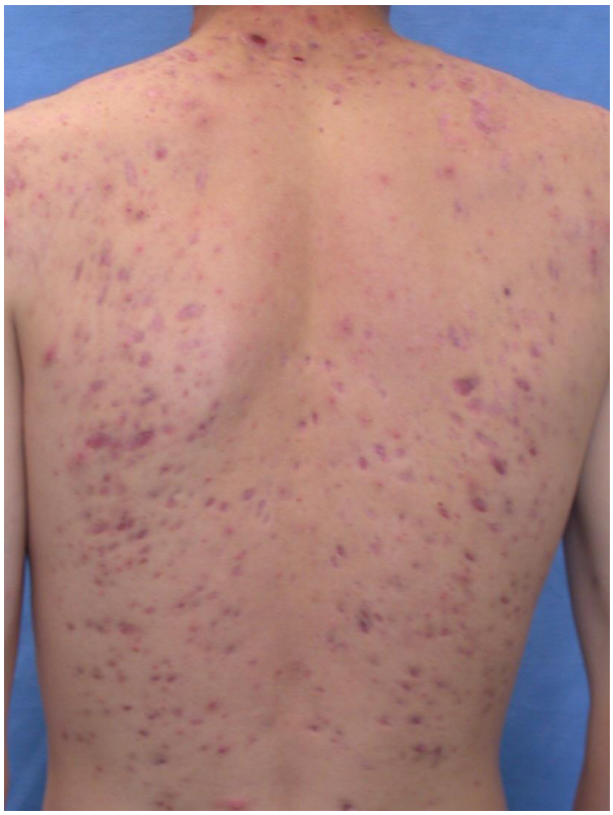

Figure 5 Extensive acne scarring on the back. *Source: Courtesy of DermNet New Zealand.*

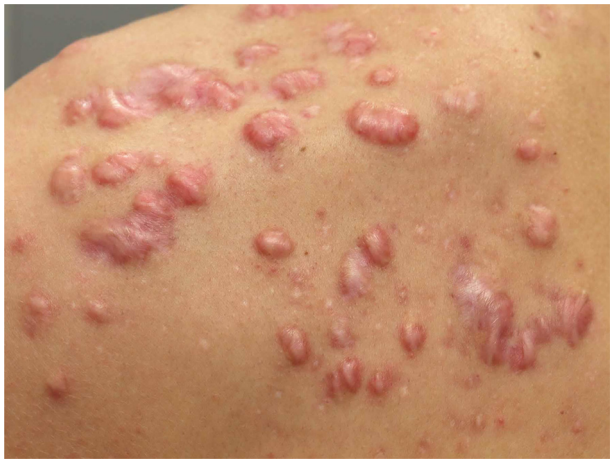

Figure 6 Hypertrophic and keloid acne scarring. *Source: Courtesy of DermNet New Zealand.*

CD4+ T cells are present in early acne lesions (Jeremy et al., 2003) and in vitro *P. acnes* can promote T helper (Th) 17/Th1 responses by inducing interleukin 17, which is a proinflammatory cytokine and interferon γ from CD4+ T cells (Kistowska et al., 2015).

Psychosocial Factors

The psychosocial effects of acne even of mild disease should not be underestimated. The impact of acne is significant. It ranks second in the list of skin diseases measured by the Global Burden of Disease Study 2013 with a disability-adjusted life year score of 0.29% (Karimkhani et al., 2017). There are a number of validated skin specific questionnaires to assess quality of life in skin disease (Gieler et al., 2015). Patients with severe acne report levels of social, psychological and emotional problems as great as those with chronic disabling asthma, epilepsy, diabetes, back pain or arthritis (Mallon et al., 1999). The patient's assessment of their acne frequently differs from that of the health care professional which is a phenomenon not only confined to acne (Mallon et al., 1999; Jones-Caballero et al., 2007; Chen et al., 2015).

The largest group of acne patients with whom pharmacists will interact are adolescents and young adults as they have the greatest prevalence of the disease (see Epidemiology). Adolescence is a time of great change for the individual sometimes combined with egocentrism and preoccupation with self (Revol et al., 2015). Psychological distress and psychological vulnerability can be a particular feature of this period of life (Misery, 2011). Among adolescents with a lot, compared to those with little acne, suicidal ideation is reported three times as frequently by boys (22.6% vs. 6.3%) and twice as frequently by girls (25.5% vs. 11.9%) and those with substantial acne also report low attachment to friends, not thriving at school, never having had a romantic relationship and never having sexual intercourse (Halvorsen et al., 2011). 21st century adolescents have unprecedented access to communication and information which may help or hinder appropriate interventions for their acne. The pharmacist needs to be mindful of these special issues when advising this age group.

Adult female acne also requires particular attention to psychosocial issues. Women over 25 years of age with localised acne are more likely to report higher stress levels and having a psychologically stressful job (Dreno et al., 2015b). Facial acne in adult women also reduces quality of life, is associated with anxiety and depression, impacts self-confidence and impairs ability to concentrate on work or school (Callender et al., 2014; Tanghetti et al., 2014). Although acne tends to improve with age in women (Perkins et al., 2012) it has a significant psychosocial burden.

Diagnosis

The diagnosis of uncomplicated acne is clinical and involves taking a history and examining the patient. There are no specific investigations required unless there is suspicion of other co-morbidities. Acne can be associated with endocrine disorders such as polycystic ovarian syndrome and rarely with other disorders including: cushing syndrome, congenital adrenal hyperplasia, andogen secreting tumours and acromegaly. Rare non endocrine associations include: Apert syndome, Synovitis Acne Pustulosis Hyperostosis Osteitis Syndrome (SAPHO), Beçhet syndrome and PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne. Medication can induce acne and "acneiform" eruptions including corticosteroids, anabolic steroids, progesterones, lithium, isoniazid, phenytoin, halogen exposure, epidermal growth factor receptor inhibitors and B vitamins including riboflavin (B2), pyridoxine (B6) and cyanocobalamin (B12) (Lolis et al., 2009). Pomade acne, first described in African–American men, is due to the application of occlusive cosmetic oils and creams to the skin (Plewig et al., 1970).

Severe acne in adolescents has recently been found to be associated with other comorbidities including sinopulmonary disease; sinus infection, non-streptococcal sore throat, asthma, non-asthmatic lung disease and gastrointestinal disease including; reflux/heartburn, abdominal pain, nausea and vomiting and food/digestive allergy but the significance of these associations is uncertain (Silverberg and Silverberg, 2014).

History and Examination

In the setting of a busy pharmacy practice a quiet and private space or room should be set aside for the history and examination. Patients are unlikely to volunteer sensitive information in a public setting.

A complete history should be taken. Important elements of the history are the duration, previous treatments and psychosocial effect of the disease. Other components of the history are relevant previous illness, current medication and previous recorded drug allergy or intolerance. A positive family history of acne is often obtained. A detailed social history should include an occupational history, cosmetic usage, contraception and family planning.

Be prudent in the need to ask for a chaperone. The examination should be carried out in a well-lit area and if needed with the aid of magnification. All components of acne should be assessed including comedone, papule, pustule, nodule and scarring. Examine the face and the trunk both front and back. A papule is defined as an elevated, solid, palpable lesion $\leq$1 cm in diameter, a nodule as an elevated, solid palpable lesion $>$1 cm in diameter located primarily in the dermis and/or subcutis and a pustule as a circumscribed lesion containing pus (Nast et al., 2016b). Comedones can be difficult to see and may require gentle stretching of the skin and observation at a shallow angle (**Figs. 1** and **2**). Failure to identify significant comedonal disease can result in suboptimal therapy and significant flaring especially when patients are treated initially with isotretinoin (See Systemic Treatment) (Cunliffe et al., 2000).

Severe inflammatory, nodular acne as well as superficial inflammatory lesions, all have the potential to scar and affect both sexes equally in up to 95% of patients. Different patterns of scarring are described including ice-pick, macular atrophic, follicular macular atrophic, hypertrophic and keloid (Layton et al., 1994) (see **Figs. 4–6**).

Differential Diagnosis

Usually the diagnosis of acne is self-evident when the cardinal features of the disease are identified. Acne may co-exist with other diseases of the face and trunk. However, there are a number of common papular and inflammatory conditions on the face and truck that can potentially mimic acne. Non-inflammatory lesions mimicking comedones include milia, which are small white dome shaped keratinous cysts approximately 1–2 mm in diameter (**Fig. 7**) and adnexal tumours such as syringomata, which are 1–2 mm skin colored papules often around the eyes and derived from sweat glands (**Fig. 8**). Inflammatory conditions include rosacea (**Fig. 9**) and periorificial dermatitis (**Fig. 10**). Rosacea is an inflammatory condition causing flushing, erythema, papules and pustules on the face. The absence of comedones in the presence of these symptoms and signs is a useful diagnostic clue. Periorificial dermatitis describes erythema, papules and pustules around the eyes or mouth. It may be idiopathic or induced by creams including topical steroids and cosmetics.

Pharmacological Management of Acne Vulgaris

The choice of treatment will depend on many factors including the severity of the acne, psychosocial impact, patient choice and previous treatments (**Fig. 11**). The specific treatment options available vary between countries and will be governed by different legislation. Topical agents are usually appropriate for mild, facial acne and short term use ($<$12 months). They are difficult to use on

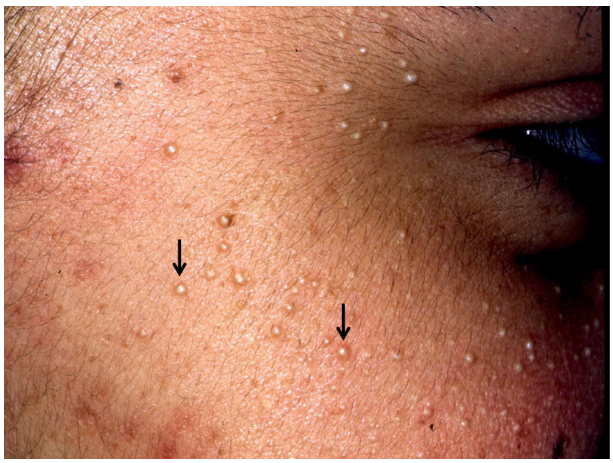

Figure 7 Milia (examples indicated by *arrows*). *Source: Courtesy of DermNet New Zealand.*

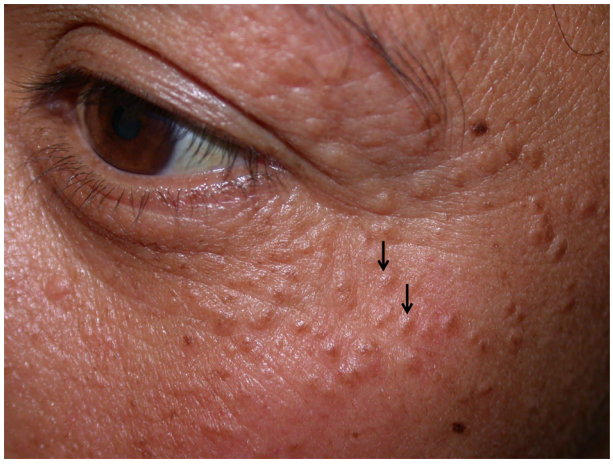

Figure 8 Syringomata (examples indicated by *arrows*). *Source: Courtesy of DermNet New Zealand.*

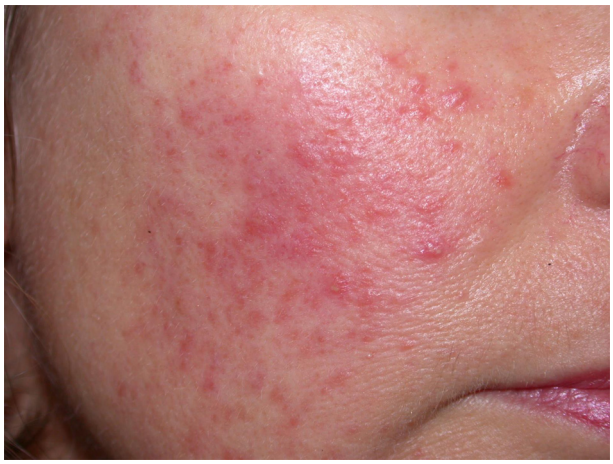

Figure 9 Rosacea. *Source: Courtesy of DermNet New Zealand.*

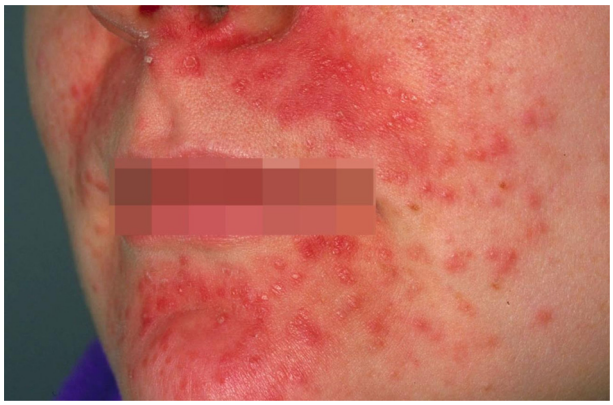

Figure 10 Perioral dermatitis. *Source: Courtesy of DermNet New Zealand.*

the trunk. Systemic treatment, with or without topical treatment, is indicated for failed topical treatment, extensive involvement including face and trunk or severe acne at any site. Women who are attempting to conceive or who are pregnant and children need special consideration. There is increasing concern about the development of antimicrobial resistance with prolonged use of topical and systemic antibiotics in the management of acne. In addition to their antimicrobial action antibiotics may have an anti-inflammatory effect in acne (Walsh et al., 2016).

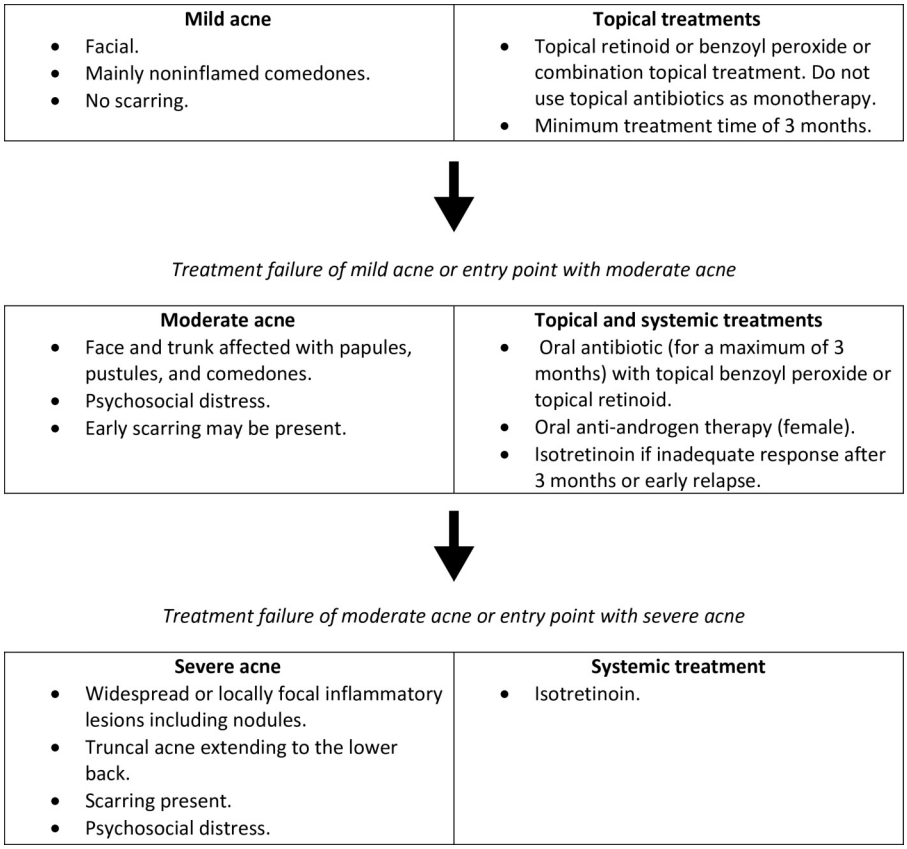

Figure 11 Pharmacological management of acne vulgaris.

Pharmacological interventions for acne should be re-evaluated after 8 weeks for mainly comedonal or mild inflammatory acne or 12 weeks for severe disease (Gollnick et al., 2016).

Topical Agents

Topical agents include salicylic acid, benzoyl peroxide, retinoids, azelaic acid, sulphones, and antibiotics. There are also combination topical treatments.

Salicylic Acid

Salicylic acid is a common over the counter preparation for acne and it is also combined with other topical agents such as clindamycin and benzoyl peroxide to treat acne (Akarsu et al., 2012). Salicylic acid can be used to treat acne because it has keratolytic and comedolytic effects (Akarsu et al., 2012; Degitz and Ochsendorf, 2008).

Benzoyl Peroxide

Benzoyl peroxide is widely available and usually accessible as an over the counter medicine in pharmacies. The exact mechanism of action is uncertain but it has both antimicrobial effect against to *P. acnes* and keratolytic activity (Lamel et al., 2015; Mohd Nor and Aziz, 2013). When benzoyl peroxide is encapsulated in nanoparticles the antimicrobial effect is mediated by direct cell wall damage (Friedman et al., 2013), which may be the reason why resistance by *P. acnes* is not described (Mohd Nor and Aziz, 2013; Lamel et al., 2015).

Benzoyl peroxide is available in differing concentrations including 2.5%, 5%, 10% and formulations including lotion, cream or a gel. A systemic review of randomised vehicle-controlled trials of different preparations and strengths of benzoyl peroxide demonstrated a statistically significant average overall reduction in non-inflammatory lesions of 41.5% and inflammatory lesions of 52.1% (Lamel et al., 2015).

Treatment should be initiated with the lower strength preparations and application is usually twice daily depending on the tolerance of the patient. Side effects include bleaching fabric and hair, irritant contact dermatitis and rarely severe hypersensitivity reactions including angioedema, periorbital oedema, bronchospasm, and syncope (Administration, 2014).

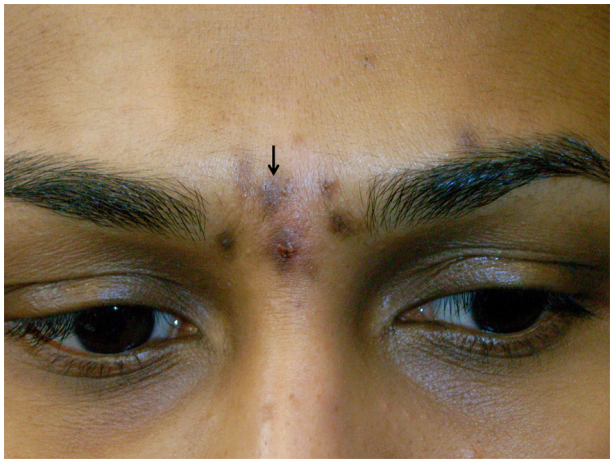

Figure 12 Post-inflammatory hyperpigmentation due to acne (example indicated by *arrow*). *Source: Courtesy of DermNet New Zealand.*

Retinoids

Topical retinoids are important agents in the treatment of acne particularly for their comedolytic effect and in combination with other agents for the treatment of all types of acne (Zaenglein et al., 2016). Consensus guidelines for the management of predominantly comedonal facial acne recommend topical retinoids as the first line approach (Gollnick et al., 2016). Multiple randomised controlled studies have verified the effectiveness of these agents for the management of acne (Vera et al., 2017). Topical retinoids include; isotretinoin, tretinoin, adapalene and tazarotene available in different formulations including cream, gel and foam. There is a role for topical retinoids in maintenance treatment after discontinuing oral therapy (Zaenglein et al., 2016). Common side effects are dryness, peeling erythema and irritation and photosensitivity. Topical retinoids are contra-indicated in pregnancy and women of childbearing age must not become pregnant while using these drugs, as retinoids are highly teratogenic.

Azeleic Acid

Azaleic acid has antibacterial, anti-keratinizing and anti-inflammatory effects (Vera et al., 2017; Zaenglein et al., 2016). Azaleic acid has an additional benefit of having reversible inhibitor tyrosinase activity, which is a key enzyme for melanogenesis (Nazzaro-Porro, 1987), which may reduce the problem of post inflammatory hyperpigmentation associated with acne, especially in those patients with skin of colour (**Fig. 12**). Local skin irritation may be experienced as a side effect.

Sulphones

Topical dapsone is available as a treatment for acne. The mechanism of action is not fully understood but it may work as an anti-inflammatory and anti-bacterial agent (Vera et al., 2017; Zaenglein et al., 2016; Aslam et al., 2015). Women may derive more benefit compared to men using topical dapsone (Tanghetti et al., 2012).

Antibiotics

Monotherapy with topical antibiotics for the treatment of acne is no longer recommended because of the development of antibiotic resistance (see section "Systemic Antibiotics") (Vera et al., 2017; Zaenglein et al., 2016; Sandoval et al., 2014). If a topical antibiotic is to be used then it should be used in combination with a non-antibiotic agent such as benzoyl peroxide to minimise the risk of resistance. Clindamycin and erythromycin are commonly used.

Systemic

Oral drugs used to treat acne are antibiotics, hormonal agents, and isotretinoin.

Antibiotics

Systemic antibiotics have been used in the treatment of acne for many years. However, the routine use of these agents as monotherapy in the management of acne is being increasingly questioned in the light of the development of resistance and the need for antibiotic stewardship (Dreno, 2016; Adler et al., 2017; Walsh et al., 2016). The use of oral antibiotics as the only treatment for acne is not recommended and guidelines suggest the addition of a non-antibiotic topical agent such as a topical retinoid, benzoyl peroxide or azaleic acid in addition to the oral antibiotic (Dreno, 2016; Adler et al., 2017). Limiting the duration of treatment with oral antibiotics ideally for 3 months, may limit resistance development (Nast et al., 2016a; Zaenglein et al., 2016). Resistant strains of *P. acnes* can result in lack of response to treatment of acne and serious infection such as endocarditis, prosthetic joint infection and

breast implant infections can occur (Walsh et al., 2016). Furthermore, the use of antibiotics for acne exerts selection pressure on other bacteria of the microbiome, which can develop resistance and this is of concern particularly for *Staphylococci* (Walsh et al., 2016).

A large number of different types of antibiotics have been used including tetracyclines (e.g., doxycycline, minocycline), macrolides (e.g., erythromycin, azithromycin), trimethoprim and trimethoprim/sulphamethoxazole (Zaenglein et al., 2016). Each group has a number of different potential side effects and these include gastrointestinal upset, drug eruptions, photosensitivity and hypersensitivity reactions of varying severity. Tetracyclines should not be prescribed to children under 12 years of age to prevent enamel staining in secondary teeth. Minocycline can induce a lupus-like syndrome in females with a rate of 52.8 cases per 100,000 prescriptions compared to 17.2 cases per 100,000 prescriptions for oxytetracycline (McHugh, 1999).

Hormonal Agents

These agents are combined oral contraceptives, cyproterone acetate and spironolactone. Combined oral contraceptives contain oestrogen and synthetic progesterone and are effective in reducing inflammatory and non-inflammatory acne (Arowojolu et al., 2012). They reduce the effect of androgens by reducing ovarian androgen production and by a secondary effect of increasing steroid hormone binding globulin, which lowers circulating testosterone levels (Shaw, 2002). Cyproterone acetate is an androgen receptor blocker and synthetic progesterone. It can be used alone and in combined oral contraceptives although it is often added at a low dose so it is uncertain if it acts through its androgen blocking role or its combined effect on cycle regulation (Shaw, 2002). The use of these medications requires considerable oversight and attention to suitable eligibility including age, smoking history, breast cancer history, hypertension, diabetes, pulmonary or deep vein thromboembolism, cardiovascular disease, weight, headache, hepatic disease and dyslipidaemia (Zaenglein et al., 2016).

Spironolactone is an androgen receptor antagonist (Garthwaite and McMahon, 2004). The use of this drug in acne is "off label". It can inhibit 5α-dihydrotestosterone in human sebaceous glands and in vitro has been demonstrated to androgen-induced human sebocyte proliferation (Akamatsu et al., 1993). A systematic review of randomised controlled trials concluded that there was limited quality evidence to use spironolactone in usual doses (≤100 mg/day) in adult females (Layton et al., 2017). Electrolyte disturbance can occur with the use of spironolactone particularly hyperkalaemia.

Isotretinoin

Isotretinoin is a derivative of retinoic acid and is an effective treatment for patients with acne. It decreases the size of sebaceous glands, the production of sebum and normalises follicular hyperkeratinisation (Zaenglein et al., 2016; Peck et al., 1979; Torma, 2001). The indications for the use of isotretinoin are: for severe nodular acne, treatment resistant acne or acne that is causing significant physical or psychosocial distress (Zaenglein et al., 2016). Depending on the severity, dose and patient tolerance of isotretinoin, treatment duration may be many months. Isotretinoin is commonly started at a low dose, which is increased. Using a lower dose of isotretinoin over a longer time period may be just as effective as a higher dose used for shorter periods but associated with significantly fewer adverse side-effects (Rademaker, 2013).

There are a number of potentially significant side effects with the use of isotretinoin. Mucocutaneous dryness is almost universal with dry skin, dry eyes and a propensity for nose bleeds. These can be mitigated by reducing or temporarily stopping the drug and with the use of appropriate emollients. It is common to experience a flare of acne when starting isotretinoin at higher doses and special care is needed initiating treatment in extremely severe cases when additional therapy such as systemic steroids or oral antibiotics may be required to reduce the risk. Isotretinoin is highly teratogenic and women must not fall pregnant whilst taking the drug. Women who are sexually active must practice effective contraception and for this to be established before isotretinoin is started. Isotretinoin causes skin fragility therefore patients should avoid hair waxing. Isotretinoin is a common photosensitising drug so care needs to be taken with sun protection where needed.

Isotretinoin can rarely cause abnormalities of lipids and liver function therefore some patients will have these monitored prior to and during therapy. A full blood count may also be monitored. Pregnancy testing prior to starting isotretinoin is essential with periodic monitoring during the treatment course.

Patients who have been treated with isotretinoin may wish to have further treatment for acne scarring. Although there are reports of adverse outcomes following treatment whilst on isotretinoin (Zachariae, 1988; Rubenstein et al., 1986) leading to the recommendation to defer such treatments for 6–12 months after stopping isotretinoin, more recent evidence suggests this restriction may not be needed (Prather et al., 2017; Zaenglein et al., 2016).

An important drug–drug interaction of isotretinoin is with tetracyclines. Tetracyclines are often used to treat acne and if they are unsuccessful it is common for a switch to be made to isotretinoin. The development of severe headache due to benign intracranial hypertension is a potential side effect of both of these drugs and more likely if they are inadvertently taken concurrently. Additionally, if patients are using a topical agent to treat their acne this should be discontinued as excessive dryness can be problematic. Patients who take vitamin supplements should avoid vitamin A. Isotretinoin is a derivative of this vitamin and side effects could be compounded if they are taken together.

The role of isotretinoin in mood change, depression and suicidal ideation is uncertain and not proven. A meta-analysis of 31 studies concluded that isotretinoin did not appear to be associated with an increased risk of depression and that the treatment of acne appeared to ameliorate depressive symptoms (Huang and Cheng, 2017). Treating patients who are depressed because of their acne is beneficial. Similarly, at present, evidence is insufficient to prove either an association or causal relationship between isotretinoin and inflammatory bowel disease (Zaenglein et al., 2016).

Non-Pharmacological Treatment

The evidence around the non-pharmacological interventions for the management of active acne and acne scarring is limited.

Light Therapy

Various light devices have been used to treat acne including intense pulsed light, narrowband blue, narrowband red, combined blue–red light and lasers but there are limited studies (Handler et al., 2016; Zaenglein et al., 2016). These devices may be more beneficial for inflammatory rather than non-inflammatory acne (Handler et al., 2016). Their mechanism of action is not fully understood but may include activating natural porphyrins produced by *P. acnes*, reducing keratinocyte inflammation and destroying *P. acnes* (Handler et al., 2016). Photodynamic therapy involves applying a photosensitizing agent to the skin such as aminolaevulinic acid, which is preferentially absorbed by the pilosebaceous units. A light emitting device is used to activate the agent damaging the pilosebaceous unit and reducing *P. acne* (Ozog et al., 2016; Zaenglein et al., 2016). Of the light therapies, most evidence exists for the use of photodynamic therapy (Zaenglein et al., 2016).

Chemical Peels

Chemical peels may improve acne and a wide variety of agents have been used including glycolic acid and salicylic acid to induce a partial-thickness skin injury by reducing keratinocyte adhesion and plugging (Kessler et al., 2008). These two agents may have a role for the management of non-inflammatory acne but repeated treatments are needed and high quality evidence is lacking (Zaenglein et al., 2016; Abdel Hay et al., 2016).

Diet

The role of diet in acne is unclear and no specific dietary changes are recommended (Zaenglein et al., 2016; Fiedler et al., 2017). There is some evidence to support an association with high glycaemic diets (Fiedler et al., 2017; Kwon et al., 2012; Smith et al., 2007).

Scarring Treatment

Scarring is the consequence of inflammatory acne. With effective treatment options, especially isotretinoin, all options should be explored to prevent scarring however it is inevitable that some patients will scar. Different types of acne scar are formed including keloid, hypertrophic and atrophic (**Figs. 4–6**). There are a wide variety of modalities to treat scars depending on the subtype including lasers, dermabrasion, chemical peels, needling, subcision, punch excision, radiofrequency, stem cell therapy, fat transplantation, platelet rich plasma and fillers (Zaleski-Larsen et al., 2016; Sanchez Viera, 2015). However, a Cochrane review noted the lack of high-quality evidence about the effects of different interventions for acne scars (Abdel Hay et al., 2016). Silicone gel sheets are available for purchase and have been used for hypertrophic and keloid scars. However, another Cochrane review reported weak evidence of benefit for the use of silicone gel sheeting (O'Brien and Jones, 2013).

Role of the Pharmacist in the Management of Acne Vulgaris

Pharmacists may be the first health care professional with whom a patient with acne contacts and this presents an opportunity to offer cost effective advice. Take a careful history with particular attention to psychosocial issues and examine the patient in a well-lit room including the chest and back. A comprehensive assessment will guide appropriate management. The pharmacist will have access to a range of topical treatments available for general sale or pharmacist only sale depending on the regulatory environment.

General advice is useful. It is important to reassure the patient that effective treatment options exist and that a therapeutic "ladder" can be followed utilising topical agents, topical and systemic agents then isotretinoin if needed, with some requiring a prescription. It is important to place the patient on the appropriate initial rung of the ladder after a thorough assessment (**Fig. 11**). Picking or squeezing comedones, papules and pustules is not recommended as if done with vigour this may contribute to the inflammatory response and subsequent scarring. A variant of acne called acne excoriée exists which can form part of a compulsive skin picking disorder, which is frequently associated with scarring. Avoiding occlusive make up and the use of non comedogenic products will help. Cigarette smoking has been associated with post-adolescent acne (Capitanio et al., 2009). Some patients perceive acne as a dirty disease and wash excessively. This should be discouraged as excessive washing will lead to irritancy and compound the effects of retinoids. Encourage the patient to wash normally using gentle soaps and washes. There is a lack of evidence for the use of complementary therapies in the treatment of acne including herbal medicine, acupuncture or wet cupping and low quality evidence from single trials for the use of tea tree oil, bee venom and low glycaemic load diet (Cao et al., 2015).

Pharmacists are well placed to manage mild, non-scarring predominantly comedonal acne of the face. Having decided on a therapy, clear and simple instructions are needed. Patients should be told that they may need to wait up to 8–12 weeks before they see any benefit. Some patients only apply topical agents to the spots that they can see on their face so it is important to clearly state

that the preparation should be applied to all of the skin of the face. The finger- tip unit is a useful concept (Long and Finlay, 1991). One finger–tip unit is the amount of cream expressed from the distal skin-crease to the tip of the index finger and approximately 2½ finger-tip units are required to treat the face and neck so approximately 1 or 2 finger-tip units would be required to treat a face. The patient should be reviewed at 8–12 weeks and if clear improvement is noted then continue with the therapy. However, if there is no improvement or deterioration despite compliant use of the preparation the patient should be referred to their primary care physician or a dermatologist. It is useful to ask the patient to bring the tube of cream so that consumption and therefore compliance can be estimated from the quantity used.

Pharmacists have a choice of the type of preparation to recommend to patients with acne, either as active treatment or an emollient to mitigate dryness due to treatment effect. Preparations may include lotions, gels, foams, creams and ointments. In many countries benzoyl peroxide is available as an over the counter medication and, provided there are no contra-indications, is a good starting point for pharmacists. Patient preference partly will drive choice as well as the need for therapeutic efficacy. Treatments will fail if the patient does not use them because they are too irritant or look unappealing when applied. Creams because of their effect of occlusion and hydration of the epidermis enhancing penetration of the product, are more efficacious than gels or lotions but less cosmetically appealing. A useful therapeutic manoeuvre is to recommend that the active treatment, if it is occlusive and cosmetically visible, is applied at night and removed in the morning. If needed a lighter and more cosmetically appealing product can be used during the day.

Patients with extensive acne, significant inflammatory acne at risk of scarring or with established scarring and those with significant psychosocial concern regardless of the extent of acne should not be managed by pharmacists but be referred to their primary care physician or dermatologist.

Pharmacists are ideally placed to work with the primary care physician or dermatologist when patients attend to have their script dispensed. A good working relationship between the health care professionals involved is important so that seamless multidisciplinary advice is offered to the patient. Pharmacists are likely to have oversight of all the patient's medications and have knowledge of their over the counter purchases so can check for potential drug–drug interactions for example the potential loss of efficacy of the oral contraceptive when starting oral antibiotics for acne if the antibiotic induces vomiting or diarrhoea and appropriate management should be advised.

Pharmacists can play a pivotal role in the management of a patient on isotretinoin. The point of dispensing offers an opportunity to reinforce the important issues around this medication. A degree of skin dryness is universal with this medication and which may also affect the lips and mucous membranes. Patients who use contact lenses can find them too irritating to use whilst on isotretinoin because of ocular dryness. It is important to give suitable advice about emollients for the skin, dry eyes and lips. Isotretinoin commonly photosensitises patients and sun protection needs to be encouraged with suitable clothing, sun protection behaviour and adequate use of sunscreens. There is confusion around sunscreens and they are often under used by patients so this is another opportunity to offer an additional health care message (Chao et al., 2017; Petersen and Wulf, 2014). Some sunscreens are combined with a moisturiser and there are lip slaves that contain sunblock, which should also be advised.

In a recent study, using a case vignette technique, pharmacists were able to confidently and appropriately recommend antibiotics when presented with a limited range of diseases, including moderate acne (Ung et al., 2016). There is the potential for expanding the pharmacist's role in the management of acne in the future. However, more research would need to be conducted to evaluate whether this would be able to be appropriately managed in the community setting given the pressing need for antibiotic stewardship, the probability of antibiotics being used less and non-antibiotic therapies being used more frequently for the management of acne in the future.

Central to good care is effective, and if needed robust, communication between the patient, pharmacist and doctor. There is a danger of fragmentation of care when individual practitioners do not communicate with the potential for adverse outcomes. Good communication ensures that all three participants in the therapeutic triad know what the other is doing.

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Resources

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Management of Dermatology Disorders and the Pharmacist's Role: Acne, Psoriasis, Atopic Dermatitis, and Fungal Infections

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Learning Objectives

After reading this chapter, the reader should be able to:

- understand the epidemiology, etiologies, clinical presentations, and diagnoses of some common skin disorders.
- discuss the management of the common skin disorders including nonpharmacological and pharmacological interventions.
- discuss the current and future role of pharmacist in the management of the common skin disorders.

Key Points

- Despite the high prevalence of some common skin disorders and high utilization of self-care, the role of the pharmacist in the management of skin disorders has not been widely explored.
- Considering patients' limited access to dermatology consultation clinics for common skin disorders, community pharmacists have the potential to provide safe and effective advice to patients on pharmacologic and nonpharmacologic interventions including personal hygiene and lifestyle modifications.
- It is also evident that pharmacist interventions for common skin disorders can be cost-effective for both consumers and health care system. In an interprofessional team of health care providers, pharmacists are considered as "initial screeners" and the "final checkers."

- Community pharmacists have the opportunity to identify drug-related problems and to develop suitable pharmaceutical care plan to follow-up with patients for an optimal skin disease management.

Introduction to Common Skin Disorders

Skin is the largest organ constituting 17% of a person's body weight. The major function of skin is to serve as a barrier and to protect human body from moisture, humidity, variation in temperature as well as a protection against the invasion of pathogenic microorganisms (McGrath et al., 2004). Skin conditions are known to bring a significant change in patient's health-related quality of life (HRQoL), affecting daily life, and causing physical discomfort and psychological problems. In this chapter, we will describe the prevalence, etiologies, signs and symptoms, diagnosis, and pharmacotherapy of common skin disorders, particularly acne vulgaris, psoriasis, atopic dermatitis (AD), and fungal infections. The chapter discusses the pharmacist's role in the management of these skin disorders.

Prevalence of Common Skin Disorders

The Global Burden of Disease (GBD) 2010 estimates for 1990–2010 from 187 countries reported skin conditions as the 4th leading cause of nonfatal disease globally affecting 985 million people after dental caries, tension-type headache, and migraine (Hay et al., 2014). Fungal infections, subcutaneous skin diseases, and acne are the most commonly occurring skin diseases globally. Taking into account the disability adjusted life years (DALYs), skin remains the 18th leading cause of health burden globally (Hay et al., 2014). Several factors such as environment, access to proper health care, socioeconomic status, and cultural practices could contribute toward the high prevalence of certain skin disorders such as acne vulgaris (Lynn et al., 2016).

Acne vulgaris is a universal teenage problem which affects people between the ages of 15 and 17 years (Bhate and Williams, 2013). As per Global Burden of Disease (GBD) study, acne vulgaris affects nearly 85% of young adults aged from 12 to 25 years (Celgene, 2014). Regardless of sex and socioeconomic status, the production of androgens during puberty explains the prominence of acne among young adults (Lynn et al., 2016). Although genetic influence of acne remains uncertain, a study conduct among Chinese undergraduates found acne to have a 78% heritability in first-degree relatives (Wei et al., 2010). Atopic dermatitis (AD) is commonly seen in the early stages of life affecting up to 20% of children and up to 3% of adults, where it is evident that its prevalence is still increasing, especially in low-income countries (Nutten, 2015). On the other hand, the reported prevalence of psoriasis ranges between 0.09% and 11.4%, causing great emotional, physiological, and psychological burden which may occur at any age (Celgene, 2014; World Health Organization, 2016).

Etiology of Common Skin Disorders

In general, three important factors explain the etiology of skin disorders (i.e., hygiene, climate, and overcrowding) (Hay et al., 2014). Specific to skin conditions such as acne, a number of hormonal, genetic, dietary, and environmental factors are associated with its progression (Wells et al., 2000). During puberty, a prevalent cause is hyperplasia of sebaceous glands. Overproduction of androgen stimulates the production of sebum which is associated with acne (Gollnick et al., 1991). Bacterial colonization and release of proinflammatory mediators and lipases are also linked with acne (Leyden et al., 1975). Mechanical trauma, cosmetics, and steroids are some of the external factors which may attribute to acne. Psoriasis, on the other hand, is associated with genetic predisposition and an abnormal immune response. In genetically susceptible individuals, it is assumed that T cells and dendritic cells (DCs) cause inflammatory cytokines to create an environment in the skin that stimulates proliferation of endothelial cells causing psoriasis (Liu et al., 2007). AD often referred to as eczema, is linked with environmental and genetic factors. It is observed that patients with AD have positive family history (Al-Shobaili et al., 2016) and is influenced by genes with general effects on dermal inflammation and immunity (Cookson et al., 2001). Environmental factors such as food allergens particularly eggs, milk, peanuts, and soya may contribute to AD (Leung et al., 2004). Besides that, fungal infections can be acquired both endogenously and exogenously. The endogenous fungal infections of skin and mucosa are commonly seen among patients with compromised immune system. Furthermore, malnutrition and diabetes mellitus also contributes to fungal infections (Alldredge et al., 2013). Similarly, ecological factors such as excessive heat and humidity contribute to fungal skin infections (De Pauw, 2011).

Clinical Presentations of Common Skin Disorders

Acne lesions are most commonly located on face, neck, back, and chest area. In severe cases, they may extend to the buttocks. Acne vulgaris could be inflammatory and noninflammatory. The noninflammatory acne is often characterized by open and closed comedones. The closed comedones are smaller in size (1–2 mm) which are visible as whiteheads on a stretched skin. However, the open comedones, also called blackheads are relatively larger in size (2–5 mm) and are dark in color (Gollnick, 2003). The inflammatory acne is characterized by pustules, which appear as white lesion filled with pus and are approximately 5 mm in

diameter (Gollnick, 2003). These lesions may be itchy and can be painful upon eruption. Nodular lesions are the most severe type of inflammatory acne, having warm lesions often 5 mm or greater in diameter.

The main clinical feature of AD is intense itch with dry skin. AD is commonly associated with inflammation and exudation. Because of its chronic nature, it can cause physical and emotional distress especially in adult patients. The symptoms of AD usually appear during the first 8–12 months of childhood, while in severe cases it may continue until adulthood (Ring et al., 2012). The child may have dry and scaly patches on the skin of the forehead, face, cheek, and scalp. During acute phases of the disease, red itchy skin with sometimes blisters is commonly seen (Ellis et al., 2003).

Psoriasis, most commonly involves the skin and nails causing great physical and emotional burden (Fortune et al., 2002). Skin lesions are localized or generalized causing itching, stinging, and pain. The lesions are well demarcated, mostly sharp red papules usually covered with white or silver scales which sometimes crack and bleeds (World Health Organization, 2016).

Superficial fungal infections may vary in their presentation. *Tinea pedis*, particularly affects the web of the toe and the planter surface of the foot. *Tinea capitis* can cause hair loss with broken hairs at the surface. On the other hand, *Tinea unguium* (onychomycosis) causes separation of the nail from the nail bed. The four major types of onychomycosis are: distal subungual, proximal subungual, superficial, and total dystrophic onychomycosis (Faergemann and Baran, 2003). *Tinea corporis* may have vesicles and pustules typically appearing on exposed skin of leg, arms, and trunk. *Tinea manuum*, usually affect one hand with prominent redness and scaling (Patient.info, 2015).

Diagnosis of Common Skin Disorders

In order to diagnose skin infections, it is critical to consider patient assessment, including signs and symptoms, genetic history as well as dietary and lifestyle habits. Furthermore, psychological issues and drug-induced skin disorders need consideration for an accurate diagnosis.

The diagnosis of acne vulgaris generally depends on clinical history and physical findings. Although a misdiagnosis is rare, it is critical to differentiate between acne rosacea, which is similar in presentation in adults (Wang and Zane, 2008). A variety of drugs provoke acne, including steroids, anti-epileptics, antituberculosis drugs, and lithium (Kazandjieva and Tsankov, 2017). The diagnosis may include a detailed history of drug consumption as well as ruling out other clinical factors known to trigger acne. Similarly, the diagnosis of AD is based on clinical presentation of the skin and no objective test is available for confirmation. Several criteria are suggestive of the accurate clinical diagnosis such as age dependent eczematous skin lesions, early onset, pruritus, stigmata of atopy, personal and family history of atopy, and IgE mediated sensitization (Leung, 2013).

Diagnosis of psoriasis is usually made based on clinical presentation rather than laboratory data. The disease is generally classified into mild, moderate, and severe. Disease assessment often includes severity of symptoms, body surface area involved and the effects on patient's HRQoL (Dipiro et al., 2016). The diagnosis of fungal infection remains a challenge for most clinicians. Due to nonspecific clinical presentation and difficult colonization in case of invasive disease, blood culture reports are usually negative (Stevens, 2002). Several tests on body fluid may be useful for an accurate diagnosis.

Management of Common Skin Disorders

Nonpharmacological Treatment

Acne Vulgaris

In accordance with recent dermatological guidelines (Zaenglein et al., 2016), drugs such as antibiotics, retinoid, benzoyl peroxide, and hormonal agents are first line treatment for acne. However, these drugs have associated risks such as antibiotic resistance and side effects. Although data on safety and efficacy of nonpharmacological therapies are scarce, these therapies are often used by health care professionals. The most common types of nonpharmacological therapies used are laser and light-based therapies, chemical peels, and fractional micro-needling radiofrequency (De Vries et al., 2018). Cleansing with warm water and mild facial cleanser twice daily is recommended. The patient must not squeeze or prick at the acne lesions. This will prevent the scarring and recurrence. Oil free moisturizers may improve the penetration of anti-acne medicines into the skin. Although limited evidence on surgical comedones extraction is available, comedones removal is often helpful in the management of comedones that are resistant to other therapies (Zaenglein et al., 2016). Chemical peels such as glycolic acid and salicylic acid chemical peels may end in slight improvement in comedonal acne (Grover and Reddu, 2003). A number of laser and light devices have been investigated for acne. However, among all, the most evidences exist for photodynamic therapy (PDT) (Pollock et al., 2004; Zaenglein et al., 2016).

Atopic Dermatitis (AD)

Nonpharmacological therapies in the management of AD aim to complement the conventional therapies, but not a substitute. These therapies are to reduce the episodic symptoms of AD and to improve patient's HRQoL (Criton and Gangadharan, 2017). Dry skin is one of the characteristic of AD. Gentle cleansing and bathing (only 5 minute duration) is suggested to get rid of crust and contaminants in case of bacterial infection (Wollenberg et al., 2018). Adding antiseptics such as sodium hypochlorite in the bathing

water may also benefit AD patients (Wollenberg et al., 2018). To avoid dehydration of the skin, use of bath oil or mild emollients may help to keep the skin soft and hydrated (Wollenberg et al., 2016). Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate to severe AD to decrease disease severity and water loss during flares (Criton and Gangadharan, 2017; Eichenfield et al., 2014). Food sensitization happens in approximately 50% of children with severe AD. Thus, AD patients should be evaluated for any food allergies (Wollenberg et al., 2016). Probiotics such as lactobacillus mixtures have been shown to have beneficial effects in preventing the development of AD (Grüber, 2012; Isolauri et al., 2000).

Psoriasis

Nonpharmacological treatment is recommended in all stages of psoriasis (Menter et al., 2009). This mainly includes stress-reduction strategies, moisturizers, and sunscreens. Stress-reduction approaches such as mindfulness-based stress reduction (MBSR) intervention have shown some positive effects among psoriasis patients. In a randomized clinical trial, psoriasis patients undergoing photochemotherapy were introduced to MBSR intervention delivered by audiotape, which showed that MBSR can increase the rate of resolution of psoriatic lesions (Kabat-Zinn et al., 1998). Use of moisturizers can help to retain moisture on the skin by forming a thin layer. A randomized placebo-controlled trial of *aloe vera* gel for the treatment of mild to moderate psoriasis reported beneficial moisturizing effects (Syed et al., 1996).

Fungal Infections

Although most of the superficial fungal skin infections require pharmacological therapies however, home remedies have been used traditionally since ages. These include use of baking soda, apple cider vinegar, coconut oil, garlic, etc. Coconut oil can help to kill the species of yeast due to the presences of medium chain fatty acids which act as a fungicide (DebMandal and Mandal, 2011). Applying crushed garlic is useful to treat some fungal infections under the nail-bed (Ledezma et al., 1996).

Pharmacological Treatment

Acne Vulgaris

Topical therapies, systemic antibiotics, hormonal agents, and isotretinoin are the mainstay of treatment of acne vulgaris. As per recent acne vulgaris guidelines, the treatment plan in **Table 1** can be applicable for patients with mild, moderate, and severe acne (Zaenglein et al., 2016).

Therapy choice may be influenced by the age of the patient, site of involvement, severity of acne, and patient preferences. Topical therapy benefits treatment in mild-moderate acne. In severe acne, systemic therapy is recommended together with topical therapies. Topical therapy should start with caution and should be compatible for patients as initial irritation may lead to nonadherence to therapy. Once control is achieved, simplify the regimen according to the response. For moderate to severe cases, systemic antibiotics must be used in combination with a topical retinoid and benzyl peroxide. Tetracycline antibiotics are recommended; however, caution should be taken for pregnant women, children <8 years of age and known history of tetracycline allergy. Doxycycline 20 mg twice daily to 40 mg daily has shown efficacy in patients with moderate inflammatory acne (Toossi et al., 2008). Topical retinoid Vitamin A derivatives are recommended as a first line therapy. They are marketed as tretinoin (0.025%–0.1% in cream, gel, or microsphere gel vehicles), adapalene (0.1%, 0.3% cream, or 0.1% lotion), and tazarotene (0.05%, 0.1% cream, gel, or foam) (Zaenglein et al., 2016). Benzyl peroxide either alone or in combination can be considered in all stages of acne. It is available in the form of topical washes and creams. Strengths available for acne therapy range from 2.5% to 10% (Zaenglein et al., 2016).

Atopic Dermatitis

Effective topical therapies are the mainstay of AD treatment. Sufficient dose, sufficient strength, and correct application of topical agents are the fundaments of topical management of AD. As per most recent clinical practice guidelines, following treatment plan (**Table 2**) can be applied for patients with mild, moderate, and severe AD (Wollenberg et al., 2016).

Table 1 Treatment outline of acne vulgaris

Severity	*Treatment outline*
Mild	Single agent therapy: Benzoyl peroxide (BP) **or** topical retinoid **or** Topical combination therapy[a]: BP + antibiotic **or** Retinoid + BP **or** Retinoid + BP + antibiotic
Moderate	Topical combination therapy[a]: BP + antibiotic **or** retinoid + BP **or** retinoid + BP + antibiotic **or** oral antibiotics + topical retinoid + BP **or** oral antibiotics + topical retinoid + BP + topical antibiotics
Severe	Oral antibiotics + topical combination therapy[a]: BP + antibiotics **or** retinoid + BP **or** retinoid + BP + antibiotics **or** oral isotretinoin

[a]The drug may be prescribed as a fixed combination product or as separate component.

Source: Zaenglein, A.L., Pathy, A.L., Schlosse, R.B.J., Alikhan, A., Baldwin, H.E., Berson, D.S., Bowe, W.P., Graber, E.M., Harper, J.C., Kang, S., 2016. Guidelines of care for the management of acne vulgaris. J. Am. Acad. Dermatol. 74, 945–973. e33.).

Table 2 Treatment of atopic eczema for adults

Baseline *Basic therapy*	***Mild*** *SCORAD <25*	***Moderate*** *SCORAD 25–50*	***Severe*** *SCORAD >50*
Simple eczema • Educational programs • Emollients bath oils • Avoidance of clinically relevant allergens	Transient eczema • Therapy with TCS class II • TCIs • Antiseptics incl. silver, silver coated textiles	Recurrent eczema • Therapy with topical tacrolimus or class II or class III TCS • Wet wrap therapy • UV therapy (UVB 311 nm, medium dose UVA1) • Psychosomatic counseling • Climate therapy	Persistent eczema • Hospitalization • Systemic immunosuppression with: ◦ Cyclosporine A ◦ Oral TCS ◦ Dupilumab ◦ Methotrexate ◦ Azathioprine ◦ Mycophenolate mofetil ◦ PUVA ◦ Alitretinoin

SCORAD, Scoring of atopic dermatitis, a composite score; *TCS*, topical corticosteroids; *UV*, ultraviolet; *UVA*, ultraviolet A; *UVB*, ultraviolet B; *PUVA*, psoralen and ultraviolet A; *TCIs*, topical calcineurin inhibitors. *Source: Wollenberg, A., Barbarot, S., Bieber, T., Christen-Zaech, S., Deleuran, M., Fink-Wagner, A., Gieler, U., Girolomoni, G., Lau, S., Muraro, A., Czarnecka-Operacz, M., 2018. Consensus-based European guidelines for treatment of atopic eczema atopic dermatitis in adults and children: part II. J. Eur. Acad. Dermatol. Venereol. 326, 850–878.*

Topical corticosteroids (TCS) are the mainstay of treatment in AD. The dose, frequency, duration of therapy, and quantity of application may vary from one patient to another and depends on the severity and site of the AD. Diluted topical corticosteroids with wet wrap dressing may be useful for short-term periods in acute AD. In mild AD, a small amount of TCS twice to thrice weekly (approximately 15 g in infants, 30 g in children, and 60–90 g in adults allows good maintenance (Wollenberg et al., 2016). A variety of skin changes such as scars, stretch marks, and hypertrichosis may develop as side effects of TCS. These side-effects should be recognized and patient must be counseled adequately in order to avoid noncompliance (Aubert-Wastiaux et al., 2011; Lee et al., 2015). Topical calcineurin inhibitors (TCIs) such as tacrolimus ointment and pimecrolimus cream have shown efficacy in reducing the symptoms, severity, and extent of AD (Carr, 2013). In children, twice-weekly treatment with tacrolimus 0.03% ointment has been observed to be effective and cost-saving in children with moderate to severe AD (Thaci et al., 2010). Twice-weekly application of tacrolimus ointment may reduce relapses. Patients should be advised for effective sun protection (Wollenberg et al., 2018). Phototherapy is recommended as a second line therapy in AD when TCS and TCIs are not effective (Alldredge et al., 2013). Ultraviolet (UV) light sources have immunosuppressive, anti-inflammatory as well as antipruritic effects on skin which ultimately benefits AD patients (Hong et al., 2008).

Psoriasis

Topical treatments are the standard of care in mild to moderate psoriasis (*affects <5% body surface area*). TCS are useful as monotherapy in patients with mild psoriasis (Menter et al., 2009). TCS are effective because of their anti-inflammatory, immunosuppressant, antimitotic, and antipruritic properties (Alldredge et al., 2013). TCS can be used as monotherapy 1–2 times daily or combined with other topical agents, UV light, and systemic agents (Cornell and Stoughton, 1985). Topical vitamin D analogs such as calcitriol or calcipotriene ointment show 70%–74% improvement in treating psoriasis (Menter et al., 2009). Use in combination with TCS may provide added benefit (Kragballe et al., 1991). For moderate to severe cases of psoriasis with minimal response to topical therapies, management with ultraviolet B (UVB), or psoralen plus ultraviolet A (PUVA) phototherapy is recommended (Menter et al., 2009). In severe psoriasis (*affects >5% body surface area*), systemic therapies with or without topical agents or phototherapy is recommended. Systemic therapies include PUVA; the systemic retinoid, acitretin; cyclosporine and methotrexate. Photochemotherapy is used to control severe, recalcitrant, disabling plaque psoriasis. More than 80% of psoriatic patients experience clearing of symptoms after 10–20 treatments over the course of 4–8 weeks, which can be maintained with periodic (twice monthly) treatments (Alldredge et al., 2013).

Fungal Infections

Topical treatments are the mainstay in the management of superficial fungal infections. Any infections, covering >20% of body surface area (nail, follicular, or widespread) should be treated systemically due to poor penetration of topical applications (Baran and Kaoukhov, 2005). In Invasive fungal infections, topical applications are slightly ineffective due to poor penetration; however, newer agents such as ciclopirox and amorolfine have shown improved efficacy (Bohn and Kraemer, 2000). Oral antifungals are often associated with risks of side effects and interaction with other drugs which in turn affects the efficacy of the drug therapy as well as patient's compliance. Newer classes such as itraconazole and terbinafine are better options. For *Tinea unguium* (Onychomycosis) initial therapy, nail scrapping and culture is recommended. Terbinafine 250 mg/day or itraconazole 200 mg/day can be recommended after culture results. The duration of therapy is varied from 6 weeks (finger nail) to 12 weeks (toenail) and in some cases,

therapy may be required for 6–12 months for toenail infections. Therapeutic outcome can be confirmed when a 25% reduction in size of the infected nail has been achieved. Griseofulvin can be recommended as an alternative if the patient is contraindicated to itraconazole or terbinafine. The adverse effects of itraconazole or terbinafine include rash, headache, and gastrointestinal (GI) distress. Toxicity of griseofulvin includes hypersensitivity reactions, dermatitis, GI distress, and neurologic complications (Crawford and Hollis, 2007). An alternative to daily therapy for fingernail infections called antimycotic pulse therapy has been approved. A pulse course of itraconazole 200 mg twice a day for 1 week/month in two or four cycles appears to be safe and effective treatment for toenail onychomycosis caused by some nondermatophyte molds alone or in combination with dermatophytes (Chen et al., 1999; De Sá et al., 2014). Efinaconazole and tavaborole are the newest topical agents available to treat onychomycosis (Elewski et al., 2013; Gupta et al., 2014). However, systemic therapy is recommended for the successful outcomes. Treatment failure can be either relapse or re-infection. Immunocompromised, diabetes and congestive heart failure patients are more prone to treatment failure. The use of combination therapy (topical + systemic) may improve therapeutic outcome (Ameen et al., 2014). *Tinea capitis* treatment should focus on cleaning the contaminated combs and brushes. Topical therapy may not penetrate into hair follicles. Hence systemic therapy is recommended (Meadows-Oliver, 2009). Daily shampooing with antifungal agents (ketoconazole 2% or selenium sulfide 1%) along with oral therapy is recommended. For *Tinea barbae* removal of mustache or beard is recommended (Goldstein et al., 2000) followed by antifungal shampoo application. In some cases, oral therapy can be recommended. Most cases of *Tinea pedis* are self-treated with nonprescription topical antifungals. These include butenafine hydrochloride, clotrimazole, miconazole nitrate, terbinafine hydrochloride, and tolnaftate, considering safe and effective treatment for mild to moderate fungal skin infections (Newton and Popovich, 2012).

Counseling Patients About Common Skin Disorders

Adherence to treatment and understating of own disease is crucial in the management of skin disorders. Environmental, emotional, and hormonal factors must be discussed with patients suffering from acne. Emerging data suggest that high glycemic index (GI) diets and some dairy products like skim milk may influence acne (Eichenfield et al., 2014). Patients should be advised to complete the course of systemic antibiotics to prevent antibiotic resistance. All possible medication side effects should be discussed with the patients along with the management strategies. Education about the disease, treatment expectations, and prevention of recurrence, should be made clear to the patient to improve adherence (Eisman and Sinclair, 2014). In case of fungal infections, patients should be counseled about the importance of proper foot hygiene, wearing breathable footwear, cotton socks, keeping nails clean and short to expedite healing (Alldredge et al., 2013; Dipiro et al., 2016).

Role of Community Pharmacist in Health Care Team—Current and Future Trends in Management

Skin disorders are often considered minor health ailments. However, the long-term impact of untreated skin conditions may affect patients physically and psychologically. Community pharmacists are the most accessible professionals to provide advice for skin disorders (Tucker and Duffy, 2014). Since self-care is a cornerstone for many skin disorders, community pharmacists can play an important role in providing advice to patients about drug management, personal hygiene, and lifestyle modifications. To make an appropriate treatment plan for a skin condition, pharmacist should have considerable knowledge on diagnosis. A review of the literature revealed that pharmacist participation in self-care of skin conditions is valuable, but their dermatological diagnostic skills need to be further developed (Tucker et al., 2014). This section will focus on the current and future roles of pharmacists in the management of four major skin disorders (i.e., acne vulgaris, AD, psoriasis, and fungal infections) which has been the focus of this chapter.

Diagnosis, Counseling, and Consultation Roles in Dermatological Care

Pharmacist needs to be an expert in making a provisional and differential diagnosis of common skin disorders. They should be adequately trained to make a clinical judgment in assessing the severity of the disease before recommending any OTC medicines. Similarly, the side effects of the drugs dispensed must be known by the pharmacists and the patient must be counseled properly to avoid noncompliance. Self-reported adherence to dermatological treatment has been estimated to be about 60%, which means certain factors to nonadherence still need to be addressed (Richards et al., 1999). Pharmacist's consultation on common skin disorders may help to improve patients' HRQoL. AD is reported to affect the HRQoL of patients and their caregivers and insufficient consultation is among the reasons of parental dissatisfaction toward AD treatment (Cork et al., 2003). In a study conducted among parents having children with AD, pharmacists' interventions regarding proper use of emollient was reported to make a significant impact on therapy outcomes (Carr et al., 2007). Similarly, community pharmacists are known to play a vital role in counseling patients regarding safe and effective use of topical corticosteroids for AD (Lau and Donyai, 2017; Smith et al., 2016).

Pharmacist-led steroid counseling for skin conditions shows that lack of confidence among pharmacists creates a mistrust and fear of steroid use among patients (Raffin et al., 2016). Since self-medication is common among patients with psoriasis, community pharmacists can play an important role in the disease management through follow up with their patients and

developing innovative strategies to enhance patients' understanding of their disease and its management. According to a survey conducted on consumer satisfaction and economic evaluation of pharmacist-led dermatological consultations, it was reported that pharmacist's advice appeared to be cost-effective for both the consumer and the government (Lindblad et al., 2006).

Role as "Initial Screener" and "Final Checker" in Dermatological Care

Disease management by a coordinated team of health care professionals ensures better treatment outcomes. Dermatological disorders demand an interprofessional team effort involving doctors, nurses, and pharmacists in order to improve patients' adherence and HRQoL. A focus group investigated the team efforts of dermatologists as "*diagnosis maker*" and "*prescribers*," nurses as "*the coach*," and pharmacists as "*initial screener*" and "*final checker*" (Lindblad et al., 2006). Patients reported that there was a lack of holistic approach in dermatological disorders management; even though dermatologists wish to collaborate with pharmacists, but lack of time prohibits them to do so.

Community pharmacies must have an agreement between the dermatologists and nurses to share patients' data for a complete patient history in order to develop effective therapeutic care plans. Conversely, primary care providers are in immediate need of refining their skills to handle dermatological conditions in order to cultivate trust in their patients (Federman et al., 2001). For mild to moderate skin conditions, hospital admissions are not commonly seen. However, in severe cases, patients may need hospitalization to overcome the acute phase of the disease. It is also evident from certain case reports that wrong drug administration, drug–drug interactions, or anaphylactic reactions due to certain antibiotics used for acne management may lead to hospitalization (Christodoulou et al., 1999; Kent and Drummond, 1989). Hospital pharmacists must be well trained to handle complicated skin conditions in order to provide optimal care to the patients.

Health Promotion Roles in Dermatological Care

The role of community pharmacists in health promotion is well established (Anderson, 2000). Specific to skin conditions, pharmacists can get involved in a variety of health promotion activities such as appropriate use of skin products to prevent skin cancer (Mayer et al., 1998; Ring et al., 2007). Pharmacists' advice on proper use of emollient is reported to reduce the severity of eczema and prevent disease exacerbation (Carr et al., 2007). Emotional stress has long been associated with the exacerbation of acne, AD, and psoriasis (Chiu et al., 2003; Garg et al., 2001; Heller et al., 2011). Community pharmacist-led stress reduction programs may help patients to understand their health condition and to prevent the recurrence of their disease (Kabat-Zinn et al., 1998; Winchell and Watts, 1988). Pharmacists can also play their role in screening psychiatric disorders in patients with skin diseases (Picardi et al., 2004).

Roles in Medicine Use Review and Personalized Dermatological Care

Community pharmacists constitute the third largest group of health care professionals in the world, and despite their potential role in managing minor ailments (Mansell et al., 2015; Taylor and Joubert, 2016) and promoting the safe and effective use of medicines, outside the hospital setting (Carr et al., 2007; Mossialos et al., 2015), they remained underutilized (Mossialos et al., 2015). In skin care, community pharmacists could play a major role, particularly in helping those patients with skin complaints that do not visit general medical practitioners frequently. Community pharmacists are also known to compound individualized therapies for dermatological problems which continue to improve in both esthetic and therapeutic aspects of customized medications, offering alternatives strategies for dermatology care (Community pharmacy, 2018). Supporting patients with long-term skin conditions is also critical. Medicine use review (MUR) service is another effective means to help patients with conditions such as eczema and psoriasis, which require a high degree of self-management (Pharmaceutical Services Negotiating Committee, 2014).

Pharmacist Remuneration in Dermatological Care

Historically, community pharmacists' remuneration is solely based on retail activities (Mossialos et al., 2015); usually they are not paid for services. However, in the recent years, limited models of practices around the world have been introduced whereby, pharmacists can be paid for "Patient Centered Activities-Services" (Law et al., 2012; Rigby, 2010). These remunerated services are highly variable which range from emergency contraception services to minor health ailments (Houle et al., 2014). Minor ailments programs are operational in Saskatchewan, England, and Northern Ireland (Davidson et al., 2009; Northern Ireland Executive, 2018; Pharmaceutical Services Negotiating Committee, 2018).

In Saskatchewan, Pharmacy Services Compensation Program for minor health ailment including acne, a net amount of $18 is paid to pharmacists per consultation (Pharmacy Association of Saskatchewan, 2018). Similarly, an increasing number of pharmacists are now working in collaboration with other health care professionals, providing a wide range of services; under these collaborative systems remuneration of services is influenced by various factors, including, value of services, budgetary constraints, the payer perspective, and the attitude of physicians, pharmacists, and patients (Bernsten et al., 2010). Despite these roles of pharmacists in dermatological care, there are limitations in the current community pharmacy practice models, including lack of space in maintaining patient privacy, access to patient prior record and clinical history, which could be overcome by information sharing between the physicians and the pharmacists (Lindblad et al., 2006).

Conclusion

Skin disorders are common conditions which affect patients of all ages. Community pharmacists can play a vital role in addressing issues related to safe and effective interventions including personal hygiene and lifestyle modifications. There are a variety of treatments available for common skin disorders. The pharmacological and nonpharmacological therapies can be individualized as per patient's needs. Identification and resolution of drug-related problems make pharmacist key players in skin disease management.

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Management of Infectious Diseases and the Pharmacist's Role—Antibiotic Stewardship

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Introduction and Need

Infectious diseases are among the most common reasons for patients to receive medical treatment. Approximately 10% of consultations in primary care are for infectious diseases (Hemkens et al., 2017), and infectious diseases are the principal reasons for approximately 10% of hospital admissions (McLaws et al., 1988). Furthermore, approximately 5%–15% of adults admitted to hospital develop nosocomial infections (Allegranzi et al., 2011; Graves et al., 2003).

Fortunately, very many human infectious diseases can be successfully treated with antimicrobial medicines. Almost all bacterial and fungal infections and a large number of major viral infections can be cured or controlled. The remarkable success of antimicrobial treatment in very many infections has led to a common belief that antimicrobial treatment will be beneficial for almost every infection. Consequently, patients often seek medical attention for relatively minor infectious diseases, including many for which there is no effective antimicrobial treatment. Unfortunately, in very many developed and developing countries, this has resulted in excessive prescribing and dispensing of antimicrobials (Van Boeckel et al., 2014).

In most developed countries, approximately 90% of total antimicrobial dispensing is for people in the community and approximately 10% is for people in hospital (Duffy et al., 2018). The number of antimicrobial courses dispensed per 1000 population per year varies widely between countries. For example, the number of antimicrobial courses dispensed per 1000 population, during 2015, was 323 in Sweden (Swedres-Svarm, 2016) but was approximately four times higher—1280 in Australia (Australian Commission on Safety and Quality in Health Care, 2017). Many studies suggest that approximately 30%–50% of antimicrobials dispensed in the community are inappropriate, providing no significant health benefit for the patient (Dyar et al., 2016; Fleming-Dutra et al., 2016). A similar proportion of hospital antimicrobial prescribing is inappropriate (Reddy et al., 2015).

An inevitable consequence of sustained high levels of antimicrobial consumption has been a relentless increase in the prevalence of antimicrobial resistance in the microbes that commonly colonize humans. The spread of antimicrobial resistance in these commensal microbes has dramatically reduced the utility of many antimicrobial agents. For example, penicillin, which was active against almost all strains of *Staphylococcus aureus* when discovered in the 1920s (Fleming, 1929), is now active against only 10%–15% of strains (Chambers, 2001). Similarly, resistance to quinolone antibiotics, such as ciprofloxacin, in *Escherichia coli* has risen from less than 5% in the early 1980s, (Wise et al., 1983) to more than 30% in recent years (Ip et al., 2017). In some human pathogens, such as *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*, strains have emerged that are resistant to all but a small number of antimicrobial agents. These highly resistant strains inevitably will spread globally and pose a major threat causing large numbers of untreatable infections (Huang et al., 2017). These untreatable infections will result in increased deaths and disability from infection and dramatically challenge the acceptability of many medical procedures that currently depend on effective treatment of infectious complications, such as intensive care of severely ill patients, invasive surgery, and solid organ and bone marrow transplantation (O'Neill, 2014).

The rapid global spread of clones of many common human pathogens that are resistant to almost all antimicrobials has led to increased awareness of the need for actions to limit the dissemination and health impacts of these organisms. These actions include improved infection control and enhanced immunization, to try to slow the spread of microbes within the community and within health-care facilities; enhanced testing for antimicrobial resistance and provision of the results of such testing, to increase prescribers' awareness of the risk that infection may be due to resistant organisms; and education of prescribers and the public to reduce inappropriate antimicrobial use and thus reduce the selective pressure that favors the proliferation of antimicrobial resistant microbes.

Antimicrobial stewardship (AMS) is a set of coordinated strategies intended to (1) reduce inappropriate antimicrobial use, (2) optimize prescribing with regard to antimicrobial selection, dose, route of administration, and duration of treatment, to maximize clinical benefits and limit unintended adverse effects, and (3) slow the emergence of antimicrobial resistance (Dellit et al., 2007). AMS has a long history. Alexander Fleming, who discovered penicillin, stated in 1945 that "*the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism*" (Anonymous 1945). In the introduction to Good Antimicrobial Prescribing published in 1982 AM Geddes wrote:

Table 1 Useful resources for pharmacists engaged in AMS services

Nation	*Organization*	*Guideline (date published)*	*Site*
Australia	Australian Commission on Safety and Quality in Health (ACSQHC)	Antimicrobial stewardship clinical care standard (2014)	https://www.safetyandquality.gov.au/publications/antimicrobial-stewardship-clinical-care-standard/
United Kingdom	National Institute for Health and Care Excellence (NICE)	Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015)	https://www.nice.org.uk/guidance/ng15
United States	Centers for Diseases control and Prevention (CDC)	Core elements of hospital antibiotic stewardship programs (2017)	https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html

"Much has been said and written about the abuse of antibiotics and the dire effects that can result. There are predictions of widespread bacterial resistance, possibly culminating in 'supergerms' resistant to all antimicrobial compounds" (Geddes 1982). The emergence in recent years, of multiple "superbugs," including extremely drug resistant *Mycobacterium tuberculosis* (XDRTB) and carbapenem-resistant *Enterobacteriaceae* (CRE), has demonstrated the prophetic nature of these predictions and led to a much greater emphasis on AMS in both hospital and community practice.

AMS teams, that usually include a pharmacist, an infectious diseases physician, and a clinical microbiologist, now are common in most large hospitals in developed countries. The core functions of these teams include (1) ensuring that clinicians have ready access to appropriate antimicrobial prescribing guidelines, (2) ensuring that there are effective systems to limit the prescribing of antimicrobials of last resort to prolong their utility, (3) ensuring that reporting of antimicrobial susceptibility results by the clinical microbiology laboratory is designed to encourage prudent antimicrobial prescribing, and (4) conducting prospective audit with feedback and intervention to improve antimicrobial prescribing. AMS teams within hospitals have the potential to improve patient outcomes, reduce costs, and reduce the incidence of infection due to antimicrobial resistant microbes (Dellit et al., 2007).

In many countries, AMS is less developed in the community than it is in hospitals. There are however some striking exceptions. The Swedish Strategic Program against Antibiotic Resistance (STRAMA) was started in 1994 as an informal network of clinicians within each of the 21 Swedish counties, with funding from central government since 2006 (Molstad et al., 2008). The level of community antimicrobial consumption in Sweden is among the lowest in developed nations and continues to decline, with a sustained, approximately 1.2% reduction in total consumption during each year between 2005 and 2016. Not surprisingly the prevalence of antimicrobial resistance in bacterial pathogens has remained very low in Sweden when compared with most other countries (Molstad et al., 2008). A national, community-based, campaign ("Antibiotics are not automatic"), resulted in an approximately 5% reduction in community antibiotic prescriptions, during each year between 2002 and 2007, across all regions of France (Sabuncu et al., 2009). A UK national campaign set a target of a 1% annual reduction in total community antimicrobial prescribing between 2013 and 2018 (Johnson et al., 2015). After 2 years, there had been a 6.8% reduction in total antimicrobial prescriptions per head of population (Global and Public Health Group/10200, 2017).

It is very likely that the need for AMS services, within hospitals and the community, will increase dramatically in the next decade. An increase in the incidence of infections due to multiresistant microbes will require more pharmacists with the expertise to advise on use of last-line antimicrobials. Concurrently increased clinician and public concern about the rising risk of untreatable infections is likely to result in greater demand for pharmacists to enhance efforts to reduce inappropriate prescribing. **Table 1** lists some especially useful resources for pharmacists engaged in AMS services.

The Role of the Pharmacist in Antimicrobial Stewardship

Improving the appropriate use of antimicrobials is necessary across all facets of health care and pharmacists are well placed to deliver and lead this improvement, in both the secondary and primary care settings. As with all conditions, pharmacists advise on optimal treatment for infection, taking into account pharmacokinetic and pharmacodynamic parameters such as renal function and drug concentrations.

In secondary care, pharmacists are well established as key members of the AMS team. International guidance on the delivery of AMS in secondary care and who should be involved always includes the need for pharmacist involvement, if not pharmacist leadership (Barlam et al., 2016; Duguid and Cruickshank, 2011; NICE, 2015). As members of this team pharmacists have often led the development of appropriate antimicrobial prescribing guidelines, introduced audit and feedback of prescribing habits, reviewed medication use, and provided expert pharmacological input into medicines management (McLellan et al., 2016; Weier et al., 2017; Wickens et al., 2013). Traditionally, the involvement of pharmacists in AMS has been from individuals working within a multidisciplinary infectious diseases team; however, AMS is increasingly incorporated into the standard clinical practice of all pharmacists (Brink et al., 2016; DiDiodato and McArthur, 2017).

Case study: Optimizing the route and dose of antimicrobial therapy Optimizing antimicrobial prescribing is one of the main purposes of an Antimicrobial Stewardship program. This includes selecting the optimal antimicrobial agent, together with the

optimal dose, duration, and route of administration in order to maximize benefit and minimize adverse effects for patients. With fewer new antimicrobials being brought to the market, (Butler et al., 2017) more research is being undertaken to look at optimal use of existing agents.

Scenario: A patient is being managed at your institution with an infected wound. Methicillin susceptible Staphylococcus aureus (MSSA) has been isolated from debrided tissue and the patient commenced on treatment with intravenous flucloxacillin 1 g every 6 h. The patient is referred to you by the ward pharmacist for review on your AMS ward round.

AMS ward rounds have demonstrated improvements in antimicrobial prescribing across a range of settings (Cairns et al., 2015). This type of ward round review is different to the traditional infectious disease review for expert advice in clinically complex scenarios. Pharmacists and physicians review patients referred to the AMS service for optimization of their therapies, for example, narrowing spectrum, switching from intravenous to oral therapy, and optimizing dosing.

On review, the patient had completed 72 h of intravenous antibiotic and was clinically stable, afebrile, and eating a normal diet. You need to consider whether the patient is suitable for conversion to an oral antibiotic regimen.

Promoting intravenous to oral switching is a key part of an AMS program due to the clear benefits of reduced morbidity, reduced length of stay, reduced intravenous cannula-associated hospital acquired infections, and reduced healthcare costs. Implementation though is often challenging to achieve with limited uptake, despite the clear evidence of benefit without any compromise in clinical efficacy. Switching criteria can be used to make the process more consistent and consensus guidelines suggest the following key parameters, improving or stable vital signs, resolved fever, a functioning gastro-intestinal tract, a well-absorbed oral option, and an infection that doesn't require prolonged intravenous therapy (e.g., endocarditis) (Akhloufi et al., 2017).

You decide that the patient could be changed to an oral antibiotic, but together with the patient you note that taking oral flucloxacillin 4 times a day on an empty stomach may be logistically difficult. You need to consider whether to change the dosing regimen or switch to a broader spectrum oral antibiotic, such as cefalexin taken less frequently.

Flucloxacillin has a short half-life necessitating frequent dosing, every 6 h, and has historically been recommended to be taken on an empty stomach based on studies showing reduced absorption in fasting as compared to fed patients. The key pharmacokinetic-pharmacodynamic target for flucloxacillin is, as for all beta-lactams, $fT>MIC$, so AUC or Cmax measurements are less important for efficacy, and any impact on these may not be clinically relevant, if $fT>MIC$ is maintained. A recent study has demonstrated that flucloxacillin taken at a dose of 1 g every 8 h with food achieves sufficient concentrations to meet targets for all *Streptococcus pyogenes* and most *Staphylococcus aureus* isolates from skin and soft tissue infections (Gardiner et al., 2018). Treating patients with the narrowest spectrum agent for their infection is a tenet of AMS. The benefits gained from utilizing broader spectrum antibiotics for practical purposes, for example, once daily dosing or palatability, should always be carefully weighed against the harms incurred, for example, greater microbiome disturbance and development of antimicrobial resistance.

In smaller, or more remote, settings there may be limited access to Infectious Disease physicians or Clinical Microbiologists. In these situations, pharmacists are often the best placed clinicians to establish themselves as the leads for AMS, working together with regional specialists to deliver improved care to their patients. In settings where this has been implemented, there have been reductions in inappropriate antimicrobial use, and consequent reductions in the adverse effects of antimicrobial therapy, such as *Clostridium difficile* colitis (PHA Canada, 2017; Yam et al., 2012).

Working in primary care, pharmacists can be involved in delivering AMS, either through their community practice and also by working in a facilitator role with primary care physicians or general practitioners to improve prescribing (Essack et al., 2017; RPS, 2017). In this role, pharmacists are undertaking many of the same tasks that colleagues in secondary care have established as key functions of an AMS program.

In order to improve prescribing, AMS teams must be able to monitor the use of antibiotics. The measures used will differ depending on the population being surveyed, for example, in the hospital setting defined daily doses (DDD) or days on therapy (DOT) per 1000 occupied bed days are the commonly used measures of antimicrobial consumption, while in the community setting the number of antimicrobial prescriptions dispensed or DDDs per 1000 population are the commonly used measures. Pharmacists are involved in monitoring antimicrobial consumption, and expenditure on antimicrobials, using pharmacy dispensing data to produce monitoring and usage reports, as well as in assessing reports for intended or unexpected changes, that may have resulted from changes in policy or clinical practice.

Case study: an audit of inpatient antimicrobial dispensing that led to improved prescribing and better patient outcomes

An audit of total antimicrobial dispensing in a regional secondary care hospital in New Zealand found that the overall level of dispensing was less than in two large New Zealand tertiary hospitals, but that the level of dispensing of lincosamides (principally clindamycin) was higher than in any other hospital in New Zealand or Australia (Hopkins, 2014). Lincosamides were dispensed at a rate of 3.2 defined daily doses (DDDs)/100 inpatient days, while the rates of dispensing were only 0.8 and 2.1 DDDs/100 inpatient days in two tertiary hospitals in New Zealand (Ticehurst and Thomas, 2011; Beardsley et al., 2011) and were less than 3.0 DDDs/100 inpatient days in 34 large public acute hospitals in Australia (South Australian Department of Health, 2011).

The clinician performing the audit of antimicrobial dispensing at this hospital then looked for adverse consequences of the very high rate of lincosamide consumption. Treatment with a lincosamide was found to be associated with a 14% incidence of *Clostridium difficile* associated diarrhoea (CDAD). The incidence of disease in patients treated with clindamycin was surprisingly high; twice the incidence reported in an outbreak of CDAD in a US hospital that also had a very high rate of clindamycin dispensing (Pear et al., 1994). Treatment with clindamycin has repeatedly been shown to be strongly associated with CDAD in hospitalized patients

Table 2 Standard elements of AMS programs[a]

Element	*Purpose*
Leadership Commitment	To dedicate the resource and support the program
Accountability	Having a clear clinician leader
Drug Expertise	Pharmacist involvement
Action	Implementing activities such as standard reviews or audit and feedback
Tracking	Monitor prescribing and resistance patterns
Reporting	Provide reports on prescribing to prescribers
Education	Ongoing for all clinicians involved in antimicrobial use

[a]Modified from: Centres for Disease Control and Prevention, 2014. Core Elements of Hospital Antibiotic Stewardship Programs. US Department of Health and Human Services, CDC, Atlanta, GA. Available from: http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html.

(Bignardi, 1998; DePestel and Aronoff, 2013) and reducing the rate of clindamycin dispensing has resulted in the control of nosocomial outbreaks of CDAD (Pear et al., 1994).

The mechanisms by which treatment with broad-spectrum antimicrobials causes CDAD remain unclear, but the commonly accepted explanation is that these medicines disrupt the normal flora of the colonic mucosa, and thus enhance the proliferation of *C. difficile* (Buffie et al., 2015). Reducing inappropriate prescribing of broad-spectrum antimicrobials is a common goal of hospital AMS programs, and has been shown to reduce the prevalence of colonization by antimicrobial resistant bacteria, the incidence of infection caused by antimicrobial resistant bacteria, and the incidence of CDAD, in hospital inpatients (Baur et al., 2017). Given that the mortality of CDAD is commonly 10%–30% (Bloomfield et al., 2012) reducing the incidence of this disease is an important goal of AMS programs.

Recognition of the very high rate of clindamycin dispensing within the regional hospital led to an AMS program intended to change the clinician prescribing behavior and reduce the incidence of CDAD. The annual level of dispensing of clindamycin within the hospital fell dramatically during the subsequent 6 years, from 1103 DDDs in 2011 to 640 DDDs in 2017 (Richardson, 2019, personal communication). This large reduction in clindamycin consumption was associated with a dramatic reduction in the incidence of CDAD, which fell from 69 cases in 2011 to 18 cases in 2017 (Gilbert, 2019, personal communication). This example illustrates the beneficial outcomes that can result from an audit of antimicrobial dispensing within an institution or region.

The development and regular review of prescribing guidelines are core components of AMS programs. Pharmacists lead in this area, writing guidelines in collaboration with infection specialists and other relevant specialists, for example, respiratory physicians for pneumonia or general surgeons for peritonitis, in order to gain maximal acceptance of the developed guideline. On-going review is also needed to ensure practice remains up-to-date with the latest evidence and recommendations (**Table 2**).

An effective way of supporting appropriate antibiotic use is through restricting the prescription of very broad-spectrum or specialist agents. With traditional paper-based prescribing, this is often a role of the pharmacist, who will decline to dispense restricted antimicrobials unless appropriate authorization or approval has been obtained, for example, from an infection specialist. With electronic prescribing, systems can be developed with pharmacist input, either to restrict the ability to prescribe some antibiotics or to provide decision support that encourages the prescriber to prescribe alternative agents (Schuts et al., 2016). Restricting antibiotics is a hard-stop measure to ensure appropriate use, and is sometime seen as confrontational or dis-empowering to the prescriber, but has repeatedly been shown to be one of the most effective ways to improve antibiotic usage (Davey et al., 2017).

Patient's reported allergies influence the choice of antibiotics used and can sometimes lead to prescription of unnecessarily broad-spectrum agents, especially when patients report penicillin allergy. Over 90% of patients with a history of penicillin allergy have negative skin testing and will experience no increased risk of adverse reactions if treated with a penicillin (Blumenthal et al., 2017; Park et al., 2011). In consultation with patients, pharmacists can evaluate the patient's allergy history and determine if they are likely to have true allergy, using questionnaires or skin testing. Identifying patients without true allergy allows the prescriber to use first line beta-lactam-based therapy in a number of scenarios (du Plessis et al., 2019).

As medicines experts, pharmacists are involved in all aspects of the medication management pathway and new roles and functions within this pathway, more than just dispensing, are becoming available to assist in appropriate use of antimicrobials.

Prescribing of antimicrobials has traditionally been the domain of doctors, dentists, and midwives; however, this is changing in many countries where pharmacist prescribing is becoming more accepted. In the United Kingdom, nonmedical prescribers, including pharmacist and nurse prescribers, were responsible for 6.5% of all antibiotic prescriptions in 2017. The majority of these nontraditional prescribers work in primary care and often are better than traditional prescribers in their level of adherence to prescriber guidelines (Courtenay et al., 2017a), including recommending nonantibiotic strategies to patients as appropriate. Pharmacist prescribers in the United Kingdom have also been shown to be appropriately managing patients' expectation of antimicrobial treatment for respiratory tract infections, a common condition where antibiotics have frequently been overprescribed (Courtenay et al., 2017b). Patient expectation is thought to be a large driver for community prescribing of antibiotics due to the interactional nature of primary health care. It is therefore promising to see pharmacists dealing with this issue well and having appropriate strategies for managing this while maintaining patient satisfaction.

In many countries, pharmacists are also supplying antibiotics without prescription. It is therefore important that those pharmacists are able to make informed decisions about the legal status of antibiotics, appropriate choice and monitoring of patients, and when to refer to a designated prescriber. Evidence suggests that in many situations antibiotics are supplied when they are inappropriate or unnecessary (Chang et al., 2017; Hadi et al., 2016; Kalungia et al., 2016; Shet et al., 2015). Pharmacists in primary care must be engaged with AMS efforts to ensure that supply is appropriate in all situations. With appropriate training and support of the community, pharmacist supply of antibiotics in primary care can be a success. In New Zealand, strict criteria were established in conjunction with infectious disease specialists and the support of the medical fraternity, for primary care pharmacists to supply trimethoprim to women with cystitis without prescription following an accreditation training program. Follow-up reviews of supply by trained pharmacists showed high levels of satisfaction from treated women and no increase in overall antibiotic usage or subsequent prescription of second-line agents by general practitioners (Gauld et al., 2017). Providing advice about appropriate self-care, and non antibiotic treatment, for self-limiting infections such as gastroenteritis or upper respiratory tract infections, is also an important function of community pharmacists in assisting in reducing antibiotic use.

Other options for pharmacist-led optimization of prescriptions include the use of automatic stop and IV to oral switch policies. As part of standard clinical review, pharmacists may identify patients who are clinically improving and who meet criteria to have their therapy modified in line with local guidelines. Automatic stop policies are useful to encourage prescribers to consider and document treatment durations, as otherwise pharmacists may enact a stop of a prescribed antibiotic at a recommended course duration, for example, 7 days which is adequate for most uncomplicated infections. Intravenous to oral switch policies can be applied to patients who no longer need treatment with intravenous therapy and are suitable for oral therapy, thus reducing the time devoted to nursing care, the risks of infection and thrombosis of intravascular cannulae, and health-care costs (Schuts et al., 2016).

A key strategy to reduce antimicrobial resistance is prevention of infection. Vaccination is a highly effective way of reducing the incidence of infectious diseases and a promising area of pharmacist involvement. Primary care pharmacy is well placed as a community-based health care provider to offer vaccination to at-risk members of the community. Influenza infection is a common precursor to antibiotic use, either appropriately for post-influenza bacterial pneumonias or inappropriately for purely viral infections. Reducing influenza spread and therefore antibiotic use is therefore desirable from an AMS standpoint. Modeling has suggested that utilization of community pharmacies in pandemic influenza vaccination campaigns could significantly reduce the time to achieve high levels of vaccine coverage, and thus reduce the incidence of disease (Schwerzmann et al., 2017). This has been supported by studies looking at the impact of pharmacies offering routine autumn influenza vaccination. Eligible patients are more likely to receive vaccination (Drozd et al., 2017), and higher vaccination rates were seen regardless of the role pharmacists played in the vaccination process (Isenor et al., 2016). Pharmacists may be involved as educators of vaccinators or of patients, facilitators of vaccine supply, or direct administrators of vaccines to patients. While most evidence is seen in primary care, significant improvements in the proportion of vaccinated inpatients were achieved with the introduction of a pharmacy technician-led vaccination program (Hill et al., 2017). Similarly beneficial effects have also been demonstrated in programs where pharmacists have been involved in vaccination against pneumococcal disease (Pizzi et al., 2017).

While antibiotic use is very widespread, with 65% of respondents to a WHO survey across 12 countries having used antibiotics within the previous 6 months, knowledge among the general public about appropriate use of antibiotics is relatively poor (WHO, 2015). Educating the public and specifically patients about the appropriate use of antibiotics is very important. Pharmacist-initiated educational interventions have been shown to increase patients' knowledge of appropriate antibiotic use and antibiotic resistance (Rodis et al., 2004). This educative role should also be part of an overarching involvement in the promotion of public health initiatives as part of practice. Primary care or community pharmacists are particularly well placed to engage in health promotion messaging, with continual engagement of their local community and population (APHA, 2006). In addition to taking an opportunity to increase general knowledge, and potentially influence future decision making and understanding, pharmacist counseling around antibiotic use can have immediate impacts on AMS. Improving patient adherence to antimicrobial prescriptions can be critically important in reducing development of antimicrobial resistance and has been clearly demonstrated in infections such as tuberculosis and HIV (Clark et al., 2007; Saberi et al., 2012). Pharmacist-directed patient counseling resulted in significantly greater adherence to their treatment regimen in patients with tuberculosis (Clark et al., 2007). A meta-analysis of pharmacist provided counseling showed similar findings with regard to the levels of adherence to their antiretroviral medications in patients with HIV infection, with consequent benefits in the suppression of HIV infection and the need for hospital admission (Saberi et al., 2012).

While optimizing the use of existing antimicrobials is a critically important component of preventing the development and spread of antimicrobial resistance, there is clearly a need for research and development of novel agents to treat multiresistant organisms. Research- and academic-based pharmacists play a large role in the development of these agents, with expertise in drug development, pharmaceutical formulation science, and clinically based research identifying pharmacokinetic and pharmacodynamic properties.

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Bacterial Infections and the Role of the Pharmacist

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Learning Objectives

After reading this paper, readers will be able to:

- Understand the various factors that determine the clinical effectiveness of antibacterials.
- Recognize the various clinically relevant classes of antibacterials and the commonly used antibacterials within each class.
- Appreciate the role of the pharmacist in optimizing antibacterial therapy in practice.

Take-Home Messages

- Numerous antibiotic classes exist. Different antibacterials in the same class will have different indications, routes of administration, contraindications, and adverse effects.
- Potential routes of administration include oral, intramuscular, intravenous, inhalation, nasogastric, nasoenteric, and percutaneous endoscopic gastrostomy (PEG). The oral route of administration is appropriate in most situations as it does not require vascular access, often has less serious adverse effects, and is cheaper.
- Increasing antimicrobial resistance is being seen in both hospital- and community-acquired infections, and multidrug-resistant organisms are associated with higher mortality and a high economic cost. Inappropriate use of antibacterials contributes to this increasing resistance.

- The pharmacist has an essential role in optimizing the use of antibacterials in practice. This can include being involved in therapeutic drug monitoring, recommending appropriate antibacterial therapy and doses, recommending a change from intravenous to oral therapy when appropriate, and providing education to medical and nursing staff and patients.

Introduction

Accidental discovery of penicillin by Alexander Fleming in the year 1928 has revolutionized the practice of medicine across the globe (Gaynes, 2017). Today, there are numerous classes of antibacterials and each class has a number of unique members. In fact, a summary of all the available antibacterials is beyond the scope of this paper and can be found elsewhere. The following discussion covers some of the contemporary issues surrounding the pharmacotherapy for bacterial infections followed by the clinical applications of such issues specific to each class of antibacterial. Importantly, all these contemporary issues are related to the effective use of antibacterials and may contribute toward limiting the ever-increasing threat of antimicrobial resistance (AMR). Recent modeling data have shown that AMR is becoming a global problem that may lead to the death of 10 million individuals a year by the year 2050 (O'Neill, 2016).

Bacterial infections continue to make a large contribution to morbidity and mortality, especially in developing countries. The use of certain medical treatments such as chemotherapy and the presence of conditions such as the human immunodeficiency virus (HIV) infection can increase a person's risk of complications from serious bacterial infections, which is seen in both developed and developing countries. While the discovery and development of antimicrobials has improved the survival of people who have contracted various bacterial infections, increasing resistance has meant that treatment options for certain infections are diminishing. Ensuring antibacterials are used judiciously and appropriately is an essential role of the pharmacist and may assist in improving the time that certain antibacterials are effective for (Hauser et al., 2016; Rossi, 2018; World Health Organization, 2001).

Types of Bacteria and Clinical Spectrum of Antibacterials

Given the fact that the clinical use of antibacterials is often targeted at certain types of bacteria, it is important to understand the broader classification of these organisms. The most frequently used clinical classification of bacteria is based on two distinct criteria: Gram stain and oxygen consumption. Hans Christian Gram in the year 1884 developed a method of staining bacteria with a crystal violet-iodine complex and a safranin counterstain (Coico, 2005). Bacteria containing a distinguished cell wall retain this complex after treatment with alcohol and appear purple and, therefore, are called Gram-positive bacteria as they retain the Gram stain. On the contrary, bacteria without a distinct cell wall do not retain the complex after treatment with alcohol and appear pink. They are therefore called Gram-negative bacteria (Beveridge, 1999; Coico, 2005). Gram-positive and Gram-negative bacteria are further subclassified as per their morphological appearances as bacilli (rod-shaped) or cocci (sphere-shaped).

Bacteria vary in their oxygen requirements. Anaerobic bacteria do not require oxygen and obtain energy through fermentation or anaerobic respiration (Werth, 2018i). These bacteria are commonly seen in the gastrointestinal tract, vagina, dental crevices, and chronic wounds with impaired blood supply. Aerobic bacteria need oxygen for energy and use aerobic cellular respiration to produce energy. Facultative bacteria can survive with or without oxygen and will adapt based on if oxygen is present. Fermentation or anaerobic respiration is used if oxygen is not present and aerobic cellular respiration occurs when oxygen is present (Werth, 2018i).

Antibacterials can be broadly classified as broad and narrow spectrum. Antibacterials that are effective against a variety of bacteria such as Gram-positive and Gram-negative bacteria are categorized as broad-spectrum antibacterials, whereas those that are effective against limited bacteria are considered narrow spectrum. **Table 1** shows a summary of major antibacterial groups and their respective spectrum; specific information about the example antibacterials is provided under the Notes section of this table. It is important to note that the table is intended to provide a clinically relevant summary of spectrum, and therefore it may not represent a theoretical and microbiologically accurate summary of the quoted antibacterials.

Source of Infection

Quite often the obvious signs and symptoms of an infection may provide clues about the location of the source of the infection. Nevertheless, occasionally the source of infection can be hard to locate. Ironically, locating the main source of infection is often challenging in serious and life-threatening infections such as septicemia and septic shock. Presence of bacteria in the bloodstream should be taken seriously and every attempt should be made to detect the source of infection so the most suitable treatment is commenced. Failure to identify and control the source of infection has been associated with high patient mortality (Vincent, 2016). Controlling the source of infection is particularly important in internal and external abscesses as specific surgical techniques are equally important to treat the infection as the initiation of appropriate antibacterial treatment (Korownyk and Allan, 2007). Pharmacokinetics properties of antibacterials differ considerably between various classes and within each class. Certain antibacterials may not be effective in treating an infection despite being effective against the bacteria due to their inability to penetrate into the source of infection. For example, vancomycin has very limited penetration into respiratory fluids, and therefore it is not the treatment of choice for a methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia infection (Rubinstein et al., 2008).

Table 1 Antibacterial spectrum of the major antibacterial groups (Antibiotic Expert Group, 2015; Australian Commission on Safety and Quality in Health Care, 2016; Baldwin et al., 2008; BPAC, 2011, 2012; Breilh et al., 2013; Gonzalez and Spencer, 1998; Kang and Park, 2015; MEDSCAPE, 2018b,c; Pham and Bartlett, 2014; Rossi, 2018; Smith and Pham, 2016; Stanaway, 2001; Werth, 2018a,b,c,d,e,f,h,j,l; World Health Organization, 2001; Zhanel et al., 2007)

Class of antibacterial	*Spectrum*	*Example*	*Notes*
Aminoglycosides	Broad	Amikacin	Amikacin has the broadest spectrum, and often effective for infections resistant to gentamicin and tobramycin (structure of amikacin is less susceptible to inactivating enzymes)
	Narrow	Gentamicin	Most common aminoglycoside used due to low cost and efficacy. Similar activity against Gram-negative bacilli to tobramycin, but more effective against *Serratia marcescens* and less effective against *Pseudomonas aeruginosa*
Carbapenems	Broad	Meropenem	Carbapenems have a broad spectrum of activity. Meropenem is used for empirical treatment of nosocomial or life-threatening infections when other antibiotics are inappropriate or when multidrug Gram-negative bacteria are suspected
	Limited	Ertapenem	More limited spectrum of activity compared to imipenem, meropenem, and doripenem as not effective against *P. aeruginosa* and *Enterococcus* spp. May be dosed once daily (half-life of approximately 4 h) making it a suitable treatment option for community-acquired infection and outpatient intravenous therapy
Cephalosporins	Broad	Ceftriaxone	Cephalosporins are broad-spectrum antibiotics and should not be used when antibiotics with a narrower spectrum will be effective. Third-generation cephalosporins (like ceftriaxone) have the broadest spectrum of activity. Active against *Haemophilus influenzae*, some Enterobacteriaceae, some Gram-positive organisms (particularly streptococci). Intravenous or intramuscular administration
	Moderate	Cefalexin	Effective for staphylococci and streptococci infections, and against some Gram-positive anaerobes. First-generation cephalosporin—oral administration
Fluoroquinolones (quinolones)	Extended	Moxifloxacin	Moxifloxacin is effective for Gram-positive infections (including staphylococci and streptococci), many Gram-negative infections and against anaerobic infections. It is not effective against *P. aeruginosa*
	Broad	Ciprofloxacin	Ciprofloxacin is effective for infections caused by Gram-negative bacteria (e.g., *H. influenzae*), enteric Gram-negative rods, Gram-negative cocci, some Gram-positive cocci, *P. aeruginosa*, and intracellular organisms (e.g., Legionella). Not effective against anaerobic bacteria
Glycopeptides	Narrow	Teicoplanin, vancomycin	Bactericidal, prevent formation of peptidoglycan polymers which inhibits synthesis of bacterial wall. Used for severe infections caused by Gram-positive pathogens (e.g., Enterococci, methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*). More experience with vancomycin and cheaper than teicoplanin, therefore the glycopeptide recommended
Lincosamides	Broad	Clindamycin	Clindamycin may be used as an alternative to penicillins and cephalosporins for patients with severe allergy
Macrolides	Broad	Erythromycin	Indications for erythromycin include upper and lower respiratory tract infections, rheumatic fever prophylaxis, chlamydial infections and prevention and treatment of pertussis
Nitroimidazoles	Broad	Metronidazole, tinidazole	Indications include Gram-positive and Gram-negative anaerobic bacterial infections, protozoal infections, intestinal and extraintestinal amoebiasis, bacterial vaginosis, and surgical prophylaxis. Have a similar spectrum of activity, with some cross-resistance
Penicillins	Broad	Amoxicillin+clavulanic acid	Amoxicillin + clavulanic acid is used for infections such as pneumonia, urinary tract infection, bites and clenched fist injuries, acute otitis media, and sinusitis not responding to amoxicillin
	Narrow	Dicloxacillin	Indicated for Staphylococcal skin infections, Streptococcal infections, pneumonia, pharyngitis, osteomyelitis, and septic arthritis. May be used interchangeably with flucloxacillin
Rifamycins	Broad	Rifampin	Rifabutin, rifampin, and rifapentine have a similar spectrum of activity, and effective for infections caused by most Mycobacteria and Gram-positive bacteria, and some Gram-negative bacteria
Tetracyclines	Broad	Doxycycline	Spectrum of activity includes Gram-positive and Gram-negative bacteria, Chlamydia, Rickettsia, Mycoplasma, spirochaetes, and some nontuberculous mycobacteria and protozoa. Doxycycline is the tetracycline of choice in most cases, and is better tolerated than minocycline and tetracycline. Doxycycline should be taken with food or milk

Table 2 Intention of antibacterial treatment (Antibiotic Expert Group, 2015)

Intention of treatment	*Appropriate example*	*Inappropriate example*
Prophylactic	Single dose of cefazolin half an hour before incision in most clean-contaminated surgeries	Multiple doses of cefazolin or scheduled doses of cefazolin in a patient undergoing clean-contaminated surgery where there is no sign of infection
Empiric	Broad-spectrum antibiotics in a patient admitted with septic shock while pending diagnostic workup	Continued use of broad-spectrum antibiotics after 72 h in the absence of diagnostic rationale (Microbiology/Radiology, etc.)
Directed	Pneumonia that has been confirmed to be caused by *Streptococcus pneumoniae* is treated with benzylpenicillin until the patient significantly improves, then changed to amoxicillin for a total of 7 days treatment	Continuing to use broad-spectrum antibiotics after the pathogen has been confirmed and could be effectively treated with a narrower spectrum antibiotic

Intention of Antibiotic Use and Ongoing Review

Given the unprecedented increase in AMR, it is important to clarify and document the intention of any antibacterial use and a plan for ongoing review. Antibacterial treatment can be broadly classified into prophylactic, empiric, and directed treatment (**Table 2**). Regardless of the intention of the initial treatment, it is crucial that all antibacterial treatments are reviewed within an appropriate time frame and decisions are made regarding the total duration of treatment.

Many bacterial infections are empirically treated based on a presumptive diagnosis that is guided by the clinical history and physical presentation. In practice, empirical treatment should be guided by local epidemiological data on the most likely causative pathogens as well as local patterns of resistance and susceptibility. The antimicrobial with the narrowest spectrum of activity should be used to treat the suspected pathogen(s). If cultures are required, these should be taken prior to beginning empirical treatment where possible (Antibiotic Expert Group, 2015; World Health Organization, 2001). If antibiotics are used empirically, the dosage regimen should be based on recommended treatment guidelines and treatment should be reviewed after 48–72 h (Antibiotic Expert Group, 2015).

Directed treatment is when an organism has been identified as the source of infection in a given patient and the treatment is directed towards eradicating that organism. Adequate specimens for microbiological testing should be obtained before antimicrobial therapy is begun where possible (World Health Organization, 2001). Once culture results are obtained it is important to determine whether the results identify true infection, or colonization or contamination, to ensure antimicrobial treatment is only initiated or continued when appropriate. Treatment duration should be based on evidence where possible and the shortest possible duration should be used (Antibiotic Expert Group, 2015).

Prophylactic treatment with antibacterials aims to prevent infection and is used in situations where there is a significant risk of infection. It may be primary prophylaxis (where it is used to prevent an initial infection), secondary prophylaxis (when used to prevent the recurrence or reactivation of an infection), or used to remove a colonizing organism in order to prevent an infection. Prophylactic treatment should only be used when evidence exists for its effectiveness or when there are serious consequences (morbidity or mortality) if an infection develops. Some prophylactic regimens are evidence-based; however, most practices in this area are either based on expert opinion or have low evidence to support their use (Antibiotic Expert Group, 2015; Enzler et al., 2011).

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is what a body does to a medicine, whereas pharmacodynamics is what a medicine does to the body. As such, absorption, distribution, metabolism, and elimination of antibacterials are important pharmacokinetic factors that determine the effectiveness of these medicines. On the contrary, the relationship of an antibacterial concentration with that of the antibacterial effect is an important pharmacodynamics parameter that determines the clinical effectiveness of these medicines.

Pharmacokinetics

Adequate absorption of the antibacterial is essential for antibiotics administered through the oral route. Various antibacterials can have impaired absorption if taken with or without meals while others are not affected by food. Fluoroquinolones are best taken on an empty stomach, at least half an hour before food or 2 h after food (Rossi, 2018). The same applies to the penicillinase-resistant penicillins dicloxacillin and flucloxacillin (Rossi, 2018). On the contrary, certain antibiotics (e.g., nitrofurantoin and cefuroxime) should be taken with food to improve absorption (Rossi, 2018). Some antibacterials have intrinsically poor oral absorption, and therefore oral treatment should only be used when a local action is desirable or as a maintenance treatment to finish a regimen. Neomycin, an oral aminoglycoside, and vancomycin, a glycopeptide, are often used in clinical practice for surgical bowel preparation and treatment of *Clostridium difficile* infection, respectively (Kumar et al., 2013; Rossi, 2018).

Distribution of an antibacterial at the site of infection is one of the crucial steps that determines its clinical effectiveness. Some bacteria are concentrated inside the cell, and therefore antibacterials that are capable of penetrating cells are required to achieve the

needed antibacterial effect. Macrolides such as erythromycin and fluoroquinolones such as ciprofloxacin are some of the antibacterials that can distribute inside the cells and are effective treatment options for pneumonia caused by *Legionella pneumophila* and *Mycoplasma pneumoniae* (Cilloniz et al., 2016). Other examples that highlight the importance of adequate distribution at the site of infection are penetration of antibiotics in bone, meninges, and endocardium tissues when treating osteomyelitis, meningitis, and endocarditis.

The metabolism characteristics of individual antibacterials can affect the suitability of these medicines in various patient populations. Penicillins and cephalosporins usually have poor oral absorption. Quite often these medicines are formulated as a salt for better absorption and rely on metabolism to release the active antibacterial molecule. A number of antibacterials become inactivated by hepatic enzymes and, although in the majority of cases no dose adjustments are required in patients with hepatic insufficiency, some antibacterials such as antituberculars, tetracyclines, and macrolides require dose reduction in severe hepatic impairment (Rossi, 2018).

Elimination takes many forms when it comes to antibacterials, though most active antibacterials or their inactive metabolites are excreted in urine. Therefore, renal function plays an important role in eliminating antibacterials from the human body. The majority of beta-lactams such as aminopenicillins (ampicillin), extended-spectrum penicillins (piperacillin), the majority of all four generations (first, second, third, and fourth) of cephalosporins (e.g., cefazolin, cefuroxime, cefotaxime, and cefepime), and carbapenems (meropenem, imipenem, ertapenem and doripenem) are eliminated via the kidneys and require dose adjustments in renal impairment (Antibiotic Expert Group, 2015). Inadequate dose reduction of the abovementioned antibacterials in renal impairment has been associated with negative patient outcomes such as seizures, tubular damage leading to further worsening of kidney function, and increased incidence of adverse effects due to higher drug concentrations (National Institute for Health and Care Excellence, 2019).

Pharmacodynamics

A number of pharmacodynamics parameters relate to antibacterials such as dose–response curve, the minimum inhibitory concentration (MIC) and its derivatives such as MIC_{50} and MIC_{90} (minimum concentration of antibacterial that inhibits 50% and 90% of the bacterial growth), and relationship of MIC with serum concentration and area under the curve (AUC) of individual antibacterials (Levison and Levison, 2009; Schwarz et al., 2010). Another important pharmacodynamics concept of antibacterials is the postantibiotic effect, that is, the ability of the antibacterial to show bacteriostatic (halting the growth of bacteria) or bactericidal (killing bacteria) effects despite dropping of its serum concentration beneath MIC_{50} or MIC_{90}. The discussion later will be limited to two of the most contemporary issues informing clinical practice, namely, the relationship between the ratio of serum concentration of antibacterials and MIC, and the postantibiotic effect.

Pharmacodynamically, antibacterials can be classified in three major groups. The first group is antibacterials that exhibit maximum bacterial killing when the serum concentration is maintained above the MIC for an extended period of time or a time-dependant killing effect is observed (often abbreviated as T > MIC). The second group, concentration dependent killing, covers antibacterials that achieve maximum bacterial killing when highest possible peak concentrations are achieved. The third group of antibacterials achieves best bacterial killing effects when a certain ratio of area under the curve and MIC is achieved. The second and third groups of antibacterials also exhibit variable degrees of postantibiotic effect. Specific examples of all these three pharmacodynamics parameters are shown in **Table 3**.

Route of Administration

The most appropriate route of administration for antibiotic therapy will depend on the clinical presentation; however, in most situations, the oral route is most appropriate. Oral therapy has numerous advantages, including removing the requirement for vascular access, is often linked with less serious adverse effects, and is more cost-effective (through both the cost of the drug and administration costs) (Antibiotic Expert Group, 2015; World Health Organization, 2001).

Table 3 Pharmacodynamics-based classification of antibacterials with few examples

Group of antibacterials	*Preferred pharmacodynamic parameter*	*Example regimen*
Penicillins	Time dependant killing (T > MIC)	Benzylpenicillin 1.6–2.4 g every 4 h as 30–60 min infusion in meningitis or endocarditis
Carbapenems		Meropenem 1–2 g every 6–8 h for the treatment of hospital-acquired pneumonia
Aminoglycosides	Cmax/MIC	Gentamicin 5–7 mg/kg daily
Macrolides		Azithromycin 2 g once for community-acquired pneumonia
Quinolones	AUC/MIC	Ciprofloxacin 400 mg every 8 h is better than 400 mg every 12 h to achieve the target AUC/MIC of 125 for pneumonia caused by *Pseudomonas aeruginosa*
Glycopeptides		Vancomycin 2 g every 6–8 h has been used instead of the traditional every 12 h to achieve better clinical cure rate in methicillin-resistant *Staphylococcus aureus*

Other routes of administration include nasogastric, nasoenteric, PEG, and parenteral (usually intravenous). The parenteral route of administration is appropriate when the oral route is not practical or possible—gastrointestinal absorption is either significantly reduced through patient factors such as vomiting or the drug is already poorly bioavailable and reduced absorption will accentuate this, higher doses are needed which is difficult to achieve with oral treatment, urgent treatment is required, or when the preferred antimicrobial treatment is not available in an oral formulation. The patient should be changed to oral therapy when possible (Antibiotic Expert Group, 2015).

Nebulized antibiotics are sometimes used; however, this should only be done in specific situations. Topical use of antibiotics should only be used for certain indications, and generally antibiotics used topically should be from different classes than those available for systemic treatment (Antibiotic Expert Group, 2015).

Adverse Effects

Like all other medicines, use of antibacterials is associated with adverse effects. A number of adverse effects are common with most antibacterials such as gastric upset, mild nausea, mild diarrhea, dizziness, and skin rashes (Dancer, 2004). Fortunately, most of the common adverse effects are tolerable and disappear once the antibacterial course is completed and therefore do not interfere with the treatment of infections. Nevertheless, some antibacterials have serious adverse effects and the risk of these adverse effects should be weighed against the benefits associated with their use. For example, the use of aminoglycosides is associated with nephrotoxicity and ototoxicity, the use of fluoroquinolones in young children and adolescents is linked with bone deformity, and the use of the antitubercular drug isoniazid has been associated with hepatic failure and subsequent death in some patients (Ali and Goetz, 1997; Takayama et al., 1995; Wu et al., 2007).

Summary of Major Antibacterial Classes

The discussion so far has been restricted to the general concepts of antibacterials and some of the contemporary issues in optimizing antibacterial regimens. The following section will briefly summarize the clinical indications, usage, and adverse effects profile of each antibacterial class followed by a section on the role of pharmacists in optimizing antibacterial regimens.

Aminoglycosides

Owing to the significant nephrotoxicity and ototoxicity of aminoglycosides, these antibacterials are reserved for clinical indications where other less toxic antibacterials are either contraindicated or ineffective. As such, the most common indications for aminoglycosides use are treatment of serious Gram-negative bacteria infections such as septicemia in combination with penicillins, hospital-acquired pneumonia, and treatment of endocarditis (Gonzalez and Spencer, 1998; Werth, 2018a).

The use of aminoglycosides is contraindicated in patients who have had an allergic reaction to an aminoglycoside in the past, and also contraindicated in patients who have previously experienced vestibular or auditory toxicity when taking an aminoglycoside. They should be used with caution in patients with neuromuscular disease (such as myasthenia gravis) due to an increased risk of muscle weakness and respiratory depression. In patients with hypocalcemia, hypermagnesemia, general anesthesia, and large transfusions of citrated blood, there is an increased risk of neuromuscular adverse effects when aminoglycosides are used (Rossi, 2018; Werth, 2018a).

Common adverse effects associated with aminoglycoside use include nephrotoxicity and ototoxicity. Infrequently, they can cause anaphylaxis, bronchospasm, neuromuscular blockade, oliguria, and peripheral neuropathy. Nephrotoxicity is often reversible, and usually presents as nonoliguric renal failure that gradually worsens through increased serum creatinine and proteinuria. However, it may also present as acute tubular necrosis. Ototoxicity occurs in 2%–4% of people treated with aminoglycosides, and is reversible approximately 50% of the time (Rossi, 2018; Werth, 2018a).

Carbapenems

Doripenem, ertapenem, imipenem, and meropenem are the most notable examples of carbapenem antibacterials. Carbapenems have the broadest spectrum of antibacterial activity and are usually reserved for serious life-threatening infections caused by bacteria that are resistant to other first-line antibacterials. Due to ertapenem and imipenem having the potential to cause seizures, using these antibiotics in combination with other drugs that increase the risk of seizures may potentiate this risk, therefore combination should be avoided, if possible. Carbapenems can also reduce the concentration of valproate, if given in combination, and increasing the dose of valproate may not overcome this. It is generally recommended to avoid this combination (Rossi, 2018; Zhanel et al., 2007). Carbapenems are contraindicated in patients who have had a history of allergy to carbapenems. Due to cross-reactivity between penicillins, cephalosporins, and carbapenems, care should also be taken in patients who have an allergy to penicillins or cephalosporins. Use of carbapenems is also contraindicated in patients with an immediate or severe hypersensitivity to penicillins (Rossi, 2018).

Cephalosporins

There are five generations of cephalosporins (beta-lactam antibiotics), which classify cephalosporins in the order that they were developed. The most notable member of the first generation is cefazolin, and it is most commonly used to treat skin and soft tissue infections and as a surgical prophylaxis for clean-contaminated surgeries (Rossi, 2018; Werth, 2018c; Yuson et al., 2018). Cephalosporins have good penetration into most body fluids and the extracellular fluid of the majority of tissues, which is enhanced when inflammation is present (Werth, 2018c). Second and third generations of cephalosporins are active against Gram-positive and Gram-negative bacteria, but are ineffective against enterococci, methicillin-resistant staphylococci, and anaerobic Gram-negative bacilli (except for cefotetan and cefoxitin). Ceftriaxone, cefotaxime, ceftazidime, and cefepime are the only cephalosporins that reach the cerebrospinal fluid in high enough concentrations for the treatment of meningitis (Werth, 2018c).

Cephalosporins are contraindicated in patients with a history of an allergy to cephalosporins or who have had an immediate or severe hypersensitivity reaction to penicillins. As there is cross-reactivity between carbapenems, cephalosporins, and penicillins, care should be taken if patients have had an allergic reaction to carbapenem or penicillin antibiotics (Rossi, 2018; Werth, 2018c).

Adverse effects associated with cephalosporins include hypersensitivity/allergic reactions, *C. difficile*-induced diarrhea, leukopenia, thrombocytopenia, gastrointestinal effects (e.g., diarrhea, nausea, and vomiting), rash, headache, dizziness, and superinfection (such as with *Enterococcus* spp. and *Candida*, in particular when broader-spectrum cephalosporins are used and with prolonged treatment). Pain at the injection site may occur with intramuscular administration and thrombophlebitis is possible with intravenous use (Rossi, 2018; Werth, 2018c).

Fluoroquinolones (Quinolones)

Fluoroquinolones are concentration-dependent bactericidal antibiotics and inhibit DNA gyrase and topoisomerase IV, thereby inhibiting bacterial DNA synthesis. Resistance to fluoroquinolones is increasing worldwide so careful use is advised to optimize their clinical use. They are contraindicated in patients who have had a previous allergic reaction to fluoroquinolones, as well as in patients who have disorders that predispose them to arrhythmias (such as prolonged QT interval, significant bradycardia or uncorrected hypokalemia or hypomagnesemia). Traditionally, fluoroquinolones have been contraindicated in children because they can cause cartilage lesions and damage; however, the evidence to support this is weak. Fluoroquinolones should only be used in children and adolescents for severe infections if the benefit seen is greater than the risk of arthropathy (Rossi, 2018; Werth, 2018d).

Common adverse effects of fluoroquinolones include rash, itch, and gastrointestinal effects (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Tendon damage is also possible, and risk factors include current corticosteroid use, age >60 years, organ transplant (kidney, heart, or lung), renal impairment, rheumatoid arthritis, hyperparathyroidism, musculoskeletal disorders, diabetes, and athletes in training. Patients should be advised to stop taking fluoroquinolones and see their doctor if they experience sore or inflamed tendons. When fluoroquinolones are taken orally their absorption can be reduced if aluminum, magnesium, calcium, zinc, or iron supplements are taken at the same time, and their doses should be separated by 2 h (Rossi, 2018; Werth, 2018d).

Glycopeptides

The glycopeptides include teicoplanin and vancomycin. They are bactericidal, and work by preventing the formation of peptidoglycan polymers that inhibit the synthesis of the bacterial wall. They are used to treat severe infections caused by Gram-positive pathogens (e.g., *Enterococci*, MRSA, and *C. difficile*). There is more experience with vancomycin that is cheaper and therefore the glycopeptide recommended to be used. Glycopeptides should be used with caution in patients with hearing impairment or receiving treatment with ototoxic medicines (e.g., aminoglycosides) as the risk of ototoxicity may be increased, particularly if vancomycin is used. The risk of nephrotoxicity may also be increased if patients are taking nephrotoxic drugs concurrently (e.g., aminoglycosides), and renal function and drug concentration should be monitored in these situations. Similarly, in patients with renal impairment the risk of ototoxicity and nephrotoxicity may be increased (particularly with vancomycin) and the dose should be reduced (Kang and Park, 2015; Rossi, 2018).

Side effects associated with parenteral administration include nausea and hypersensitivity. Red man syndrome may also occur (more common with vancomycin), and symptoms due to the release of histamine can occur (e.g., fever, chills, erythema, rash on the face and upper torso, hypotension, angioedema, and itch). Due to the potential risk of ototoxicity, hearing should be monitored if treatment is prolonged. Renal function and complete blood count should also be monitored at least once a week, and this should be more frequent if treatment is prolonged and/or a high dose of antibiotic is being used, and in patients with reduced renal function (including the elderly) (Rossi, 2018).

Lincosamides

The lincosamides class includes clindamycin and lincomycin. They are bacteriostatic antibiotics, and act by binding to the 50S ribosomal subunit that inhibits protein synthesis. Due to a similar mechanism of action, cross-resistance occurs between lincosamides and macrolides for *Staphylococci* and *Streptococci* infections. There is also complete cross-resistance between clindamycin and lincomycin. They are not active against *Enterococci*. While lincomycin is the cheaper antibiotic, clindamycin is often used in

preference because it is more potent. Adverse effects of lincosamides include diarrhea (which may be mild to severe), nausea, vomiting, abdominal pain/cramps, rash, itch, and contact dermatitis when used topically. *C. difficile* infection can occur infrequently. When administered intravenously, hypotension and thrombophlebitis may occur rarely, and cardiac arrest is possible with rapid injection. When given intramuscularly pain, induration and sterile abscess may occur. If patients are receiving prolonged treatment complete blood count, hepatic, and renal function should be monitored (Antibiotic Expert Group, 2015; Rossi, 2018; Werth, 2018e).

Macrolides

Macrolides are mainly bacteriostatic, and bind to the 50S ribosomal subunit that inhibits the synthesis of bacterial protein. They also have anti-inflammatory and immunomodulatory effects, which is used in diffuse panbronchiolitis and cystic fibrosis. Macrolides generally have poor oral absorption. There is a risk of potentially fatal cardiac arrhythmias occurring if clarithromycin or erythromycin is administered in conjunction with astemizole, cisapride, pimozide, or terfenadine. Therefore, macrolides are contraindicated in conjunction with these drugs. Gastrointestinal upset is most common with oral erythromycin, but is less common with the use of clarithromycin and azithromycin. Numerous drug interactions can occur with macrolides (BPAC, 2012; Werth, 2018f).

Nitroimidazoles

The nitroimidazole class of antibacterials includes metronidazole and tinidazole. They are bactericidal, and are believed to inhibit DNA synthesis. They are indicated for the treatment of Gram-positive and Gram-negative anaerobic bacterial infections, protozoal infections (e.g., giardiasis and trichomoniasis), intestinal and extraintestinal amoebiasis, bacterial vaginosis, and surgical prophylaxis. They should be used with caution in patients with a history of central nervous system disorders (e.g., seizures) as they are neurotoxic and can aggravate existing conditions, and in patients with a history of blood dyscrasias as they may cause leukopenia. Common side effects include gastrointestinal adverse effects and central nervous system effects. Alcohol should be avoided while patients are taking nitroimidazoles and for 72 h afterwards as a disulfiram-like reaction may occur. If treatment is for longer than 10 days, blood count and neurotoxic reactions should be monitored (Antibiotic Expert Group, 2015; MEDSCAPE, 2018a; Pasupuleti et al., 2014; Rossi, 2018; Werth, 2018g).

Penicillins

Penicillins are bactericidal beta-lactam antibiotics, and work by binding to penicillin-binding proteins that interrupt the synthesis of bacterial cell wall peptidoglycans. This mechanism causes cell lysis or death. Beta-lactamases are produced by some bacteria that inactivate beta-lactam antibiotics. Beta-lactamase inhibitors include clavulanic acid, sulbactam, and tazobactam, and prevent this activation from occurring (Rossi, 2018; Werth, 2018j).

Hypersensitivity reactions can occur with penicillins, and their use is contraindicated in patients who have a history of immediate or severe hypersensitivity. Cross-reactivity between penicillins, cephalosporins, and carbapenems can occur. While penicillins are generally well tolerated, potential adverse effects include gastrointestinal effects, pain and inflammation at the injection site (less common with benzylpenicillin), superinfection (e.g., candidiasis), and *C. difficile* infection. When high-dose treatment is used for longer than 10 days, complete blood count and renal and hepatic function need to be monitored (Rossi, 2018; Stanaway, 2001; World Health Organization, 2001; Werth, 2018j).

Rifamycins

Rifamycins are bactericidal, and inhibit RNA polymerase that is bacterial DNA-dependent, which suppresses RNA synthesis. Rifabutin, rifampin, and rifapentine are similar in their pharmacokinetics, spectrum of activity, and adverse effects. Rifampin is more likely to cause hepatitis and allergies, whereas rifabutin can cause neutropenia and uveitis. Rifampin is also more potent (compared to rifabutin) in inducing transporter proteins such as P-gp and hepatic and intestinal CYP enzymes. Potential adverse effects associated with rifamycins include gastrointestinal effects, rash, hepatitis, central nervous system effects, and myelosuppression. Rifampin, rifabutin, and rifapentine may cause a red–orange discoloration of body fluid (i.e., urine, saliva, sweat, sputum, and tears) and may stain contact lenses; patients should be advised of this (Rossi, 2018; Werth, 2018l).

Tetracyclines

Tetracyclines are bacteriostatic, and bind to the 30S subunit of the ribosome to inhibit bacterial protein synthesis. They are effective for infections such as those caused by *Rickettsia* species, *Mycloplasma* species, *Chlamydophila* species, *Chlamydia* species, spirochetes, and protozoa. Tetracyclines are contraindicated in combination with oral retinoids due to the increased risk of benign intracranial hypertension and in children younger than 8 years due to its potential to discolor teeth, cause enamel dysplasia, and cause deformities and bone growth inhibition through being deposited in bone. However, for severe infections where other treatment is unsuitable, tetracyclines may be used in children. Systemic lupus erythematosus may be worsened by tetracyclines (rarely). Metallic cations (e.g., aluminum, calcium, magnesium, and iron) may decrease the absorption of tetracyclines and if taken in

supplements or other formulations the dosing should be separated by 2 h from tetracyclines. Adverse effects associated with tetracyclines include gastrointestinal effects, photosensitivity, rash, stomatitis, fungal overgrowth, fatty liver, esophageal ulcers, and *C. difficile*-associated disease. Patients should be advised to avoid sun exposure and to wear sunscreen and protective clothing while being treated with tetracyclines. Tetracyclines should also be taken with a large glass of water and patients should avoid lying down for 1 h after taking the tetracycline to avoid esophageal damage (Rossi, 2018; Werth, 2018m).

Other Antibacterials

A greater number of antibacterials exist that are not covered in the above section and, in fact, a discussion of all such medicines is beyond the scope of this paper. Therefore, the following discussion will be limited to those antibacterials that are in common clinical use such as colistin, linezolid, trimethoprim, and trimethoprim/sulfamethoxazole.

Colistin is an older antibacterial of the late 1950s that was abandoned due to its neurotoxicity and nephrotoxicity in the early 1970s as relatively safer alternatives were discovered (Werth, 2018k). Colistin use has been recently resurrected because of the emergence of multidrug-resistant bacteria resistant to carbapenems and extended spectrum penicillins (Werth, 2018k). Colistin is available as a methate salt that needs to be converted to its active form. Conflicting evidence is available on the most effective dose of colistin; some clinicians advocate for a high-dose approach, whereas others advocate a low-dose approach. Nevertheless, high-dose colistin has been associated with a greater degree of nephrotoxicity and discontinuation of treatment (Benattar et al., 2016). Colistin use should be well guarded, as it is the only antibacterial that is effective against carbapenem-resistant Gram-negative bacteria.

Linezolid is an oxazolidinone antibiotic that is effective against multidrug-resistant Gram-positive bacteria. Linezolid is available as an injectable and oral dosage form and has an excellent bioavailability to ensure early transition to oral treatment (Dzintars and Pham, 2018). Linezolid also offers superior tissue penetration compared to vancomycin and has been shown to achieve similar clinical cure rates and lower toxicity in MRSA pneumonia when compared to vancomycin (Wang et al., 2015). As linezolid is effective against the treatment of vancomycin-resistant enterococci, routine clinical use of linezolid is rightly discouraged (Dzintars and Pham, 2018).

Trimethoprim and a combination of trimethoprim with sulfamethoxazole is perhaps one of the oldest antibacterials that is still used extensively. Both antibacterials are antimetabolites and disrupt the bacteria's utilization of folic acid that is integral to their protein synthesis (Werth, 2018n). Trimethoprim is the first-line agent for uncomplicated urinary tract infections, whereas the combination with sulfamethoxazole is used for skin and soft tissue infections, upper respiratory tract infections, and as a chemoprophylaxis for opportunistic infections in immunocompromized patients. Trimethoprim with sulfamethoxazole is the drug of choice for the treatment and prevention of *Pneumocystis jirovecii* pneumonia (Dzintars, 2018).

Role of the Pharmacist in Optimizing Antibacterials

With increasing AMR being seen for commonly available antibiotics, there has been an increased focus on ensuring antibiotics are used appropriately and judiciously (World Health Organization, 2001). Pharmacists, as medication experts who have a unique knowledge of areas such as pharmacokinetics and pharmacodynamics principles, have an essential role in promoting optimal use of antibiotics and improving their use in practice. Pharmacists are identified as essential members of the antimicrobial stewardship (AMS) team; however, all pharmacists working in clinical practice have an important role to play in providing education and advice to patients and other health professionals and making recommendations to improve the management of bacterial infections where required (Bond, 2015; Liaskou et al., 2018). The following section will discuss the role of pharmacists in optimizing antibacterials in three distinct yet interrelated categories: therapeutic drug monitoring, antimicrobial stewardship, and education and counseling of patients.

Therapeutic Drug Monitoring

Pharmacists can play a vital role in measuring the levels of various antibacterials to individualize drug treatment in high-risk patients, thus minimizing adverse effects while maximizing the therapeutic effects. Aminoglycosides and vancomycin are two of the most frequently studied antibacterials; a therapeutic monitoring service of these drugs can make a considerable difference in achieving positive patient outcomes.

One study based in a hospital in Boston looked at the impact pharmacist involvement had in improving aminoglycoside use and optimizing therapy (correct treatment, dose, and frequency). Patients receiving aminoglycosides were identified and referred to the pharmacist, and the pharmacist was responsible for reviewing therapy daily, making recommendations where required, and writing consult notes in the patient's chart. Pharmacist intervention occurred in 50% of cases. After pharmacists were involved in reviewing therapy the percentage of patients receiving optimal aminoglycoside therapy increased from 44% to 80%. Patients who had not been reviewed by a pharmacist also had a higher rate of acute renal function changes and nephrotoxicity (Greenwood et al., 2009).

A multicenter study reviewing the role of pharmacists in managing aminoglycosides and vancomycin in 961 US hospitals involving 199,088 patients found significant differences in various clinical and process outcomes between hospitals that do and do not have clinical pharmacists managing these antibacterials. The study found higher in-patient mortality of around 7%, higher length of stay of around 14%, higher drug and laboratory charges of around 8%, and >30% rise in the incidence of hearing loss and renal impairment when aminoglycosides or vancomycin treatments were not reviewed by a clinical pharmacist (Bond and Raehl, 2005).

Traditional practice of therapeutic monitoring of antibacterials has been restricted to medicines with significant toxicity profiles. However, recent adoption of pharmacodynamics-based antibacterial dosing (**Table 3**) is leading the way for therapeutic drug monitoring to enhance the antibacterial effects of these medicines. Experts have argued for the measurement of the serum drug concentration of beta-lactam antibacterials in high-risk patients such as those who are obese, critically ill, elderly, and those undergoing continuous renal replacement therapies (Huttner et al., 2015; Wong et al., 2018). Augmented renal clearances of up to 1.5–2 × normal renal clearances have been noted in young patients experiencing sepsis. Therefore, close monitoring of the antibacterial level and appropriate dosing calculations to maintain the required drug concentrations is critical for such patients (Mahmoud and Shen, 2017). Pharmacists are well placed to offer their professional opinion not only about the suitability of the best available analytical method to measure the serum drug concentration but also to estimate the doses required to meet the clinical needs of their patients.

Antimicrobial Stewardship

Pharmacists are considered an integral part of any AMS initiative in hospital settings. This is because hospital pharmacists have a long history of safeguarding the use of antibiotics and implementing antibiotic restriction policies in their practice settings (Lawton et al., 2000). A comprehensive review of all the published studies demonstrating the value of pharmacists' participation is beyond the scope of this discussion; however, it is important to note that the guidelines of most professional bodies recommend infectious diseases physicians and pharmacists at a minimum are included as part of an antimicrobial stewardship team (Australian Commission on Safety and Quality in Health Care, 2018; Barlam et al., 2016; Oberje et al., 2017).

Pharmacy departments are uniquely positioned to safeguard the access to antibacterials due to their operational responsibilities of supplying medications in health-care settings. As such, pharmacy departments and pharmacists representing them can enforce the restriction policies of antibacterial prescribing. Studies have shown that implementing a structured restriction policy can serve as an effective means in limiting the inappropriate use of antibacterials (Claeys et al., 2018; Davey et al., 2017; Lee et al., 2018).

Pharmacists can also play a more active role in engaging with doctors at the point of prescribing. Participation of pharmacists in daily antimicrobial clinical rounds has been shown to reduce the usage of carbapenem antibacterials to around 40% of the baseline values (Al-Somai et al., 2014). Pharmacists' participation in routine patient care rounds has been effective in improving antibacterial use, as well as patient outcomes in a variety of settings (Apisarnthanarak et al., 2015; Dubrovskaya et al., 2017).

Another aspect of AMS where pharmacists have shown an impact is the implementation of AMS-related computer applications such as web-based approvals initiatives for restricted antibacterials and computerized decision support systems with or without the electronic order entry system (Evans et al., 2015; Nault et al., 2017; Ohashi et al., 2017). Pharmacists are experienced in clinical computing applications as most drug dispensing software has capabilities of computerized decision support such as dose adjustments in renal impairment, detection of drug–drug interactions, and alerts for contraindications (Cufar et al., 2012; Fox et al., 2015). Therefore, pharmacy departments are often asked to play a leading role in the development and implementation of computerized initiatives surrounding AMS.

Research has also looked at the role of the pharmacist in identifying and confirming penicillin allergies in patients. While it is common for patients to identify as being allergic to penicillin (up to 10% of the population in the United States and United Kingdom state they have a history of penicillin allergy), it is estimated that only 10% of these people are truly allergic to penicillin (Drug and Therapeutics Bulletin, 2017). While administering a penicillin to a person who is truly allergic can lead to serious adverse events or death, inappropriate labeling can mean a patient is exposed to adverse effects or inappropriate treatment (including the use of broad-spectrum and/or more expensive antibiotics) that is not required. Pharmacists have been shown to effectively manage a penicillin allergy-testing program to identify patients who have been incorrectly labeled as being allergic to penicillin (Gugkaeva et al., 2017).

Academic detailing of doctors and nurses is another unique area where pharmacists can play an important role as antimicrobial stewards (Wathne et al., 2018). It is a well-known fact that pharmaceutical companies spend a significant amount of money and resources to shape prescribing behaviors involving their medicines (Wood et al., 2017). Pharmacists have been shown to provide effective academic detailing programs to improve the rational use of medicines, including but not limited to antibacterials (Ndefo et al., 2017; Wathne et al., 2018).

Education and Counseling of Patients

Pharmacists often routinely provide patient education and counseling related to medicines. Patients' perceptions of the effectiveness of antibiotics and expectations for antibiotic prescriptions are known determinants of inappropriate antibiotic prescribing by doctors (Coenen et al., 2006). Pharmacists often provide consultations for upper respiratory tract symptoms in community pharmacies and can educate patients about the importance of AMR and the ineffectiveness of antibacterials in managing common viral infections. Increasingly, pharmacists are getting involved in initiatives to improve the management of common community-based presentations and can offer specific interventions such as delayed antibacterial dispensing according to a particular criteria or a comprehensive educational program to reduce the demand of antibacterials (Avent et al., 2018; Essack et al., 2018).

Antibacterials constitute a significant proportion of day-to-day pharmacy practice and will continue to offer opportunities and challenges for pharmacists working in acute care settings and community health. Pharmacists have shown that they can contribute significantly to optimizing the use of antibacterials through their medication knowledge and skills. The role of pharmacists in infectious diseases will continue to evolve and the future will offer unique opportunities for the profession.

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Management of Infectious Diseases and the Pharmacist's Role: Fungal Infections

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Learning Objectives

At the end of this chapter, the reader will be able to

- Develop basic understanding of the epidemiology, etiopathogenesis, and clinical manifestations of fungal infections.
- Understand the relative benefits and risks of all available systemic antifungal agents with respect to patient characteristics and routes of administration.
- Identify the key roles of pharmacists in optimizing the drug therapy through patient-oriented care plan, therapeutic drug monitoring, patient education, evaluation of therapeutic outcomes, and monitoring of adverse drug effects.

Introduction

Fungal pathogens are widespread in nature and are adaptable to all ecosystems, including air, water, soil, plants, and human body. Fungi mainly reproduce by forming spores that are spread by air, water, and direct contact with infected source. The inhalation of

airborne spores and inoculation into skin and mucous membrane are the major modes of transmission of fungal infections into human beings.

Fungal infections being difficult to be differentially diagnosed are associated with significant mortality despite the presence of a number of antifungal agents. Fungal infections commonly affect immunocompromised individuals such as individuals with cancer or acquired immunodeficiency syndrome (HIV/AIDS) and those undergoing organ transplant (Garbee et al., 2017). Fungal infections are also prevalent in nosocomial settings. *Candida* spp., *Aspergillus* spp., *Mucorales*, *Fusarium* spp., and other molds including *Scedosporium* spp. are the common nosocomial fungal pathogens. Therefore, early diagnosis, reversal of underlying host defects, and initiation of effective pharmacological therapy continues to be the mainstay of treating fungal infections (Perlroth et al., 2007).

Mucocutaneous Fungal Infections

Mucocutaneous infections are superficial infections of the mucosal surfaces and skin that are commonly caused by Candida species, primarily the *Candida albicans*. Mucocutaneous candidal infections are among the most common infections worldwide, having unique treatment requirements that may last for months or years (Brown and Chin, 2017). The following sections discuss the various types of candida infections including vulvovaginal candidiasis (VVC), oropharyngeal candidiasis (OPC), and esophageal candidiasis (EC).

Vulvovaginal Candidiasis

VVC, whether asymptomatic or symptomatic, refers to the infections in women whose vaginal cultures are positive for *Candida* species. Based on episodic frequency, VVC may be classified as sporadic or recurrent, which is essential for understanding the pathophysiology and selection of effective pharmacotherapy. Complicated VVC is difficult to treat and requires special consideration for successful treatment, whereas uncomplicated VVC refers to sporadic infections and are susceptible to all types of antifungal therapy (Dovnik et al., 2015).

Epidemiology and Etiology

Vulvovaginal complaints are considered to be the most common reason for women to seek medical care, of which, vaginitis accounts for 20%–25% of the total cases (Paladine and Desai, 2018). VVC is the second most common cause of vaginitis after bacterial vaginosis. An estimated 75% of women will have at least one occurrence of VVC during their lifetime.

C. albicans is the major pathogen responsible for VVC, accounting for 80%–92% of symptomatic episodes (Brown and Chin, 2017). The rest are caused by non-*C. albicans* species, predominantly the *Candida glabrata*.

Pathophysiology and Risk Factors

Candida organisms are dimorphic that exist in two distinct forms: blastospores that are responsible for the transmission and spread and germinated form that causes tissue invasion and symptomatic infections. In order to colonize vagina, attachment of *Candida* species to mucosal walls is vital. The process of attachment is a complex phenomenon. For colonization, not only the candidal surface structure is important but the presence of receptors on epithelial cells is also essential for attachment. Therefore, women having a high number of epithelial receptors are at higher risk of colonization compared with others (Brown and Chin, 2017).

Several risk factors that are linked to higher rates of VVC and increased vaginal colonization with *Candida* include high estrogen levels, hormone replacement therapy, oral contraceptives, intrauterine device, pregnancy, sexually active women, poorly controlled diabetes, corticosteroid use, and oral-genital contact (Goncalves et al., 2016).

Antibiotics, particularly the broad-spectrum agents, may also increase the risk of VVC by inhibiting the growth of protective vaginal bacterial flora (e.g., *Lactobacillus* spp.), resulting in the overgrowth of *Candida*. Furthermore, an excess of refined carbohydrates, douching, and tight-clothing may also predispose patients to a higher risk of VVC. Alterations in the vaginal environment by any of the aforementioned factors permit the overgrowth of organisms that are normally suppressed, resulting in the increased risk of vulvovaginitis (Arfiputri et al., 2018).

Clinical Presentation and Diagnosis

Patients with VVC may present with symptoms of vulvar pruritus, irritation, dyspareunia, and/or external dysuria with or without abnormal vaginal discharge. Vaginal examination often reveals erythema and edema of the labia and vulva, excoriations from scratching, and thick white discharge. In patients with VVC, vaginal pH appears normal (4–4.5), while elevated pH suggests the presence of bacterial infection. Diagnosis should be confirmed with microscopic examination of vaginal secretions. Microscopic examination reveals the presence of blastospores or pseudohyphae. The presence of yeast cells or hyphae can be determined by a wet mount preparation with saline and 10% potassium hydroxide preparation. *Candida* cultures are not recommended for uncomplicated VVC; however, cultures are required if microscopic examinations are inconclusive or a recurrence is suspected (Workowski et al., 2015).

Pharmacological Management

Vulvovaginal candidiasis is commonly caused by *C. albicans*, but other *Candida* species may also be implicated in its etiology that contributes to uncomplicated (90%) or complicated (10%) disease (Pappas et al., 2016). The complicated disease is characterized by the presence of a severe or recurrent infection, infection with non-*C. albicans* species, and/or infection in an immunocompromised host (Pappas et al., 2016).

Various topical and systemic antifungal agents can be used for the treatment of vulvovaginal candidiasis. All antifungal agents including oral or topical formulations have a comparable efficacy with no specific drug or route of administration considered as superior to the other (Sobel, 2007; Watson et al., 2002). Furthermore, studies report a similar response to antifungal therapy in HIV-positive and HIV-negative individuals. The Infectious Diseases Society of America (IDSA) 2016 guidelines recommend topical antifungal agents as the first-line therapy for the treatment of uncomplicated vulvovaginal candidiasis with a cure rate of 90% or more (Watson et al., 2002). Alternatively, a single dose of oral fluconazole (150 mg) may be used (Pappas et al., 2016). However, complicated vulvovaginal candidiasis should be treated with intravaginal medications (topical formulations) for 5–7 days or with 3 doses of oral fluconazole (150 mg) administered at an interval of 71 h (Sobel et al., 2001).

Most candida species except *Candida krusei* and *C. glabrata* respond well to fluconazole therapy; however, treatment of non-*C. albicans* infection is often challenging and requires special consideration for antifungal susceptibility (Sobel, 2007). *C. glabrata*-related infections should initially be treated with boric acid capsules (600 mg once daily) for 14 days or nystatin vaginal suppositories (100,000 units) for 14 days (Sobel et al., 2003). Topical flucytosine (17%) and amphotericin-B (3%), either alone or in combination, for a duration of 14 days should be considered in patients refractory to boric acid or nystatin (Sobel et al., 2003; White et al., 2001).

Recurrent vulvovaginal candidiasis is defined as an occurrence of four or more episodes of symptomatic infection within a year (Sobel et al., 2004). Recurrent infections should initially be treated with topical or oral fluconazole for a duration of 10–14 days, followed by maintenance therapy with fluconazole (or other antifungal agent) for a minimum of 6 months (Donders et al., 2008; Rosa et al., 2013; Sobel et al., 2004). Oral fluconazole (150 mg) once weekly is the most preferred regimen for maintenance therapy with 90% or more cure rates (Sobel et al., 2004). Alternatively, topical clotrimazole cream (200 mg) twice weekly or clotrimazole suppositories (500 mg) once weekly can be considered (Iavazzo et al., 2011; Witt et al., 2009) (**Table 1**).

Oropharyngeal and Esophageal Candidiasis

OPC is an opportunistic infection which is commonly caused by *Candida* species. In humans, *Candida* are considered as normal flora of the gastrointestinal (GI) and genitourinary (GU) tracts that are capable of transforming from commensal organisms to pathogenic forms, resulting in the symptomatic mucosal infections.

Epidemiology and Etiology

The exact prevalence of OPC is difficult to determine as the risk of these infections varies with the presence of certain underlying medical conditions. The prevalence of OPC, as part of the normal oral flora, shows large geographic variations; however, an estimated 35% prevalence of the infection has been projected in several studies (Ghasempour et al., 2011). The incidence of

Table 1 Recommended intravaginal regimens for the treatment of vaginal candidiasis

Drug	*Formulation(s)*	*Dosage*
Butoconazole	• 2% cream (OTC)	• 5 g intravaginally daily for 3 days
Clotrimazole	• 1% cream (OTC) • 2% cream (OTC)	• 5 g intravaginally daily for 7–14 days • 5 g intravaginally daily for 3 days
Miconazole	• 2% cream (OTC) • 4% cream (OTC) • 100 mg vaginal suppository (OTC) • 200 mg vaginal suppository (Rx) • 1200 mg vaginal ovule (OTC)	• 5 g intravaginally daily for 7 days • 5 g intravaginally daily for 3 days • 1 suppository intravaginally daily for 7 days • 1 suppository intravaginally daily for 3 days • 1 ovule intravaginally daily for 1 day
Nystatin	• 100,000-unit vaginal tablet (Rx)	• 1 tablet intravaginally daily for 14 days
Terconazole	• 0.4% cream (Rx) • 0.8% cream (Rx) • 80 mg vaginal suppository (Rx)	• 5 g intravaginally daily for 7 days • 5 g intravaginally daily for 3 days • 1 suppository intravaginally for 3 days
Tioconazole	• 6.5% ointment (OTC)	• 5 g intravaginally daily for 1 day
Fluconazole	• 150 mg tablet (Rx)	• One tablet × 1 day

OTC, over the counter; Rx, prescription only.

Source: Information from Workowski, K.A., Bolan, G.A., 2015. Sexually transmitted diseases treatment guidelines, MMWR Recomm. Rep. 64 (RR-03), 1–137; Monistat product information. Prestige Brands Holdings, Inc. 2018. www.monistat.com.; Vagistat product information. Novartis Consumer Health, Inc. 2015. www.vagistat.com.

Table 2 Predisposing factors for oropharyngeal candidiasis

Local factors
• Denture wearing
• Smoking
• Atopic constitution
• Inhalation steroids
• Topical steroids
• Hyperkeratosis
• Imbalance of the oral microflora
• Quality and quantity of saliva
General factors
• Immunosuppressive diseases
• Impaired health status
• Immunosuppressive drugs
• Chemotherapy
• Endocrine disorders
• Hematinic deficiencies

Source: Information fromMillsop, J.W., Fazel, N., 2016. Oral candidiasis. Clin. Dermatol. 34, 487–494.

OPC and EC is an indicator of the suppression of immune system, often developing in infants, elderly, and in the immunocompromised patients. Oral candida colonization has been reported in around 40%–70% of healthy children and adults. The risk for candida colonization is higher in children with dental caries and in elderly wearing dentures (Daniluk et al., 2006; Rozkiewicz et al., 2006). The incidence of EC is the highest among diabetic patients or individuals who receive higher doses of corticosteroids.

C. albicans is the major causative pathogen of OPC. However, only a small number of infections are related to *C. glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *C. krusei*, or *Candida dubliniesis* (Meiller et al., 1999; Redding et al., 2004; Redding et al., 2000).

Pathophysiology and Risk factors

There is an apparent association between oral candidiasis and the influence of local and general predisposing factors. The local predisposing factors (**Table 2**) are able to promote the growth of the yeast or influence the immune response of the oral mucosa. The risk of candida infections is higher in patients with diabetes, HIV/AIDS, and in those undergoing chemotherapy. In general, predisposing factors are often related to an individual's immune and endocrine status. Drugs as well as diseases which suppress the adaptive or the innate immune system can also affect the susceptibility of the mucosal lining (**Table 2**) (Millsop and Fazel, 2016).

To invade the mucosal lining, the fungus must adhere to the epithelial surface. Penetration into mucosal wall is facilitated by the secretion of protease enzymes, especially the secretory aspartyl proteinases and phospholipase B (Reichart et al., 1995; Sherwood et al., 1992).

Clinical Presentation and Diagnosis

Painless, creamy white, plaque-like lesions of the oral mucosa represent the most common characteristics of OPC. Symptoms of OPC include a painful mouth, burning sensation on the tongue, and dysphagia. A presumptive clinical diagnosis is usually made according to the appearance of lesions and the ability to easily scrape off the superficial plaque. Culture is not required to make a diagnosis and does not distinguish colonization from infection (Farah et al., 2010; Leigh et al., 2004). However, in patients with infection refractory to treatment, cultures should be considered to identify the causative agent associated with the infection.

Untreated OPC can lead to the development of EC; however, about 10% of EC cases do occur in the absence of OPC. Symptoms of EC may include dysphagia, odynophagia, and retrosternal pain. A reliable diagnosis of EC can be made by endoscopic evaluation of lesions, together with histopathologic evidence of *Candida* on tissue biopsy. Fungal cultures of esophageal brushings are not useful in the diagnosis of EC because they do not distinguish between colonization and infection, but are helpful in identifying more resistant *Candida* spp.

Pharmacological Management

Oropharyngeal and esophageal candidiasis is commonly associated with compromised immunity such as patients with HIV/AIDS, diabetes mellitus, use of corticosteroids, antimicrobial therapy, and use of dentures (Bodhade et al., 2011; Pappas et al., 2016). Effective therapies for the management of these diseases such as the use of antiretroviral therapy for HIV infection and disinfection of dentures can reduce the incidence of OPC or EC and its relapse (Schwarcz et al., 2013) (**Table 3**)

Table 3 Antifungal agents used in the treatment of oropharyngeal candidiasis

Topical (mild disease)			
Drug	*Form*	*Dosage*	*Comments*
Amphotericin B	Lozenge, 10 mg	Slowly dissolved in mouth 3–4×/day after meals for 2 weeks minimum	Negligible absorption from gastrointestinal tract.
	Oral suspension, 1 mg/mL	1 mL swish-and-swallow, 4×/day for 2 weeks	
Nystatin	Cream	Apply to affected area 3–4×/day	Negligible absorption from gastrointestinal tract.
	Pastille, 100,000 U	Dissolve 1 pastille slowly after meals 4×/dayd, usually for 7 d	
	Oral suspension, 100,000 U	1 mL swish-and-swallow,4×/day for 2 weeks	Contains sucrose, prolong use may be cariogenic
Clotrimazole	Cream	Apply to the affected area 2–3 times daily for 3–4 weeks	Requires frequent application
	Solution	5 mL 3–4 times daily for 2 weeks minimum	
Miconazole	Oral gel	Apply to the affected area 3–4 times daily	Occasional mild local reactions. Avoid in pregnancy and liver disease.
	Cream	Apply twice per day and continue for 10–14 day after the lesion heals	
Systemic (moderate–severe disease)			
Primary regimen			
Fluconazole	Capsules	100–200 mg/day once daily for 7–14 days	Interacts with anticoagulants, terfenadine, cisapride, and astemizole. Contraindicated in pregnancy and liver and renal disease. May cause nausea, diarrhea, headache, rash, liver dysfunction.
Alternative regimens			
Itraconazole	Solution	200 mg/day taken immediately after meals for 7–14 days	Interacts with terfenadine, cisapride, and astemizole. Contraindicated in pregnancy and liver disease. May cause nausea, neuropathy, rash.
Posaconazole	Oral suspension	400 mg orally twice daily for 3 days, then 400 mg every day for 7–14 days	Take with full meal and/or acidic carbonated beverage (e.g., ginger ale).
Voriconazole	Tablet	200 mg twice daily for 7–14 days	Reduce maintenance dosage by 50% in mild to moderate hepatic impairment
Caspofungin	Intravenous infusion	70 mg loading dose, then 50 mg/day i.v. for 7–14 days	Dosage adjustment with concomitant use of an enzyme inducer (e.g., rifampin, Patients receiving carbamazepine, dexamethasone, efavirenz, nevirapine, or phenytoin) is recommended

i.v., intravenously; p.o., per oral.

Source: Adapted from: Pappas, P.G., Kauffman, C.A., Andes, D.R., 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin. Infect. Dis. 62 (4), e36–e37; Ellepola, A.N.B., Samaranayake, L.P., 2000. Oral candidal infections and antimycotics. Crit. Rev. Oral Biol. Med. 11 (2), 172–198.

Oropharyngeal candidiasis

Most patients with oropharyngeal candidiasis respond to the topical treatment. However, relapse following topical therapy is common, particularly in patients with HIV/AIDS. For mild diseases, clotrimazole troches (10 mg) 5 times daily or miconazole mucoadhesive tablets (50 mg) once daily for 7–14 days is the recommended first-line therapy. Alternatively, 4–6mL of nystatin suspension (100,000 units/mL) or 1–2 nystatin pastilles (200,000 units) 4 times daily for 7–14 days may be used (Pappas et al., 2016).

Oral fluconazole and itraconazole solutions are more effective than ketoconazole and itraconazole capsules and are recommended as first-line therapies for the treatment of moderate to severe diseases (Pappas et al., 2016; Queiroz-Telles et al., 2001). Oral fluconazole should be used at a dose of 100–200 mg, once daily for 7–14 days. In the case of resistance to fluconazole, once daily itraconazole solution (200 mg) is suggested with cure rates between 64% and –80% (Pappas et al., 2016). Posaconazole has a similar efficacy as fluconazole and has been approved by the Food and Drug Administration for prophylaxis in high-risk patients (Pappas et al., 2016). Posaconazole suspension (400 mg) twice daily for 3 days followed by once daily administration for a maximum of 28 days may be used as an alternative to itraconazole solution (Skiest et al., 2007). Other alternatives for the management of fluconazole-resistant diseases are voriconazole (200 mg) twice daily or amphotericin-B deoxycholate oral suspension (100 mg/mL) 4 times daily (Pappas et al., 2016).

The refractory disease should be treated with intravenous echinocandins such as caspofungin, micafungin, or anidulafungin (de Wet et al., 2004; Krause et al., 2004; Villanueva et al., 2001, 2002). Caspofungin 70 mg loading dose followed by 50 mg once daily, micafungin 100 mg once daily, or anidulafungin 200 mg loading dose followed by 100 mg once daily should be used. Alternatively, oral or intravenous amphotericin-B deoxycholate at a dose of 0.3 mg/kg/day can be used (Pappas et al., 2016). Moreover, adjuvant therapy with granulocyte-macrophage colony-stimulating factor or interferon-gamma may be considered (Bodasing et al., 2002; Vazquez et al., 2000).

Long-term therapy with fluconazole (100 mg) 3 times weekly is an effective approach for the prevention of OPC, particularly in immunocompromised patients due to the increased risk of refractory disease (Bodhade et al., 2011; Patel et al., 2012). On the contrary, oral amphotericin-B deoxycholate, nystatin solution, and itraconazole capsules have limited efficacies and are best avoided for the prevention of OPC (Pappas et al., 2016).

Esophageal candidiasis

Fluconazole is more effective than ketoconazole, itraconazole capsule, and flucytosine, while it has similar efficacy as itraconazole solution for the treatment of EC, with most patients achieving resolution of symptoms in 7 days (Pappas et al., 2016; Sobel et al., 2001). The IDSA 2016 guidelines recommend the use of oral fluconazole (200–400 mg) once daily for 14–21 days as the recommended first-line therapy. Alternatively, intravenous fluconazole (400 mg) once daily or high-dose intravenous echinocandins including micafungin (150 mg), caspofungin (70 mg loading dose followed by 50 mg once daily), or anidulafungin (200 mg) may be considered for patients who cannot tolerate oral therapy (de Wet et al., 2004; de Wet et al., 2005; Krause et al., 2004; Pappas et al., 2016). Moreover, amphotericin-B at a dose of 0.3–0.7 mg/kg/day may be used in EC. De-escalation to oral fluconazole should be considered once the patient is able to tolerate the oral therapy (Pappas et al., 2016).

Patients refractory to fluconazole should receive itraconazole solution (200 mg/day) or intravenous or oral voriconazole (200 mg twice daily) for 14–21 days (Ally et al., 2001; Pappas et al., 2016). Alternatively, posaconazole suspension (400 mg) twice daily or the extended-release tablets (300 mg) once daily may be used. Intravenous echinocandins (micafungin, caspofungin, or anidulafungin) or amphotericin-B (0.3–0.7 mg/kg\day) for a duration of 14–21 days can be used as an alternative. Chronic preventive therapy with fluconazole (100–200 mg) 3 times weekly is recommended in patients with refractory disease particularly in the immunocompromised patients (Goldman et al., 2005; Pappas et al., 2016) (**Table 4**).

Invasive Fungal Infections

Invasive fungal infections (IFIs) pose a significant threat to immunocompromised patients. The most frequently occurring IFIs are those caused by *Candida* spp. and *Aspergillus fumigatus*. However, previously uncommon and new pathogens are also on the rise (Chen et al., 2010; Richardson and Lass-Flörl, 2008). Timely diagnosis and management of IFIs are necessary for optimal clinical

Table 4 Antifungal agents used in the treatment of esophageal candidiasis

Drug	*Dosage*
Azole therapy	
Fluconazole	400 mg as a loading dose and then 200– 400 mg daily for 14– 21 days given p.o. or i.v.
Itraconazole	200 mg p.o. twice daily
Voriconazole	200 mg p.o./i.v. twice daily
Posaconazole	Oral suspension, 400 mg twice daily
Echinocandins	
Caspofungin	70 mg i.v. on day 1 followed by 50 mg i.v. every 24 h. less toxic alternative to intravenous amphotericin B
Micafungin	150 mg i.v. per day
Anidulafungin	200 mg i.v. on day 1 followed by 100 mg/day i.v.
Amphotericin B	
Amphotericin B deoxycholate	0.3–0.7 mg/kg daily as single infusion Infection with *C. glabrata* or *C. krusei* may require higher doses (0.7 mg/kg)

i.v., intravenously; p.o., per oral.

Source: Information from Panel on opportunistic infections in HIV-infected adults and adolescents. guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the centers for disease control and prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.; Pappas, P.G., Kauffman, C.A., Andes, D.R., 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin. Infect. Dis. 62 (4); Klotz, S.A., 2006. Oropharyngeal candidiasis: a new treatment option. Clin. Infect. Dis. 42 (8), 1187–1188.

outcomes. However, despite the availability of highly effective antifungal therapies, the mortality rates for IFIs remain high (30%–80%) (Chen et al., 2010).

Epidemiology and Etiology

The true burden of IFI is probably underestimated because of the absence of reliable diagnostics tools. IFIs are relatively uncommon compared with superficial fungal infections; however, they are of great medical concern because of their disproportionately high rates of mortality. Widespread adoption of aggressive immunosuppressive therapy among certain patient populations (e.g., chemotherapy, transplants) together with the increased use of invasive devices such as central venous catheters (CVC) contribute toward the varying epidemiology of IFIs (Enoch et al., 2017).

Candida species are undoubtedly the most important species among the opportunistic fungal infections, accounting for 8%–10% of all nosocomial bloodstream infections with an incidence rate of 6–23 infections per 100,000 persons annually in the United States (Pfaller et al., 2006). Recently, the incidence of invasive candidiasis (IC) has significantly increased, most commonly affecting patients at the risk of opportunistic infections, such as the elderly or the immunosuppressed patients (Lamoth et al., 2018). On the contrary, a significant decrease has been reported in the incidence rates of neonatal IC (Aliaga et al., 2014; Cleveland et al., 2012). IC is associated with a high mortality rate between 10% and 49% and a prolonged hospital stay of 3–30 days (Pfaller et al., 2006). Candidemia is associated with a significant economic burden that is estimated to be one billion dollars each year in the United States (Pfaller et al., 2006). Moreover, a worldwide shift has been reported from *C. albicans* to non-*C. albicans* species. (Lamoth et al., 2018).

Invasive aspergillosis is not as common as the milder allergic forms of aspergillosis and is most commonly caused by *A. fumigatus* (Richardson, 2005). A recent increase in the incidence of *Apergillus* infections has been reported, though little is known about the relative occurrence due to the presence of specific species (Richardson, 2005). With the increasing number of solid organ and stem cell transplant recipients and the emergence of newer immunosuppressive agents, the incidence of *Aspergillus* infections is changing. Approximately, 1%–15% patients with cystic fibrosis suffer from allergic bronchopulmonary aspergillosis (ABPA) (Stevens et al., 2003). As much as 2.5% of asthmatic patients also suffer from ABPA that makes it approximately 4.8 million people affected with the disease (Denning et al., 2013). Of these ABPA-affected patients, as much as 400,000 also suffer from chronic pulmonary aspergillosis (CPA) (Denning et al., 2013). Invasive aspergillosis has been reported to be the most common fungal infection in stem cell transplant recipients and second most common fungal infection among solid organ transplant recipients during 2001–06. (Pappas et al., 2010).

Pathophysiology and Risk factors

A complex interplay of host and pathogen factors influences the acquisition and development of invasive fungal infections (Carver, 2017). A breach in skin or mucosal surfaces (serve as primary barriers to infection) allow the organism to enter the deeper tissues and bloodstream (Carver, 2017).

The most common route of infection is the respiratory tract, where aerosolized fungi pathogens are inhaled into the lungs (Garcia-Vidal et al., 2013). The first response to this invasion is phagocytosis led by neutrophils and monocytes/macrophages in the alveoli and bronchioles (Garcia-Vidal et al., 2013). These cells have receptors for fungal cell wall components termed pathogen-associated molecular patterns (PAMPs) that lead to the activation of intracellular signaling pathways. This activation triggers the inflammatory response, thus increasing the neutrophil accumulation and macrophage cytokine production (Garcia-Vidal et al., 2013). Ingested yeasts are killed by oxidative and non-oxidative mechanisms (Segal, 2009). Patients with low CD4 cells and those on treatment that inhibit cellular immunity (chemotherapy, high-dose corticosteroids, or tumor necrosis-α blockers such as infliximab) are at a high risk of acquiring localized mucosal infections with *Candida* species, but not at risk for getting invasive candidiasis/candidemia. Neutropenia is a major risk factor for IFI, particularly for the disseminated infections caused by *Candida* and *Aspergillus* species (Carver, 2017).

Clinical Presentation and Diagnosis

Invasive candidiasis encompasses several infectious syndromes broadly categorized as candidemia or deep-seated infections (infections of tissue sites beneath mucosal surfaces) (Clancy and Nguyen, 2012). Approximately, one-third of all patients with invasive candidiasis fall within any of the following three groups at the time of diagnosis: (1) patients with uncomplicated candidemia in the absence of deep-seated candidiasis most frequently arising from an infected catheter; (2) candidemia associated with deep-seated candidiasis most frequently arising from the gastrointestinal tract or secondary seeding from a separate infection site; and (3) deep-seated candidiasis without candidemia (Clancy and Nguyen, 2013).

Invasive candidiasis is most frequently diagnosed by the blood culture that probably identifies the majority of patients with candidemia alone, fewer patients with mixed deep-seated disease and intermittent candidemia, and virtually no patients who have an infection limited to deep tissues at the time of culture (Clancy and Nguyen, 2013). As a result, half of all episodes of invasive candidiasis are not detected by blood cultures alone. Therefore, a negative blood culture cannot rule out the possibility of invasive candidiasis, especially in the patients with multiple underlying risk factors for infection. Currently, the most frequently used test is the serum β-D-glucan test (Fungitell, Associates of Cape Cod Inc.).

Signs and symptoms of IA are predictably not revealed in the immunocompromised host. Fever is common but nonspecific for infection and may be accompanied by pleuritic chest pain, cough, hemoptysis, and/or friction rub (Bicanic and Harrison, 2014; Walsh et al., 2008). Neurologic signs, including seizures, hemiparesis, and stupor, may be present in patients with dissemination to the brain (Bicanic and Harrison, 2014). Cutaneous plaques or papules characterized by a central necrotic ulcer or eschar occur in up to 10% of patients with disseminated disease; however, concomitant blood cultures are often negative. Respiratory cultures, including sputum, bronchial washings, or bronchoalveolar lavage have a low sensitivity for the diagnosis of IA but have a high positive predictive value in the immunocompromised patients (Bicanic and Harrison, 2014). The galactomannan test and other nonculture-based strategies, such as serum β-glucan serve as complementary methods to confirm the results from microbiologic, histopathologic, and radiographic investigations directed toward diagnosing IA (Bicanic and Harrison, 2014). The section "Further reading" provides references to the sources that authors have deemed useful to a reader seeking additional information on the clinical manifestations and diagnosis of IA.

Pharmacological Management

Invasive Aspergillus

Empirical therapy should be initiated, while patients suspected with invasive pulmonary aspergillosis (IPA) are being investigated (Cornely et al., 2007; Greene et al., 2007). The IDSA 2016 guidelines recommend voriconazole as the initial therapy for the treatment of IPA (Herbrecht et al., 2002). Alternatively, liposomal amphotericin-B or isavuconazole may be used (Cornely et al., 2007; Maertens et al., 2016). Echinocandins should preferably be used in patients who are intolerant to azole and polyene antifungals (Patterson et al., 2016). However, combination therapy with voriconazole and echinocandins may be considered in selected patients (Marr et al., 2004; Singh et al., 2006). The IDSA 2016 guidelines recommend a minimum of 6–12 weeks of therapy depending upon the degree and duration of immunosuppression, site of disease, and the resolution of symptoms. Preventive therapy following successful eradication of infection is recommended in order to prevent relapse (Cordonnier et al., 2010; Liu et al., 2014; Patterson et al., 2016).

An individualized approach is needed for patients who have refractory or progressive IPA despite conventional therapy. The selection of therapy should be based on the severity and extent of infection and comorbidities (Patterson et al., 2016). In general, a recurrent infection is treated with antifungal agents such as amphotericin-B, micafungin, caspofungin, posaconazole, or itraconazole. Addition of an antifungal agent to the existing therapy or combination of antifungal agents from different classes other than those used previously is recommended (Patterson et al., 2016). Surgical resection of localized necrotic lesion may be considered in selected patients (Dolton et al., 2012; Kuderer et al., 2007; Marr et al., 2004; Patterson et al., 2016).

Adjuvant measures such as dose escalation or complete withdrawal of the immunosuppressive therapy (whenever possible), administration of colony-stimulating factors or granulocyte transfusion, and recombinant interferon-gamma need to be considered in patients suspected or diagnosed with neutropenia (Kuderer et al., 2007; Martinez et al., 2013; Patterson et al., 2016; Price et al., 2015). Surgery can be performed in patients with localized disease for debridements such as invasive fungal sinusitis or localized cutaneous disease (Didier et al., 2014). In patients diagnosed with aspergillosis, continuation of chemotherapy or bone marrow transplantation should be based on the risks and benefits (Patterson et al., 2016).

Tracheobronchial aspergillosis (TBA) commonly affects the lung transplant recipients. It does not require antifungal therapy except in symptomatic and immunocompromised patients (Patterson et al., 2016; Soubani and Chandrasekar, 2002). In non-immunocompromised patients, bronchoscopic removal of mucoid impaction is recommended (Krenke and Grabczak, 2011; Soubani and Chandrasekar, 2002). However, the systemic antifungal agents (triazoles) or intravenous amphotericin-B (lipid formulation) are recommended in immunocompromised patients as invasive disease cannot be ruled out. Antifungal therapy needs to be continued for at least 3 months or until the complete resolution of symptoms (Patterson et al., 2016). Dose escalation or withdrawal of immunosuppressive therapy may be considered (if feasible). Moreover, bronchoscopic debridement can be performed in selected patients (Patterson et al., 2016).

Invasive Candidiasis

In candidemia, the source of infection including the central venous catheter should be identified and rectified at the earliest. Echinocandins (caspofungin, micafungin, or anidulafungin) are the recommended first-line therapy in both neutropenic and nonneutropenic patients (**Table 5**) (Aguilar-Zapata et al., 2015; Glöckner, 2011; Mayr et al., 2011). Fluconazole may be used in selected patients who are not critically ill and are unlikely to be resistant to fluconazole (Pappas et al., 2016). Azole susceptibility should be tested in the bloodstream and other clinically relevant *Candida* isolates. Echinocandin susceptibility should also be tested in patients who had previously been treated with echinocandin and those suffering from infections of *C. glabrata* or *C. parapsilosis* (Pappas et al., 2016). *C. glabrata*-related infection should be treated with high-dose fluconazole or voriconazole (has additional fungal coverage such as *C. krusei*) with prior susceptibility testing. Lipid formulation of amphotericin-B may be considered in patients who are intolerant or have resistant infection (Ben-Ami, 2018; Pappas et al., 2016). The IDSA 2016 guidelines recommend to continue therapy for 2 weeks after negative blood culture for candida infection and resolution of symptoms (Pappas et al., 2016).

Oral step-down therapy is recommended in clinically stable nonneutropenic and neutropenic patients with candidiasis (those who have *Candida* isolates that are susceptible to fluconazole and who have negative repeat blood cultures). Oral step-down therapy

Table 5 Antifungal treatment approach to opportunistic invasive fungal infections

Condition or treatment group	*Recommended treatment regimens*
Invasive candidiasis or candidemia	

Nonneutropenic adults	• An echinocandin is recommended as initial therapy.
	  ◦ caspofungin 70 mg i.v. loading dose, then 50 mg i.v. daily
	  OR
	  ◦ micafungin 100 mg i.v. daily
	  OR
	  ◦ anidulafungin 200 mg i.v. loading dose, then 100 mg i.v. daily) is recommended as initial therapy.
	• An alternative for patients who are not critically ill and who are considered unlikely to have fluconazole-resistant *Candida* spp[a] is fluconazole 800 mg (12 mg/kg) oral loading dose, then 400 mg (6 mg/kg) orally daily.
	• A lipid formulation of amphotericin B (3–5 mg/kg i.v. daily) is an alternative if there is intolerance, limited availability, or resistance to other antifungal agents.

Neutropenic patients	• An echinocandin is recommended as initial therapy.
	  ◦ caspofungin 70 mg i.v. loading dose, then 50 mg IV daily
	  OR
	  ◦ micafungin 100 mg i.v. daily
	  OR
	  ◦ anidulafungin 200 mg i.v. loading dose, then 100 mg i.v. daily
	• A lipid formulation of amphotericin B (3–5 mg/kg i.v. daily) is a less attractive alternative because of the potential for toxicity.
	• For patients who are not critically ill and who have had no prior azole exposure, an alternative is fluconazole 800 mg (12 mg/kg) oral loading dose, then 400 mg (6 mg/kg) orally[b] daily.
	• In situations in which additional mold coverage is desired, voriconazole[c] 400 mg orally (or 6 mg/kg i.v.) twice daily for two doses then 200 to 300 mg orally (or 3–4 mg/kg i.v.) twice daily can be used.

C. glabrata and C. krusei infections	• An echinocandin is preferred over amphotericin B for treatment of candidemia due to *C. glabrata* and *C. krusei.* • In situations in which additional mold coverage is desired, voriconazole[c] 400 mg orally (or 6 mg/kg i.v.) twice daily for two doses then 200 to 300 mg orally (or 3 to 4 mg/kg i.v.) twice daily can be used.
C. auris infection	• Initial therapy with an echinocandin at the doses provided above
Aspergillosis	
	• [d]Voriconazole 6 mg/kg i.v. every 12 h×2 doses, then 4 mg/kg i.v. every 12 h. • Voriconazole 4 mg/kg oral every 12 h OR • Lipid formulations of amphotericin B (5 mg/kg/day i.v.) OR • Echinocandin: caspofungin (70 mg/day i.v.×1, then 50 mg/day i.v. thereafter), micafungin (100–150 mg/day i.v.), OR • Posaconazole 300 mg every 12 h i.v. day 1, then 300 mg i.v. daily • Posaconazole delayed-release tablet 300 mg twice daily, day 1, then 300 mg daily • [c]oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, i.v. 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg p.o. every 12 h) OR • Combination therapy (refer to the text)

i.v., intravenous; p.o., per oral; BID, twice a day; TID, three times a day.

The doses above are intended for patients with normal organ function. The fluconazole dose requires adjustment in the setting of renal insufficiency; the caspofungin and voriconazole doses may require adjustment in hepatic insufficiency. Refer to monograph of individual drug.

[a]Fluconazole should be considered a first-line option only in patients who are stable, have no previous exposure to azoles, and are not at high risk for C. glabrata infection (e.g., older adults, underlying malignancy, diabetic).

[b]Since fluconazole is highly bioavailable, oral therapy is appropriate for most patients. i.v. therapy (at the same dose) should be given to patients who are unable to take oral medications, who are not expected to have good gastrointestinal absorption, or who are severely ill.

[c]patients with suspected aspergillosis should initially be started on i.v. therapy.

[d]Therapeutic drug monitoring should be considered due to widely variable pharmacokinetics; refer to the Fig. 1.

*Source: Data from Pappas, P.G., Kauffman, C.A., Andes, D.R. et al., 2016. Clinical practice guideline for the management of candidiasis: update by the Infectious Diseases Society of America. Clin. Infect. Dis. 62, e1; Centers for disease control and prevention. recommendations for treatment of Candida auris. https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-treatment.html.; Patterson, T.F., Thompson, I.I.I.G.R., Denning, D.W. et al. 2016. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. **63**, e1–e60.*

should be considered after 5–7 days of therapy initiation. Fluconazole in a dose of 400 mg orally once daily is the usual recommended oral step-down therapy (Pappas et al., 2016). For *C. glabrata* infection, fluconazole 800 mg (12 mg/kg) orally daily or voriconazole 200–300 mg (3–4 mg/kg) orally twice daily should be used for patients with fluconazole- or voriconazole-susceptible isolates.

For chronic disseminated candidiasis, initial treatment with amphotericin-B (lipid formulation) or with an echinocandin for several weeks followed by oral fluconazole until resolution of lesions (takes several months) has been recommended (Spellberg et al., 2006). Early discontinuation of therapy results in the increased risk of relapse, whereas short-term treatment (1–2 weeks) with nonsteroidal anti-inflammatory drugs or corticosteroids may be considered in patients with persistent fever.

Osteoarticular candidiasis should be treated with fluconazole or with an echinocandin for the initial 2 weeks, followed by fluconazole therapy for 6–12 months. Surgical debridement may be considered in some patients (Gamaletsou et al., 2012; Miller et al., 2015).

Candidiasis affecting the central nervous system should be treated with liposomal amphotericin-B either alone or in combination with flucytosine (Raman Sharma, 2010; Sanchez-Portocarrero et al., 2000). Step-down therapy with fluconazole should be considered in patients following improvement in their condition. Moreover, therapy needs to be continued until resolution of symptoms with no apparent CSF and radiological abnormalities.

Addressing predisposing factors is the initial approach for treating candida associated urinary tract infections. Antifungal therapy is recommended in patients who are at high risk for dissemination including neutropenic patients, low birth weight infants (<1.5 kg) and patients who undergo urologic manipulation (Achkar and Fries, 2010). High-risk patients should be treated in a similar fashion as candidemia. Oral fluconazole or amphotericin-B deoxycholate is recommended for patients undergoing urologic procedures that should be initiated few days before the procedure and should continue to be administered until few days after the procedure (Behzadi et al., 2015; Fisher et al., 2011).

Role of Pharmacists

Pharmacists have a critical role in the management of patients with fungal infections due to the several limitations of antifungal agents, including drug resistance, pharmacokinetics, toxicities, dosage form preferences, and cost. No single antifungal agent is considered appropriate for all patients and the treatment must be individualized and frequently modified for achieving optimal outcomes. Within a health care team, the pharmacist is responsible to assess and manage the drug interactions and recommend potential drug or dosage changes based on the individual patient characteristics, susceptibility testing, and therapeutic drug monitoring. Application of such knowledge and skills by pharmacists can substantially improve the probability of successful treatment by reducing the drug-related toxicities in patients with both superficial and life-threatening invasive fungal infections (Agrawal et al., 2016; Bauters et al., 2005). This section discusses the role of pharmacists in different domains of fungal disease management such as the product selection, patient counseling, antifungal susceptibility testing, therapeutic drug monitoring, identification and management of drug-related oral candidiasis, and monitoring/management of adverse drug reactions related toantifungal therapy.

Identification and Management of Drug-Related Oral Candidiasis

Many drug-related factors contribute toward the etiology of OPC and EC. Those at risk for candidiasis include patients with asthma who use an orally inhaled corticosteroid (van Boven et al., 2013), elderly wearing dentures (Aoun and Berberi, 2017), patients on long-term antidepressant therapy (with possible resultant xerostomia) (Cockburn et al., 2017), home-care patients undergoing treatment with cytotoxic drugs (Mosel et al., 2011), patients receiving high doses of oral corticosteroids and those with diabetes mellitus (Kanda et al., 2003). By reviewing patient profiles and taking a proper medical and drug history, pharmacists can identify patients with a greater risk of candidiasis due to the close correlation between these conditions (**Table 6**). In addition, patient counseling and education regarding various aspects can reduce the chances of OPC and EC in such high-risk patients.

Table 6 Questions for counseling patients on oropharyngeal candidiasis

Questions for counseling patients on oropharyngeal candidiasis
• Do you smoke or use any tobacco products?
• Do you wear dentures?
• How often do you brush your teeth? Clean your dentures? see your dentist for regular checkups?
• Do you suffer from any chronic illness (e.g., diabetes Mellitus, arthritis, rheumatic heart disease, asthma, seizure disorder, hypertension, etc.)?

Source: Information from Vozza, I., Cavallè, E., Corridore, D., Ripari, F., Spota, A., Brugnoletti, O., Guerra, F., 2015. Preventive strategies in oral health for special needs patients. Annali di Stomatologia 6, 96–99.

Xerostomia

Xerostomia is a condition in which salivary flow is limited or arrested. An estimated 20% of elderly have xerostomia (Nadig et al., 2017; Shinozaki et al., 2012). Drugs with anticholinergic activity and those that cause volume depletion (antihypertensives, antihistamines, antipsychotics, antidepressants, and diuretics) may affect treatment outcomes of OPC. Patients with xerostomia may have inadequate saliva to dissolve troches. For drug-induced xerostomia, using the lowest effective dose or switching to an alternative medication may help. Chewing xylitol gum enhances the salivary flow and helps control *Streptococcal mutans*-associated infections; however elderly who wear dentures may be unable to chew gum (Plemons et al., 2014).

Several artificial saliva preparations that provide more viscosity and lubrication than water are available generally without prescription and are dispensed as sprays, liquid rinses, gels, and lozenges. These compounds typically contain a unique mixture of multiple components in each preparation such as carboxymethylcellulose, polyethylene glycol, sorbitol, and electrolytes (Kho, 2014). They do not stimulate natural salivary gland production and must be considered as a replacement therapy. The artificial saliva is best used at bedtime and periodically throughout the day; however, their relief is temporary and has a variable efficacy (Alves et al., 2004; Rhodus and Bereuter, 2000; van der Reijden et al., 1996). These products should be applied to the inner lips, buccal mucosa, tongue and hard palate. Patients should be informed of the normal diurnal variation in saliva flow that decreases with time and has an altered composition at night (Hardt et al., 2005).

Denture wearing

Denture stomatitis is present in more than 40% of denture wearers (Puskar et al., 2012). Patients wearing dentures should be advised to clean the denture and avoid wearing it overnight. Pharmacists can also counsel patients on denture care procedure. Denture wearers should be advised to remove dentures before going to bed that should be then brushed vigorously and should be soaked in a solution of chlorhexidine gluconate or a dilute solution of bleach (10 drops in a denture cup filled with water). They should then be rinsed thoroughly.

Inhaled corticosteroid users

Steroid inhaler users should also be advised to brush and rinse the palate after each inhalation. Pharmacists should review the proper aerosol inhalation technique and consider the need for inhaler chamber (spacer) or an alternative metered-dose inhaler device if needed (Ng, 2013). Patients should also be advised to avoid smoking and consumption of alcohol.

Selection of Antifungal Dosage Form

Pharmacists can also play an important role in product selection by considering various factors including cost, length of therapy, formulation, convenience, and ease of use. Antifungal creams should be used at bedtime, preferably with a sanitary pad to help absorb any leakage. Ovules (vaginal suppository) have an added advantage that allows them to be used at any time of the day. Various formulations of amphotericin-B provide the most reliable and broad-spectrum therapeutic alternatives. However, the use of amphotericin-B deoxycholate is accompanied by their dose-limited toxicities, most importantly by their infusion-related reactions and nephrotoxicity. For patients with severe hepatotoxicity or instances when there is a suspected risk of drug interactions between azoles (as a class) and other agents, switching to a lipid formulation of amphotericin-B is recommended. Although, there is a limited knowledge to date with isavuconazole, it is a suitable alternative for patients with renal dysfunction and those who cannot receive intravenous voriconazole due to its cyclodextrin vehicle (Bauters et al., 2005).

Patient Counseling

Patient counseling by pharmacists should include information on the proper use of medications. Topical agents require frequent dosing and prolonged contact time (20–30 min) with the mucosal surface. Rough surfaces of tablets and troches may irritate sensitive mucosa. Topical agents containing sucrose or dextrose may increase the risk of caries or cause elevated blood sugar levels in patients with diabetes. Daily fluoride rinses can help reduce the risk of caries when used with an agent containing sucrose or dextrose (Stein Gold and Rosen, 2016). Moreover, vaginal formulations (creams or gels) necessitate the need for providing instructions to patients on cleaning the applicator when using reusable applicators. Oil-based topical antifungal creams or suppositories can weaken latex condoms and diaphragms and can consequently reduce their efficacy (Workowski and Bolan, 2015). Female patients with VVC should be advised to continue therapy even if their menstrual period begins. Pharmacists should also recommend the adoption of basic nonpharmacologic approaches for the treatment and prevention of VVC such as keeping the genital area clean and dry, avoidance of constrictive clothing, undergoing vaginal douching, and avoiding the prolonged use of soaps and perfumes in hot tubs (Workowski and Bolan, 2015).

Antifungal Susceptibility Testing and Antifungal Resistance

The need for reproducible and clinically relevant antifungal susceptibility testing has been prompted by the increased number of invasive fungal infections, expanding use of new and established antifungal agents and the emergence of antifungal resistance (Johnson, 2008; Pfaller, 2008). For instance, patients with an HIV infection are prone to the development of antifungal resistance

Table 7 Indications for antifungal susceptibility testing

- *C. glabrata* isolated from blood or deep sites (e.g., normally sterile fluids, tissues, abscesses) should be tested for susceptibility to fluconazole, voriconazole, and an echinocandin.
- Mucosal candidiasis that is unresponsive to usual antifungal therapy.
- Invasive disease that is unresponsive to the initial antifungal regimen.
- Clinical failure in patients with invasive disease caused by species with significant rates of acquired resistance (particularly among the azole antifungal agents).
- Invasive disease caused by unusual fungal species for which antifungal susceptibility patterns have not been well established or are unpredictable.

Source: Data from Pfaller, M.A., 2005. Antifungal susceptibility testing methods. Curr. Drug Targets, 6, 929; Rex, J.H., Pfaller, M.A., Has antifungal susceptibility testing come of age? Clin. Infect. Dis. 35, 982; Pappas, P.G., Kauffman, C.A., Andes, D. et al., 2009. Clinical practice guidelines for the management of candidiasis: update by the Infectious Diseases Society of America. Clin Infect Dis. 48, 503; Pfaller, M.A., Wu, W.L., 2001. Antifungal susceptibility testing: new technology and clinical applications. Infect. Dis. Clin. N. Am. 15, 1227; Spellberg, B. J., Filler, S.G., Edwards, J.E. Jr., 2006. Current treatment strategies for disseminated candidiasis. Clin. Infect. Dis. 42, 244.

and emergence of non-*C. albicans* candida species, particularly the *C. glabrata*. Susceptibility to antifungal agents varies between species of candida genus. Therefore, identification of the specific *Candida* spp.-associated infections and susceptibility testing will help in the selection of appropriate antifungal agents for their treatment. Among the *Candida* isolates, cross-resistance between fluconazole, itraconazole, voriconazole, and posaconazole has been reported (Pfaller, 2012). However, none of the triazoles exhibits meaningful activity against fluconazole-resistant isolates of *C. glabrata*, whereas voriconazole and posaconazole are active against the intrinsically fluconazole-resistant *C. krusei*. Pharmacists need to be aware of potential cases where antifungal susceptibility testing should be employed (Table 7).

Therapeutic Drug Monitoring of Antifungal Agents

Therapeutic drug monitoring (TDM) of antifungal agents may be useful in certain clinical scenarios, but it is not recommended in all patients with IFI. In general, an antifungal must meet the following criteria to be considered eligible for TDM:

1. A sensitive assay must be available in the clinical laboratory or possibly in a reference laboratory that will report results back in a timely fashion. Otherwise, the impact of TDM on clinical decisions would be limited.
2. An antifungal agent must have documented drug–drug interactions that would warrant the use of TDM.

Currently, four antifungals (flucytosine, itraconazole, voriconazole, and posaconazole) are considered to meet the aforementioned criteria and have established indications or guidelines for TDM (Andes et al., 2009; Ashbee et al., 2014).

The two primary indications for measuring serum drug concentrations are to document known concentration-related toxicities including central nervous system (auditory and/or visual hallucinations) and hepatic toxicities caused by voriconazole, and to document the drug exposure when adequate absorption is in question or when there is a lack of clinical response. A growing consensus from clinical experience and case reports suggests several circumstances where TDM would be helpful and would therefore be justified. Fig. 1 shows an overview of those clinical scenarios along with a sample algorithm for antifungal TDM in clinical practice.

Some of the triazoles (posaconazole, voriconazole, and itraconazole) have variable absorption rates that can lead to inadequate therapy. Given the pharmacodynamic profile and long drug half-lives of these agents, obtaining trough concentrations of these agents is necessary for monitoring their efficacy and/or absorption. TDM is particularly indicated for posaconazole suspension provided there are concerns about its gastrointestinal absorption. The oral bioavailability of posaconazole tablets and capsules is better than the suspension, although considerable variation exists, suggesting the need for TDM. The tablet and oral suspension formulations of posaconazole are not considered interchangeable due to their different dosages and pharmacokinetics. Voriconazole should be taken on empty stomach for an optimal response. Itraconazole shows absorption variability; capsule formulation requires the presence of adequate gastric acid, while acidic medium is not required for the absorption of the oral formulation.

On the contrary, both intravenous and oral formulations of isavuconazole have a number of advantages, including a long half-life that allows for once-daily dosage, excellent oral bioavailability, few adverse effects, and a wide spectrum of activity against *Candida*, *Aspergillus*, and some *Mucorales* (Falci and Pasqualotto, 2013). Early evidence suggests that the apparent need for TDM is low; however, any definite conclusions must be deferred until further clinical evidence about isavuconazole is available (Schmitt-Hoffmann et al., 2006).

Monitoring and Management Plan of Adverse Reactions and Drug Interactions of Antifungal Treatment

Antifungal therapy can be associated with a number of potential adverse effects. It is very important for pharmacists to be aware of all possible drug toxicities that allow them to provide concrete recommendations to prescribers and patients. The most common acute adverse effects include nephrotoxicity with amphotericin-B and infusion-related reactions with conventional and lipid-based amphotericin-B formulations and echinocandins. Potential adverse effects associated with antifungal therapy and their suggested management are outlined in Table 8.

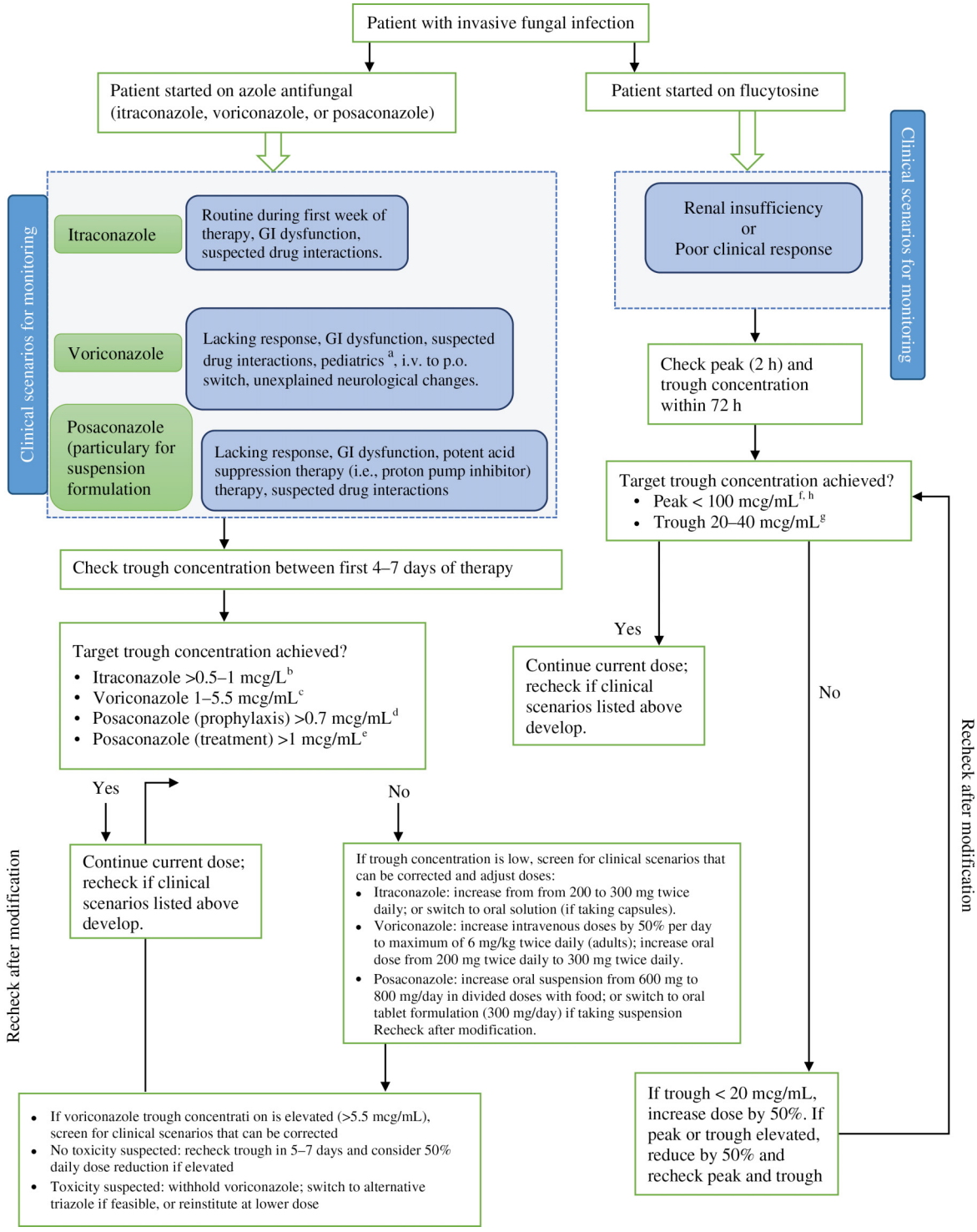

Figure 1 Clinical algorithm for antifungal therapeutic drug monitoring.

[a] Pediatric patients display accelerated linear clearance of voriconazole. Therefore, higher daily voriconazole dosing (7 mg/kg every 12 h) without a loading dose are recommended to achieve similar exposures to adults. Some children may require doses as high as 12 mg/kg every 12 h to achieve similar serum drug exposures to adults. Therefore, therapeutic drug monitoring is recommended. [b] Itraconazole serum troughs associated with efficacy, 0.5–1 mcg/mL; limited retrospective data have associated troughs of >3 mcg/mL with increased adverse effects. [c] Voriconazole troughs >1 mcg/mL are associated with a higher probability of clinical response; troughs >5.5 mcg/mL are associated with higher incidence of CNS adverse effects.[d] Posaconazole troughs of <0.7 mcg/mL are associated with higher incidence of breakthrough fungal infections during prophylaxis. [e] Posaconazole troughs >1.0 mcg/mL were associated with higher probability of treatment response for invasive aspergillosis. Currently, no recommended trough threshold has been defined for toxicity.[f] Flucytosine peak concentrations >100 mcg/mL associated with increased risk of myelotoxicity. [g] Flucytosine trough concentration of 20–40 mcg/mL recommended to prevent the rapid selection of resistance in yeast. [h] In patients receiving flucytosine orally at recommended doses, peak concentrations and trough concentrations are not significantly different. i.v., intravenous; p.o., per oral; GI, gastrointestinal.

Source: Information from Andes, D., Pascual, A., Marchetti, O., 2009. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob. Agents Chemother. 53, 24–34; Ashbee, H.R., Barnes, R.A., Johnson, E.M., et al., 2014. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J. Antimicrob. Chemother. 69, 1162–1176; Myers, E., Dodds Ashley, E., 2015. Antifungal drug therapeutic monitoring: what are the issues? Curr. Clinic. Microbiol. Rep. 2, 55–66; Pascual, A., Calandra, T., Bolay, S., Buclin, T., Bille, J., Marchetti, O., 2008. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin. Infect. Dis. 46, 201–211.

Table 8 Antifungal adverse reactions, their monitoring and management plan

Drug/Adverse reaction	*Clinical picture*	*Management/comment*
Liver injury/Hepatotoxicity		
Incidence is highest with itraconazole and voriconazole, followed by amphotericin B formulations, posaconazole, and the echinocandins/fluconazole.	↑ Serum aminotransferases ↑ Serum alkaline phosphatase ↑ Total bilirubin.	• Closely monitor transaminases, particularly in the first weeks and months of therapy. • Mild increases in serum transaminases (i.e., less than three times the upper limit of normal) often resolve spontaneously even with continued therapy. • Considering switch to alternative antifungals if liver injury markers remain elevated or continue to increase over several days • Switched from one class of antifungal to another (e.g., triazole to lipid amphotericin B) or to another drug in the same class (e.g., voriconazole to posaconazole) depending on clinical situation, infection status, and risk of toxicities or drug interactions with the alternative therapy.
Gastrointestinal distress: Main concern with oral antifungal formulations—particularly, itraconazole solution and posaconazole suspension.	Difficulty in swallowing, heartburn/reflux, nausea/vomiting, and dyspepsia.	—
Fluconazole		
Alopecia and chapped lips	—	Reversible after discontinuation of the agent
Itraconazole		
Triad of hypertension, hypokalemia, and peripheral edema	—	Contraindicated in patients with evidence of ventricular dysfunction or with a history of congestive heart failure.
Gastrointestinal distress	Due to cyclodextrin solubilizer.	Switch to another azole
Voriconazole		
Vision changes	• Abnormal vision, including photopsia or flashes of light. • Transient effects are temporally associated with drug dosing, occurs within 30 min of oral or IV administration. Symptoms usually last for approximately 30 to 60 min but can be prolonged for h.	• Generally, subside with continued therapy over several weeks. • Counsel patients regarding potential effects on operating a motor vehicle is warranted.
Neurologic toxicity	• Must be distinguished from minor vision changes, such as photopsia, is that of visual hallucinations which represent neurologic toxicity that has been linked to serum concentrations of voriconazole >5.5 mcg/mL. • Patients with neurologic toxicity may also have confusion, agitation, myoclonic movements, and auditory hallucinations. • Peripheral demyelinating neuropathy of the lower extremities, reported mostly in transplant recipients who are also taking tacrolimus.	• Consider therapeutic drug monitoring. • Screen for drug–drug interactions.
Skin toxicity	• Photosensitivity reaction.	Sun avoidance should be encouraged in patients who have experienced photosensitivity reactions during voriconazole therapy.
Periostitis	• Observed in patients on chronic treatment, appears to be due to fluoride excess and typically presents as bone pain, elevated alkaline phosphatase, and characteristic findings along the periosteum of affected bones on plain radiographs and bone scans.	Voriconazole should be discontinued in patient who develops periostitis.

(*Continued*)

Table 8 Antifungal adverse reactions, their monitoring and management plan (*cont.*)

Drug/Adverse reaction	*Clinical picture*	*Management/comment*
Cardiac toxicity	• Reported in severely ill patients with multiple comorbidities and/or concomitant use of other drugs that also could have prolonged the QT interval	See drug monograph for the management of drug interactions.
Alopecia and nail changes	• Common problems in patients taking voriconazole for a prolonged period	Reversible upon discontinuation
Posaconazole		
Renal dysfunction	• i.v. formulation of posaconazole contains the cyclodextrin vehicle, sulphobutylether-beta-cyclodextrin (SBECD) which can accumulate in the setting of renal dysfunction.	• Avoid in patients with renal insufficiency (CrCl $<$50 mL/min). • Consider IV isavuconazole as it does not contain the SBECD.
Isavuconazole		
Shortening of the QT	• In contrast with most other azoles, which cause prolongation of the QT interval), isavuconazole cause shortening of the QT interval.	Absolute contraindication in patients with familial short QT syndrome.
Echinocandins		
Hepatotoxicity	See above	See above
Infusion and hypersensitivity reactions	• Rash, pruritus, hypotension, bronchospasm, and angioedema. • Such reactions have been reported with anidulafungin when the drug is infused at a rate that exceeds 1.1 mg/min.	Slow infusion rate is advisable.
Injection site pain (Incidence is caspofungin $>$micafungin $>$ anidulafungin)		• Slow the infusion rate. • Administer in a more dilute solution.
Amphotericin b deoxycholate		
Infusion-related reactions	• Nausea, vomiting, chills, and rigors usually occurring either during infusion (within 15 min to 3 h following initiation) or immediately following administration of the dose.	• May require the use of a phenothiazine, such as promethazine (usual adult dose 12.5–25 mg every 4–6 h p.o., i.v. OR prochlorperazine (usual adult dose 10 mg IM or i.v. or 25 mg PR every 4 to 6 h), or ondansetron. • The addition of hydrocortisone (usual adult dose 25 mg) or heparin (usual final concentration 500 to 1000 U/L) to the infusion may lessen infusion-related thrombophlebitis. • Other ways to minimize amphotericin B–induced thrombophlebitis include: ◦ Infusion of the drug using a central line. ◦ Use of alternate infusion sites. ◦ Avoid final amphotericin B infusion concentrations exceeding 0.1 mg/mL.
Nephrotoxicity	• Reversible and often transient decline in glomerular filtration rate with the net effect is an elevation (above baseline) in the serum creatinine concentration • Risks of severe nephrotoxicity increase with diuretic-induced volume depletion or the concurrent administration of another nephrotoxin (such as an aminoglycoside, cyclosporine, nephrotoxic cancer chemotherapy, or foscarnet)	• Salt loading • Use of lipid formulations of amphotericin B: The liposomal preparation does not contain deoxycholate, which has direct tubular toxicity

Table 8 Antifungal adverse reactions, their monitoring and management plan (*cont.*)

Drug/Adverse reaction	*Clinical picture*	*Management/comment*
Electrolyte abnormalities	Hypokalemia, hypomagnesemia, and hyperchloremic acidosis are reflections of an increase in distal tubular membrane permeability following intravenous administration of amphotericin B	

i.v., intravenous; p.o., per oral; PR, per rectal; IM, intrmuscular; CrCl, creatinine clearance.

Ahmad, S.R., Singer, S.J., Leissa, B.G., 2001. Congestive heart failure associated with itraconazole. *Lancet*, 357, 1766–1767; Pappas, P.G., Kauffman, C.A., Perfect, J., Johnson, P.C., Mckinsey, D.S., Bamberger, D.M., Hamill, R., Sharkey, P.K., Chapman, S.W., Sobel, J.D., 1995. Alopecia associated with fluconazole therapy. *Ann. Intern. Med.*, 123, 354–357; Wang J-L, Chang C-H, Young-Xu Y., Arnold C.K., 2010. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungal use in empirical and definitive therapy for invasive fungal infection. *Antimicrob. Agents Chemother.* 54, 2409–2419; Botero Aguirre, J.P., Restrepo Hamid, A.M., 2015. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. *Cochrane Database Syst. Rev.* Cd010481.

Source: Information from VFEND (voriconazole) prescribing information. http://labeling.pfizer.com/ShowLabeling.aspx?id=618.; Pascual, A., Calandra, T., Bolay, S., Buclin, T., Bille, J., Marchetti, O., 2008. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin. Infect. Dis. 46, 201–211; Boussaud, V., Daudet, N., Billaud, E.M., Lillo-Le Louet, A., Chevalier, P., Amrein, C., Berge, M.M., Guillemain, R., Le Beller, C., 2008. Neuromuscular painful disorders: a rare side effect of voriconazole in lung transplant patients under tacrolimus. J. Heart Lung Transplant, 27, 229–232; VFEND (voriconazole) tablets, i.v. for infusion and oral suspension. Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER) https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021266s032lbl.pdf.; Philips, J.A., Marty, F.M., Stone, R.M., Koplan, B.A., Katz, J.T., Baden, L.R., 2007. Torsades de pointes associated with voriconazole use. Transpl. Infect. Dis. 9, 33–36.

Potential drug–drug interactions must also be carefully assessed and monitored in patients receiving long-term antifungal therapy. All azoles inhibit one or more cytochrome enzymes to a variable degree, particularly at the doses used to treat the invasive diseases. Thus, clinicians should monitor the symptoms of antifungal drug toxicities that could result from drug–drug interactions. Over 1000 azole drug interactions can occur and some of those interactions can lead to undetectable blood levels of triazole antifungals (Lempers and Brüggemann, 2016). For instance, concomitant intake of warfarin with any product containing miconazole (including topical) should be used with caution due to the increased risk of bleeding (Miki et al., 2011). Therefore, all patients receiving triazole antifungal agents should have their drug regimens carefully screened, preferably with an electronic medication database such as Lexicomp Lexi-Interact or Micromedex Drug-Reax (Lempers and Brüggemann, 2016).

Conclusions

Fungal pathogens cause a number of infections ranging from mild superficial to life-threatening systemic infections. Species of genus *Candida* and *Aspergillus* are commonly involved in various mucocutaneous and invasive opportunistic infections. The risk of fungal infections is common in immunocompromised individuals, including patients with an HIV-infection, malignancy, patients with recent transplantation, and those who are using corticosteroids. Appropriate selection of drug therapy, antifungal susceptibility, route of administration, and nature of disease are all crucial for the successful eradication and prevention of the recurrence of fungal infections. Pharmacists with their expertise can optimize the antifungal therapy by recommending the appropriate dosage form, provision of patient education, individualization of dosages by virtue of therapeutic drug monitoring, and management of adverse effects and drug–drug interactions.

Glossary

Aerosolized fungi pathogen Extremely small (microscopic) airborne fungi.
Candidemia The presence of candida species in the blood stream.
Commensal organisms A symbiotic relationship between two organisms in which one organism benefits from the other without harming it.
Douching Rinsing of the vaginal cavity with water or other solutions.
Dysphagia Difficulty in swallowing.
Hemiparesis Paralysis or neurologic weakening of one side of the body.
Hyphae Filamentous structure forming the structure of fungi.
Mucocutaneous Relating to the mucous and skin including the nasal, oral, and vaginal cavities.
Odynophagia Severe pain during swallowing
Refractory A condition that does not respond to therapy.
Xerostomia Abnormal dryness of the mouth.

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Pharmacotherapy of Viral Infections and the Role of Pharmacists in the Prevention and Treatment of Viral Diseases

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Learning Objectives

After reading this chapter, readers will be able to:

- Identify the disease burden caused by viral infections to society.
- Describe the pathophysiology of common viral infections, including human papilloma virus, herpes simplex, herpes zoster, varicella zoster virus, influenza, cytomegalovirus, and hepatitis.
- Select appropriate treatment options for the management of common viral infections.
- Compare and contrast antivirals available in a particular drug class and select the most appropriate treatment for an individual patient.
- Appreciate the role of the pharmacist in optimizing the prevention and treatment of viral infections in patients.

Take Home Messages

- Viral infections in humans will invade their hosts by compromising the first line of defence such as epithelial barriers in the respiratory, digestive, or reproductive tracts.
- Different viral infections will lead to different complications and consequences. Some viruses increase the risk of cancer (e.g., human papillomavirus), while others, once contracted, are lifelong infections and flare-ups of symptoms occur periodically (e.g., herpes simplex).
- Choice of antiviral treatment will depend on numerous factors, including the type of infection, the age of the patient and presence of other comorbidities, dosing schedule, proven efficacy, and safety profile.
- Vaccination is a key strategy in preventing infection for many types of viruses. The influenza vaccination needs to be done annually due to different strains of influenza predominating in different years.

- Pharmacists working in community and hospital settings can play an important role in the prevention and optimal treatment of viral infections.

Introduction

Global burden of viral diseases is enormous. It is estimated that influenza alone is responsible for more than half a million deaths annually (Iuliano et al., 2018). In 2013, viral hepatitis was responsible for 1.4 million deaths worldwide (Brown et al., 2017).

Many viral infections in humans will invade their hosts by initially crossing epithelial barriers in the respiratory, digestive, or reproductive tracts, which may or may not involve infecting the epithelial cells. Viruses use varying strategies to cross this natural barrier into the body, such as utilizing immune system cells (e.g., macrophages, dendritic cells) or utilizing the epithelial cells to gain access. The mechanism by which the virus enters the host cell and causes infection is important in designing treatment strategies to cure these viral infections (Cohen, 2016; Grove and Marsh, 2011).

Treatment will depend on the type of viral infection and individual patient characteristics and can include antiviral therapy, symptomatic treatment, and nonpharmacological strategies. While some viruses are curable, others are persistent, and the focus of the treatment is on managing viral load and controling symptoms. Depending on the virus, prevention may involve vaccinations, following general hygiene measures, or both. Given the inherent complexities of managing human immunodeficiency virus (HIV), a discussion of its prevention and treatment is beyond the scope of this chapter.

Disease State

Human Papillomavirus

Human papillomavirus (HPV) has been identified as the most common sexually transmitted infection in the United States (Centers for Disease Control and Prevention, 2017a). It affects both males and females, and there are over 100 different forms of the virus (Queensland Government, 2017).

HPV is the main cause of cervical cancer, although the type of HPV virus will determine the likelihood of it leading to cancer—HPV-6 and HPV-11 are types classified as "low risk," while HPV-16 and HPV-18 are "high-risk" types (Steben and Duarte-Franco, 2007). It is possible for someone to be infected with multiple types of HPV (Juckett and Hartman-Adams, 2010).

In additional to cervical cancer, HPV is also implicated in (Gearhart, 2017; Steben and Duarte-Franco, 2007):

- anogenital warts, which are often found not only in moist areas (e.g., perianal area, vagina, labia, vulva) but may also be found in dry areas, such as the penile shaft. All external genital warts are caused by HPV (most commonly by HPV-6 and HPV-11)
- anal cancer
- warts in areas other than the genitals (e.g., oral warts, respiratory papillomas)
- cutaneous disease in areas other than the genitals (e.g., verruca vulgaris, verruca plana)
- epidermodysplasia verruciformis.

Risk factors for HPV infections include increasing numbers of sexual partners, sex beginning at an early age, lack of condom use (although this is only about 70% effective in preventing transmission as genital contact still occurs), history of sexually transmitted infections, and tobacco use (Juckett and Hartman-Adams, 2010).

Herpes Simplex

There are two types of herpes simplex viruses—herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). They are responsible for causing recurrent infection, commonly on the skin, mouth, lips, eyes, and genitals. HSV-1 is often contracted during childhood by coming into contact with oral secretions of someone who has the virus and has traditionally been associated with infection of the mouth and face, most commonly leading to "cold sores." HSV-2 typically infects the genitals and is mainly contracted either during childbirth if the mother has an active infection or after someone becomes sexually active (Ayoade, 2017; Kaye, 2016). More recent information, however, has suggested that HSV-1 is also an important cause of genital herpes, with transmission occurring during oral sex (World Health Organization, 2015).

Transmission of the herpes simplex virus occurs through close contact with a person who is shedding the virus. This may be through coming into contact with a herpes sore, skin containing the herpes infection or genital or oral secretions (Centers for Disease Control and Prevention, 2017b; Victoria State Government, 2018a).

The signs and symptoms that present depend on where the infection is present on the body, and whether it is an initial infection or reactivation of the virus. Initial infections will also generally present with systemic symptoms, a longer duration, and a greater risk of complications, while recurrent episodes generally have milder symptoms and shorter episodes. People who are immunocompromised are more likely to experience symptoms that are more severe, longer lasting, and widespread, and episodes are more likely to recur (Ayoade, 2017).

Herpes labialis, or "cold sores," is the reactivation of the oral herpes virus infection. Tingling, itching, or burning at the site of infection (most commonly on the lips or around the mouth) may initially occur for the first day or so, before one or more red,

fluid-filled blisters appears. The blister(s) erupt and ulcerate and can last for 7–10 days. Herpes labialis can recur, though the frequency at which this occurs varies between people (American Academy of Dermatology, 2018; Ayoade, 2017; Pringle, 2013; World Health Organization, 2017).

Varicella Zoster Virus

The varicella zoster virus is a highly infectious virus that only affects humans, and primarily occurs during winter and early spring (Pergam et al., 2009; Victoria State Government, 2018b). While chickenpox is highly contagious, shingles is less so (Victoria State Government, 2018b). The virus causes chickenpox and shingles (or herpes zoster), with chickenpox generally being a mild illness in childhood (Anderson, 2018). Following the initial infection, the varicella zoster virus remains dormant in the cranial nerve and dorsal root ganglia, which can be reactivated years later as herpes zoster (Anderson, 2018; Pergam et al., 2009). Second episodes of chickenpox may occur, but it is rare (Victoria State Government, 2018b). Viral spread is usually through contact with the lesions or airborne through respiratory droplets, and occasionally through things that are soiled from discharge from the vesicles (the scabs cannot transmit infection) (Pergam et al., 2009; Victoria State Government, 2018b).

Varicella zoster infection is characterized by a vesicular rash that is widespread and itchy, and accompanying symptoms can include malaise and fever. The rash initially appears as small lumps, which change into blisters before scabbing (Centers for Disease Control and Prevention, 2016; NSW Government, 2018).

Herpes Zoster

Herpes zoster is a result of the varicella-zoster virus remaining dormant in the dorsal root ganglia, often for many years, and reactivating leading to herpes zoster, or shingles (Janniger, 2018). As over 90% of adults have had varicella-zoster, the majority of the population is at risk of herpes zoster (Wehrhahn and Dwyer, 2012).

Diagnosis is mainly based on clinical signs and a patient history, though laboratory tests can be used in atypical cases. Laboratory studies available include direct fluorescent antibody, polymerase chain reaction testing, or Tzanck smear of vesicular fluid (Janniger, 2018; Wehrhahn and Dwyer, 2012).

Influenza

Influenza viruses are single-stranded RNA orthomyxoviruses. Three types of influenza viruses occur—types A, B, or C; however, types A and B are the ones that most likely lead to severe disease in humans (Australian Government Department of Health, 2017). These two types will cause similar symptoms, but laboratory tests can differentiate between the two (WHO Collaborating Centre for Reference and Research on Influenza, 2018). Yearly outbreaks and epidemics of the influenza virus are due to constant mutations, which also require annual updates to the influenza vaccine. Infections most commonly occur during the winter season, but infections can appear throughout the year and in locations close to the equator infection may occur during the year (Australian Government Department of Health, 2017; WHO Collaborating Centre for Reference and Research on Influenza, 2018).

Transmission is through respiratory droplets and through coming in contact with respiratory secretions. The incubation period is on average 2 days but can be between 1 and 4 days—those infected with influenza are infectious from 1 day prior to symptom onset. Viral shedding is highest during the first 3–5 days of sickness; however, young children can shed the virus for up to 7–10 days, and this may be longer in patients who are severely immunocompromised (Australian Government Department of Health, 2017; SA Health, 2012).

Symptoms of influenza can include cough, sore throat, nasal congestion, fatigue, fever, headache, and muscle aches. Vomiting and diarrhea may occur though more commonly in children than adults. Influenza may be suspected in patients presenting with fever greater than 38°C and symptoms of cough or sore throat if no other explanation of symptoms is apparent. Uncomplicated influenza generally resolves within a week; however, symptoms of cough or fatigue may be more prolonged (Australian Government Department of Health, 2017; Centers for Disease Control and Prevention, 2018a; SA Health, 2012; WHO Collaborating Centre for Reference and Research on Influenza, 2018).

Cytomegalovirus

Cytomegalovirus (CMV) infection is an opportunistic infection and carries a high risk of morbidity and mortality in patients with an impaired immune system, such as those receiving stem cell or solid organ transplants. Patients are at greatest risk in the first 100 days following the organ transplant (Biron, 2006). It is a double-stranded DNA virus and a member of the human herpes viruses. Transmission occurs easily through bodily fluids or the placenta. In patients who are immunocompetent, the infection is usually benign, and minimal (if any) symptoms are present. The infection remains dormant following initial infection, although reactivation occurs if the immune system is compromised (e.g., from chemotherapy or when immunosuppression occurs for transplants) (Biron, 2006).

CMV is a common infection, particularly in children. In the United States, it is estimated that by the age of 5 years, nearly one in three children have been infected (Centers for Disease Control and Prevention, 2018b). If a woman is initially infected with the virus while pregnant, there is a risk that her unborn baby will also become infected, which has the potential to cause disability (e.g.,

hearing or vision loss, small head size, cerebral palsy, delayed development or intellectual disability, or rarely death) (NSW Government, 2017). This risk is highest if a woman has an initial CMV infection during pregnancy and when this occurs in the first half of the pregnancy. Australian studies have found that in 1000 live births, approximately 6 babies will have congenital CMV infection and 1–2 of these babies will have a permanent disability. If a virus reactivates in a pregnant woman, it does not usually cause issues to either the woman or the fetus (Centers for Disease Control and Prevention, 2018b; NSW Government, 2017).

Hepatitis A

Hepatitis A is an RNA virus that causes acute infection. While young children may not have any symptoms, older children and adults can experience symptoms, such as anorexia, malaise, and jaundice. This infection is spread through feces, including when feces contaminate the hands, objects, water, or food, which then is ingested through the mouth. Transmission can occur through children in childcare centers who are not toilet trained, sexual and household contacts of people who are infected with hepatitis A, traveling to countries with a high risk, and drug use (both injecting and noninjecting). Diagnosis is made by serologic testing. There is no specific antiviral for hepatitis A, and the treatment is supportive (Government of South Australia, 2012; Rutherford, 2017).

Hepatitis B

The hepatitis B virus consists of circular, double-stranded DNA. It is commonly transmitted in developing areas and can be spread through body fluids (e.g., blood, semen, vaginal secretions). It is estimated that approximately 2 billion people worldwide are infected with hepatitis B virus, and 350 million of these people have chronic infection. Infection may be immune or chronic (Australian Government Department of Health, 2017; NSW Government, 2013; Pyrsopoulos, 2017; Victoria State Government, 2018c).

Transmission may spread through numerous ways, including transmission from mother to child during pregnancy or childbirth; having sex without a condom; skin penetration with contaminated equipment (e.g., sharing needles, needle stick injuries, tattooing); and sharing objects that may contain blood (e.g., toothbrushes, razors). Groups that are at particularly high risk of contracting hepatitis B infection include those who inject drugs, men who have sex with men, and people with sexual partners or family members that have hepatitis B (NSW Government, 2013; Victoria State Government, 2018c).

Hepatitis C

Hepatitis C affects approximately 2% of adults in the United States (Wilkins et al., 2010). It is transmitted through blood to blood contact, and the majority of people (80%) with the infection will develop chronic infection (NSW Government, 2016). Infection is often initially asymptomatic, but symptoms can develop within 1–3 months of the infection. Symptoms can include loss of appetite, nausea (and potential vomiting), tiredness, abdominal pain, jaundice, dark urine, and pale stools. Symptoms may continue for a few days to a few weeks and then improve (NSW Government, 2016). Consequences of infection include cirrhosis, decompensated disease, liver cancer, and death (Khoo and Tse, 2016). Six different genotypes exist for the hepatitis C virus (Khoo and Tse, 2016).

Condition Management

Pharmacological Management

Neuraminidase Inhibitors

A number of neuraminidase inhibitors are available in different parts of the world—zanamivir, oseltamivir, peramivir, and laninamivir—and are indicated for the treatment and prevention of influenza (McKimm-Breschkin, 2013; Moscona, 2005). Differences in the structure of neuraminidase inhibitors mean that resistance can develop to the drugs as a class as well as individual neuraminidase inhibitors (McKimm-Breschkin, 2013).

Influenza viruses have three surface proteins—hemagglutinin, neuraminidase, and M2 protein. Neuraminidase inhibitors, by blocking neuraminidase, prevent new virions being released from the cell surface (McKimm-Breschkin, 2013). In addition, they prevent neuraminic acid from being digested in mucus and limit the virus from spreading through the respiratory epithelium (Democratis et al., 2006). Because neuraminidase is present in both influenza virus type A and B, it makes it an ideal site for treatment and prevention of the influenza virus (Democratis et al., 2006). The influenza virus replicates in the respiratory tract and peaks at 24–72 h after illness onset, meaning that neuraminidase inhibitors (that act on replication) need to be administered as soon as possible for maximum effect (Moscona, 2005). Initiation of treatment 36–48 h after symptom onset is recommended for maximal benefit in reducing times until symptom resolution (Democratis et al., 2006).

Zanamivir

Zanamivir was the first neuraminidase inhibitor developed. It has poor oral bioavailability and is not absorbed. It is delivered through oral inhalation (**Table 1**) (Democratis et al., 2006; McKimm-Breschkin, 2013). The inhaled formulation allows high concentrations of the drug to be delivered to the respiratory tract, and due to minimal systemic absorption no dose adjustment is required in renal dysfunction (Eiland and Eiland, 2007; McKimm-Breschkin, 2013). Similarly, there is a lack of drug interactions

Table 1 Neuraminidase inhibitors (Alame et al., 2016; Centers for Disease Control and Prevention, 2018c; Daiichi-Sankyo, 2016; de Jong et al., 2014; Eiland and Eiland, 2007; Greene et al., 2013; Jefferson et al., 2014; Kashiwagi et al., 2012; Kohno et al., 2010; McKimm-Breschkin, 2013; Moscona, 2005; Rossi, 2018; Tochino et al., 2017)

Drug	*Adult dose*	*Pediatric dose*	*Adverse effects*	*Comments*
Zanamivir	Treatment: 10 mg twice daily inhaled	Children ≥5 years: same as adult dose	• Headache • Throat/tonsil pain • Cough • Nasal symptoms • Bronchospasm	• No dosage adjustment required in renal impairment • Concentrates in respiratory tract and fast onset of action (within 10 s) minimizes risk of resistance developing; resistance has not been seen in immunocompetent patients • Well tolerated—adverse effects similar to placebo • Use with caution in patients with chronic airways disease as shown to cause hypersensitivity-related bronchospasm
Oseltamivir	75 mg twice daily (oral) for treatment 75 mg once daily (oral) for prophylaxis	Treatment: Orally twice daily dose • <12 months: 3 mg/kg • ≥1 year, ≤15 kg: 30 mg • ≥1 year, >15-23 kg: 45 mg • ≥1 year, >23-40 kg: 60 mg • ≥1 year, >40 kg: 75 mg	• Nausea • Vomiting • Headaches • Psychiatric symptoms (e.g., delirium, abnormal behavior)	• Reduce dose in renal impairment • Influenza treatment duration: 5 days • Prophylaxis duration: 10 days • May be taken with or without food (with food may reduce nausea and vomiting) • Conflicting results for risk of psychiatric adverse effects
Peramivir	≥18 years: 600 mg intravenously as a single dose	N/A	Mild to moderate • Diarrhea • Nausea • Vomiting • Abnormal behavior, cough, pyrexia in young children • Severe adverse effects: reduced neutrophil count, prolonged QT interval	• Given as intravenous infusion over 15–30 min • Useful for critically ill patients and patients unable to tolerate other routes of administration • Well tolerated, similar adverse effects compared to placebo (more common in young children)
Laninamivir	40 mg as a single inhalation	• Children ≥10 years: 40 mg as a single inhalation • Children <10 years: 20 mg as a single inhalation	• Psychiatric adverse effects (e.g., abnormal behaviors) • Diarrhea • Nausea • Dizziness	• Adverse effects similar to other neuraminidase inhibitors • One study found significantly fewer adverse effects versus oseltamivir • Adverse effects commonly seen on days of use, majority appear within the first 3 days and resolve or improve within 3 days

with zanamivir, and it does not have an effect on CYP450 enzymes, although it should be used with caution in people with a milk allergy as the inhalation contains milk protein or lactose (Eiland and Eiland, 2007). Children and elderly patients may also have difficulty inhaling the full dose properly, which may reduce the efficacy of treatment (Eiland and Eiland, 2007; Rossi, 2018). While intranasal and intravenous formulations of zanamivir have been studied, neither of these formulations are marketed (Eiland and Eiland, 2007). Studies have found that zanamivir improves resolution of influenza symptoms by 1–2 days when treatment is started within 36–48 h after illness onset (Moscona, 2005).

Zanamivir is also indicated as prophylaxis against influenza A and B. One study found that zanamivir 10 mg once daily for 10 days had an 81% protective efficacy against influenza. The sooner zanamivir is taken after exposure to influenza, the more effective it is as preventative treatment, and it has been suggested that a long delay may lead to treatment failure. It is recommended that treatment is started within 36 h of exposure (Monto et al., 2002; Rossi, 2018).

Oseltamivir

Oseltamivir was the next neuraminidase inhibitor designed and is taken orally as the prodrug oseltamivir phosphate and converted hepatically to the active oseltamivir carboxylate (McKimm-Breschkin, 2013). Generally, oseltamivir is more effective against influenza A viruses (H3N2) than N1 subtype viruses (McKimm-Breschkin, 2013). See **Table 1** for dosing recommendations.

Oseltamivir has been shown to be effective as both treatment and prophylaxis in older patients (including those who received the influenza vaccination) and was well tolerated (Dutkowski, 2010; Moscona, 2005). Similarly, oseltamivir has been shown to be effective in children in reducing the duration of symptoms and is well tolerated, with vomiting being the most common adverse effect seen in one study of children (Heinonen et al., 2010).

Oseltamivir is also indicated for the prevention of influenza, with one study showing that it had 89% protective efficacy of individuals (Welliver et al., 2001).

Peramivir

Peramivir has low oral bioavailability and is available as an intravenous formulation in certain countries around the world (Alame et al., 2016; McKimm-Breschkin, 2013). It is licensed by the Food and Drug Administration (FDA) for use in adults 18 years of age and over for the treatment of uncomplicated influenza and is effective against both influenza A and B. Due to its ability to tightly bind to its target neuraminidase site and slow time for dissolution, it has a half-life of over 24 h, making it longer acting than oseltamivir and zanamivir (which have a half-life of 1.25 h) (Alame et al., 2016). In addition, when administered intravenously, peak plasma concentration occurs immediately after administration and does not undergo significant metabolism by the liver, meaning dosage adjustment is not required in hepatic impairment (Alame et al., 2016). Peramivir doesn't have an effect on glucuronidation, isn't a substrate for CYP enzymes or P-glycoprotein transport, and does not inhibit P-glycoprotein (Alame et al., 2016). Peramivir is mainly renally excreted, and 90% of the drug is excreted unchanged—patients with renal impairment therefore require adjusted doses (Alame et al., 2016).

Laninamivir

Laninamivir is the most recent neuraminidase inhibitor that has become available, and while based on zanamivir, is a long-acting formulation that is administered by oral inhalation. It is administered as a single 40 mg dose of the prodrug laninamivir octanoate, which is converted to the active laninamivir in the lungs (**Table 1**) (Ikematsu and Kawai, 2011; McKimm-Breschkin, 2013). As the concentration of laninamivir in the lungs required to inhibit replication of the influenza virus is present for at least 5 days, a single dose can be used to treat influenza (Ikematsu and Kawai, 2011). Research has suggested that laninamivir is effective treatment for influenza A (H1N1)pdm09, seasonal influenza A (H1N1), and influenza B viruses; however, further research in this area is needed to confirm its efficacy (Kashiwagi et al., 2016).

Laninamivir has also been shown to be an effective treatment for postexposure prophylaxis against influenza, in both patients who have and have not received the influenza vaccination. One study compared neuraminidase inhibitors and found that there were no significant differences in the time taken to alleviate fever or any other influenza symptoms, indicating that laninamivir was as effective as other neuraminidase inhibitors available (Tochino et al., 2017). Another study in 2016 found laninamivir 40 mg as a single dose was effective in preventing influenza. This study was in patients who lived in the same household as someone with influenza, and patients received laninamivir within 48 h of symptom onset in the person with influenza (Kashiwagi et al., 2016). While it had previously been demonstrated that laninamivir given at an inhaled dose of 20 mg daily for 2–3 days was effective in preventing influenza in household contacts, this more recent research found that the higher, single-dose treatment was also effective. Laninamvir has an advantage over other treatments such as oseltamivir and zanamivir as it is a single dose, compared to these other antivirals which require multiple dosing. This has the potential to improve adherence and offer a convenient dosing option, which could be particularly useful in certain target groups such as health-care workers working in pandemic settings (Kashiwagi et al., 2016).

Being an inhalation, laninamivir may not be suitable for all patients. Younger children (particular those younger than 3 years) have difficulty inhaling the drug meaning it may not be suitable for this age group and oseltamivir is instead preferred (Tochino et al., 2017). One strategy to ensure the medication is taken correctly by patients is by having the patient inhale laninamivir in front of a health professional (such as a doctor, pharmacist or other health professional) (Tochino et al., 2017).

Adamantanes

The adamantanes—amantadine and rimantadine—can be used to treat or prevent influenza A (Moscona, 2005). Unfortunately, their treatment can rapidly lead to resistance developing (within 48–72 h after beginning treatment). Resistant strains can be transmitted to susceptible individuals, and immunocompromised patients taking these drugs can shed this virus for a long period of time. Adamantanes are also associated with potentially serious adverse effects. Due to these limitations, they are rarely used as treatment for influenza, and their place in therapy lies mainly in prevention during epidemics (Democratis et al., 2006; McKimm-Breschkin, 2013; Moscona, 2005).

Guanine Analogues

Guanine analogues include aciclovir, famciclovir, ganciclovir, penciclovir, valaciclovir, and valganciclovir. While aciclovir, famciclovir, and valaciclovir are all indicated for the treatment of herpes simplex and shingles, valaciclovir is also indicated for prevention of cytomegalovirus after organ transplantation. Ganciclovir and valganciclovir are indicated for CMV (both treatment and prevention in patients receiving bone marrow and solid organ transplants) (Rossi, 2018). Penciclovir is available as a topical treatment for herpes labialis (Medscape, 2018a).

Aciclovir, famciclovir, and valaciclovir are indicated for the treatment of herpes zoster and have been found to be safe and effective (Janniger, 2018; Rossi, 2018). They work by inhibiting viral DNA polymerase, which subsequently prevents the herpes zoster virus from replicating (Janniger, 2018). Guanine analogues may reduce the length of time that new vesicles form, the number of days until complete crusting occurs, and the days of discomfort. The earlier treatment is started the more effective they are in reducing the duration of herpes zoster and preventing or limiting the severity of associated post herpetic neuralgia. They should

ideally be started within 72 h of symptom onset; however, some research has found them to be effective in reducing pain even if started after 72 h (Janniger, 2018).

Aciclovir, famciclovir, and valaciclovir may also be used for the management of genital herpes (Emmert, 2000; Rossi, 2018). Treatment of initial infection is recommended, particularly if the patient also presents with systemic symptoms and is immunocompromised (Emmert, 2000). Treatment of recurrent infections episodically aims to reduce symptoms as well as transmission of infection—it will not reduce the frequency of recurrences (Emmert, 2000). Treatment of recurrent infections should also occur as soon as possible after symptoms first appear (Wald et al., 2002).

The use of treatment for suppression of recurrent genital herpes infection varies between individuals as recurrent infections are often mild and infrequent. Generally, treatment of subsequent infections occurs if patients experience more than six outbreaks per year (Emmert, 2000). These treatments have an effectiveness of 70%–80% in treating symptomatic recurrences (Emmert, 2000). Aims of suppressive therapy include reducing the severity and frequency of symptoms, reducing transmission of the virus to sexual partners and infants of infected mothers, and reducing transmission of associated viral diseases (e.g., HIV) (Emmert, 2000).

Oral herpes labialis may be managed with oral aciclovir, valaciclovir, or famciclovir, while topical aciclovir and penciclovir are also available (but not as effective as oral treatment). Because viral shedding only occurs for a short period of time in recurrent infections, short treatment durations are generally effective. Treatment is aimed at managing recurrent infections, although oral aciclovir and valaciclovir may be used as daily suppressive therapy (Usatine and Tinitigan, 2010).

Valaciclovir, ganciclovir, and valganciclovir are used for the prevention and treatment of CMV (Biron, 2006; Rossi, 2018). When used to treat the infection, its use should continue until symptoms have improved and blood antigenemia has resolved (Tan, 2014). When used as prophylaxis, treatment usually begins at the time of the transplant, with doses often lower than those used to treat an active infection (Biron, 2006). Ganciclovir and valganciclovir are now considered first-line treatment for the prevention of CMV in patients undergoing transplants (Biron, 2006). Patients undergoing transplants will undergo regular testing after the transplant for either CMV 65 pp65 antigenemia or CMV DNA, and when replication is seen treatment will begin. The cut-off point for when treatment should begin is not certain, however, and different thresholds for beginning treatment have been used (Tan, 2014). Ganciclovir and valganciclovir are also used for the treatment of CMV retinitis in AIDS. Because it usually takes 3–6 months after starting antiretroviral therapy for the immune response to improve, maintenance therapy needs to continue after initial treatment until CD4 counts are above 100/mm^3 and are stable or continuing to improve. Maintenance treatment can be ceased when CD4 counts are above this for several months and lesions on the retina are stable and not progressing (Tan, 2014).

Aciclovir

Aciclovir was the first guanine analogue to be developed (De Clercq, 2000). Although effective and cheaper than other guanine analogues, it has limited oral bioavailability (15%–30%) (intravenous administration can give concentrations 10-fold higher). Due to the low oral bioavailability, frequent dosing is required (Beutner et al., 1995; Emmert, 2000), which has the potential to impact on patient acceptability as well as adherence. Aciclovir is available as tablets, intravenous injection, and topical formulations. It is the preferred guanine analogue to use in pregnancy due to extensive clinical experience and is the most common treatment for the management of herpes zoster in children (Janniger, 2018; Rossi, 2018). The half-life is 2.5 h, and dosage adjustment is required in renal impairment (Emmert, 2000). It has good penetration into most body tissues, including the brain and placenta (Emmert, 2000).

Aciclovir binds viral DNA polymerase and terminates replication. Because replication can end after 48 h of a recurrence of genital herpes, if aciclovir treatment is to be effective it needs to begin early (Emmert, 2000). Aciclovir is also indicated for the treatment of primary genital herpes, with a recommended dose of 400 mg orally three times a day for 5–10 days (Emmert, 2000; Rossi, 2018). While oral therapy is effective for treatment of primary infection, intravenous treatment may be required in patients who are immunocompromised or have severe infection (Emmert, 2000). Aciclovir is effective in reducing time of viral shedding, time until lesions are crusted or healed, local pain, and constitutional symptoms (Emmert, 2000). Treatment of initial infection will not impact on the frequency or number of recurrent infections, or influence the long-term history of the infection (Emmert, 2000).

Aciclovir can also be used as suppressive therapy at 400 mg orally twice a day for adults (Emmert, 2000). It has been shown to reduce frequency by up to 80% and prevent recurrence in up to 45% of patients (Emmert, 2000). Resistance to aciclovir has not been seen in patients who are immunocompetent, however, it is recommended to cease therapy once a year to determine whether ongoing therapy is necessary (Emmert, 2000). Aciclovir has been shown to have a small benefit when taken to treat recurrent episodes of genital herpes—it should be taken early on when prodrome symptoms begin (within minutes to hours) (Emmert, 2000).

Treatment regimens for recurrent infection can differ slightly, with oral recommendations for adults including 400 mg three times a day or 800 mg twice a day for 5 days or 800 mg three times daily for 2 days (Emmert, 2000; Rossi, 2018). One study investigated the efficacy of the 2 day treatment regimen on the premise that in immunocompetent patients the duration of viral shedding is short in recurrent infections. It found that compared to placebo, aciclovir 800 mg three times a day for 2 days significantly reduced lesion duration, the episode, and viral shedding. This regimen, being shorter, is likely to be more convenient and acceptable to patients than the longer treatments. These results were also similar to other studies comparing valaciclovir and famciclovir with placebo for the treatment of recurrent genital herpes infection (Wald et al., 2002).

For herpes zoster, the recommended dose is 800 mg five times a day orally for 7 days for adults. Lower doses have not been found to be effective, suggesting that higher plasma/tissue concentrations are required for optimal efficacy (Beutner et al., 1995; Rossi, 2018). Aciclovir reduces the time to rash healing, reduces acute pain severity, and some studies have also found that it

reduces the risk, severity, and duration of chronic pain associated with herpes zoster. Aciclovir has also been found to reduce the risk and severity of particular complications of herpes zoster ophthalmicus (Beutner et al., 1995). There has, however, been shown to be viral strains resistant to aciclovir emerging, suggesting agents such as valaciclovir and famciclovir may have an increasing role in the treatment of herpes zoster in the future (Janniger, 2018).

Aciclovir is indicated for the treatment of oral herpes labialis. Oral treatment in adults of 400 mg 5 times a day for 5 days has been shown to be effective in reducing viral shedding, time until lesions heal, and duration of lesion pain when started early in the prodrome stage. Oral treatment is indicated in certain patient groups for the treatment of oral herpes labialis, such as when severe infection is present or in patients who are immunocompromised (Rossi, 2018). In addition, aciclovir may be used to treat herpetic gingivostomatitis in young children, at a dose of 15 mg/kg 5 times a day for 7 days. This has been shown to be effective in reducing the time that oral lesions are present and viral shedding, in addition to reducing the time until the resolution of fever, and eating and drinking difficulties (Usatine and Tinitigan, 2010).

Aciclovir may be used as suppressive therapy to prevent recurrences of oral herpes labialis in patients who have frequent episodes. One study looking at oral suppressive therapy at 400 mg twice a day compared to placebo found that aciclovir led to a 53% reduction in the number of clinical recurrences and a 71% reduction in the number of virus culture-positive recurrences (Usatine and Tinitigan, 2010).

Aciclovir 5% topical cream is also available and indicated for the treatment of minor recurrent episodes of oral herpes labialis (Expert Group for Dermatology, 2015; Medscape, 2018b; Spruance et al., 2002). The cream base allows aciclovir to penetrate the skin more effectively compared to an ointment base (Spruance et al., 2002). It is recommended that aciclovir cream be applied to the lesion 5 times a day (every 4 h while awake) when the symptoms first appear for 4–5 days (Expert Group for Dermatology, 2015; Medscape, 2018b). Aciclovir cream has been shown to be well tolerated, with the incidence of adverse effects similar to patients using the vehicle cream only. The most common adverse effects reported include headache, cracked lips, and dry lips (Spruance et al., 2002).

Aciclovir in general has been found to be safe and well tolerated (Emmert, 2000). Adverse effects are often mild and can include nausea, vomiting, headache, and a rash. Rarely, lethargy, seizures, delirium, and tremulousness have been seen in patients who are renally impaired. In patients who are dehydrated or have renal dysfunction aciclovir may crystallize in the renal tubules leading to elevated creatinine (which is reversible) or occasionally acute tubular necrosis (Emmert, 2000).

Valaciclovir

Valaciclovir is the prodrug for aciclovir and has been found to produce plasma levels of aciclovir significantly higher (three to fivefold) than aciclovir itself. Conversion to aciclovir occurs rapidly after oral administration, and 1000 mg of valaciclovir converts to 700 mg aciclovir (Beutner et al., 1995; De Clercq, 2000). It has been found to be very effective in preventing herpes zoster and CMV in patients following renal transplant (De Clercq, 2000).

One study compared the efficacy and safety of valaciclovir 1000 mg three times daily for 7 or 14 days to oral aciclovir 800 mg fives times daily for 7 days in immunocompetent adults 50 years of age or older with herpes zoster. During a 6 month evaluation, it was found that valaciclovir for either 7 or 14 days significantly hastened pain resolution from herpes zoster compared to aciclovir (median pain duration was 38 and 44 days with valaciclovir for 7 or 14 days, compared to 51 days for those treated with aciclovir). Adverse effects were also similar between treatment groups, which supports the use of valaciclovir with easier dosing regimens and some advantages over aciclovir, and a similar safety profile (Beutner et al., 1995).

When given to treat an initial genital herpes infection, the recommended dose of valaciclovir is 500 mg orally twice daily for 5–10 days (Rossi, 2018). Valaciclovir is indicated for preventative therapy for genital herpes, at a recommended dose of 500 mg once daily orally or 1000 mg daily in patients with ten or more recurrences a year who experience breakthroughs with the lower dose (Emmert, 2000; Rossi, 2018). When taken to treat recurrent infections, it has been shown to be slightly more effective than aciclovir (Emmert, 2000). Treatment for recurrent infection in adults is 500 mg twice daily for 3 days, which has been shown to be equally effective to 500 mg twice daily for 5 days (Emmert, 2000; Rossi, 2018; Wald et al., 2002).

Valaciclovir may be used for the treatment and prevention of oral herpes labialis recurrent infection. The adult recommended dose for the treatment of an episode is 2000 mg orally twice a day for two doses in those with severe infection (patients who are HIV positive should take 1000 mg twice a day for 5–10 days) (Rossi, 2018). Valaciclovir has been studied as preventative treatment at a dose of 500 mg daily orally. One study looked at suppressive treatment in patients who had four or more recurrences in the previous year. Treatment for 16 weeks found that 60% of people taking valaciclovir did not have a recurrence during the study period compared to 38% of patients taking placebo. The median time until the first recurrence was 13.1 weeks with valaciclovir treatment compared to 9.6 weeks with placebo (Usatine and Tinitigan, 2010).

Valaciclovir is approved for the prevention of CMV infection in patients following organ transplant (Biron, 2006; Rossi, 2018). It has several advantages as a potential treatment option for this indication as it has low toxicity and good oral bioavailability (Ong et al., 2015). Valaciclovir is given orally at a dose of 2000 mg four times a day for 90 days (Rossi, 2018). One study looking at the use of valaciclovir in patients undergoing renal transplant found that treatment significantly reduced the risk of and delayed the onset of CMV infection compared to placebo. In addition, valaciclovir was also shown to reduce the risk of acute graft rejection (Ormrod et al., 2000). Other research has found that valaciclovir is more effective than oral aciclovir in preventing CMV antigenemia and has similar efficacy to ganciclovir in preventing CMV infection (Ong et al., 2015; Ormrod et al., 2000). High dose valaciclovir being used for a prolonged period of time has been linked with a potentially fatal thrombotic microangiopathy (TMA)-like syndrome when used in patients who are immunocompromised, with a higher risk appearing to be

linked to patients with advanced HIV disease. Close monitoring of symptoms suggesting TMA should be done if immunosuppressed patients are receiving prolonged treatment of high-dose valaciclovir (Ormrod et al., 2000).

The adverse effects of valaciclovir have been shown to be similar to those of aciclovir and are mostly mild. Nausea and headache were found to occur in more than 10% of patients in one study. Other side effects include vomiting, diarrhea, constipation, asthenia, dizziness, anorexia, abdominal pain, and dyspepsia. One study found severe headache occurred in one patient taking valaciclovir 1000 mg 3 times a day for 14 days for herpes zoster (Beutner et al., 1995).

Famciclovir

Famciclovir is the prodrug for penciclovir (De Clercq, 2000). It has been shown to be equally effective to aciclovir for the treatment of herpes simplex infections in patients who are immunocompromised and may be more effective than aciclovir in reducing pain and promoting more rapid healing when used for herpes zoster (De Clercq, 2000; Janniger, 2018). It has an oral bioavailability of 77%, and is quickly converted to its active form (Emmert, 2000). Famciclovir has a much longer intracellular half-life compared to aciclovir (10 times longer) (Emmert, 2000).

Famciclovir has a recommended dose of 250 mg 3 times a day for 5–10 days for treating an initial infection of genital herpes (Emmert, 2000; Rossi, 2018). Evidence suggests that famciclovir is as effective as aciclovir in the treatment of an initial genital herpes infection (Emmert, 2000). Famciclovir may be used as preventative therapy for genital herpes, at a recommended dose of 250 mg twice daily (Emmert, 2000). When taken to treat recurrent infections, it is slightly more effective than aciclovir (Emmert, 2000). Treatment regimes for recurrent infection for adults include 125 mg orally twice a day for 5 days or 500 mg initially, then 250 mg twice a day for three doses, or 1000 mg twice a day for one day (Emmert, 2000; Rossi, 2018).

Famciclovir is indicated for the treatment of recurrent oral herpes labialis infections. Famciclovir at a dose of 1500 mg as a single dose or 750 mg twice a day for one day when taken within 1 h of prodromal symptoms appearing have both been shown to be more effective than placebo in improving healing time, with no significant difference between the two dosing regimes (Usatine and Tinitigan, 2010).

Ganciclovir

While ganciclovir has been shown to be at least as effective as other guanine analogues for the management of herpes simplex viruses 1 and 2, it was developed mainly for the treatment of CMV and can be given either intravenously or orally (De Clercq, 2000). It is now considered the gold standard treatment of CMV in most situations and is first-line treatment for CMV infection in patients having undergone transplants (Biron, 2006). Ganciclovir is favored as optimal treatment for multiple CMV infections, including CMV pneumonitis and CMV encephalitis/myelitis (Tan, 2014). It is available as an intravenous formulation and should not be used intramuscularly or subcutaneously (Biron, 2006; Rossi, 2018). An advantage of ganciclovir as an intravenous treatment is that if multiple organs are involved it allows generalized treatment. It is also beneficial in patients with renal impairment as the dose can be tailored precisely as required, compared to "rounding" doses that is needed if an oral formulation is used (Tan, 2014).

Treatment or induction with ganciclovir is generally ganciclovir IV 5 mg/kg every 12 h, and the duration will depend on the indication. Treatment/induction for CMV retinitis or CMV pneumonitis will continue for 14–21 days, prevention of CMV will continue treatment for 7–14 days, and when used for CMV colitis in HIV/AIDS treatment will continue for 21–42 days. Maintenance treatment is ganciclovir IV 5 mg/kg daily or 6 mg/kg once a day for 5 days each week. When used to prevent CMV infection after transplant treatment will continue for up to 120 days or more following transplant. Ganciclovir should only be used in children on the advice of a pediatric infectious diseases physician (Rossi, 2018).

Resistance to ganciclovir is possible and occurs due to mutations in either UL97 or UL54 genes (Biron, 2006). Risk factors for resistance developing include a high virus load, prolonged treatment with ganciclovir, and the use of oral ganciclovir (Limaye, 2002). Drug-resistant CMV may be treated with combination treatment of ganciclovir and foscarnet (Tan, 2014). Adverse effects associated with ganciclovir include hematologic abnormalities (e.g., neutropenia, thrombocytopenia, and anemia), and can potentially cause reproductive toxicity in the long term (Biron, 2006). An oral formulation of ganciclovir was developed in an attempt to improve administration convenience; however, it has a low oral bioavailability (5%) meaning it is only suitable for maintenance (not induction) therapy. The oral formulation needs to be taken three times a day, and the potential for increasing resistance due to low bioavailability and subsequent viral suppression limits its convenience and usefulness. In practice, this formulation has now been replaced by valganciclovir (Biron, 2006). Ganciclovir is considered to be carcinogenic and should be handled cautiously using hazardous drug precautions (Rossi, 2018).

Valganciclovir

Valganciclovir is the prodrug of ganciclovir and is indicated for the treatment and prevention of CMV in patients receiving stem cell or solid organ transplants (Biron, 2006; Rossi, 2018). Mild infection in patients who are immunosuppressed can generally be treated with oral valganciclovir. It is also indicated for the treatment of CMV retinitis in patients with AIDS (Tan, 2014). It was developed in an attempt to improve oral bioavailability of ganciclovir. Valganciclovir is rapidly metabolized to ganciclovir after oral administration in the intestinal wall and liver, with an oral bioavailability of approximately 60% (Biron, 2006). Valganciclovir at a dose of 900 mg orally once a day provides ganciclovir exposure equal to that from intravenous ganciclovir at a dose of 5 mg/kg once daily and 1.7-fold greater than exposure from ganciclovir orally 1000 mg three times a day (Biron, 2006).

Research has supported the efficacy of valganciclovir as a treatment option, with one study finding that valganciclovir was not inferior to ganciclovir treatment of CMV retinitis in patients with AIDS (Tan, 2014). Other studies looking at the use of valganciclovir in patients who have undergone solid organ transplant has found it to be an effective treatment option (Tan, 2014). The recommended dose in adults for initial treatment of CMV retinitis is 900 mg orally twice a day for 14–21 days. Maintenance treatment is continued at 900 mg orally once daily, which is also the recommended dose for the prevention of CMV following a transplant (Rossi, 2018). Adverse effects are similar to those seen with the use of ganciclovir (Rossi, 2018).

Penciclovir

Penciclovir is indicated for oral herpes labialis. It is available as a 0.1% cream and should be applied when symptoms first appear every 2 h while awake for 4 days (Medscape, 2018a). One study compared penciclovir cream to placebo in healthy adults and found there was a marginal improvement in healing time in those using penciclovir (4.8 compared to 5.5 days) (Usatine and Tinitigan, 2010). Adverse effects include mild erythema, reaction at the application site and headache (Medscape, 2018a).

Antivirals for Hepatitis C

Traditionally treatment for hepatitis C revolved around pegylated interferon-alfa and oral ribavirin, however, due to its associated adverse effects, interferon-alfa is no longer recommended as a treatment. Ribavirin, however, may be used as part of combination treatment (Dhawan, 2018).

Direct-acting antivirals (DAAs) are an effective treatment option for hepatitis C (particularly genotype 1), with a cure rate of over 90% provided patients are adherent to therapy. They are also well tolerated, available as oral tablets and will have a treatment course of 12–24 weeks. These antivirals are often advantageous over traditional treatments for hepatitis C, which were associated with severe adverse effects and prolonged treatment courses (Dhawan, 2018; Khoo and Tse, 2016; NSW Government, 2016). Choice of treatment will depend on whether the disease is cirrhotic or noncirrhotic, and if the patient is treatment naïve or has had treatment previously (Khoo and Tse, 2016). Specialist review is required before initiating therapy in patients with current or prior decompensated cirrhosis (e.g., encephalopathy, previous variceal bleeding, refractory ascites) (Khoo and Tse, 2016).

Choice of treatment depends on a number of patient factors, including renal impairment (many DAAs are renally cleared) and potential drug–drug interactions (Khoo and Tse, 2016). Many treatment regimens have once daily dosing. Potential adverse effects include fatigue, headache, nausea, and insomnia; however, they are not common and are often mild. They rarely lead to ceasing treatment (Khoo and Tse, 2016). Reviewing treatment response occurs 12 weeks after finishing the treatment and is determined by assessing hepatitis C viral load by polymerase chain reaction. It is important that patients are aware that although serology may remain positive following successful treatment, this does not mean they are protected and reinfection may occur (Khoo and Tse, 2016).

A number of combination treatments are now available. These include ledispasvir/sofosbuvir; elbasvir/grazoprevir; obitasvir/paritaprevir/ritonavir/dasabuvir; ombitasvir/paritaprevir/ritonavir; sofosbuvir/velpatasvir (Dhawan, 2018).

Hepatitis C virus (HCV) protease inhibitors include asunaprevir, boceprevir, paritaprevir, and simeprivir. Boceprevir and telaprevir were the first protease inhibitors available; however, they have been superseded by antivirals with greater efficacy and better safety profiles. HCV protease inhibitors exert their effect by altering replication of the virus through inhibition of NS4/4A serine protease (Dhawan, 2018; Rossi, 2018).

- Asunaprevir is indicated for the treatment of chronic hepatitis C (genotype 1) in patients with compensated liver disease, including cirrhosis, in combination with daclatasvir. The recommended dose is 100 mg twice a day orally. Research has found this combination of treatment to be successful in reaching a sustained viral response. Common adverse effects associated with this combination treatment include headache, fatigue, diarrhea, nasopharyngitis, and nausea. It is recommended to avoid this combination treatment in pregnancy and breastfeeding, and adequate contraception should be ensured while it is being used. Asunaprevir is metabolized by CYP450 3A and is a moderate inhibitor of CYP2D6, so there is a potential for drug interactions (Anon, 2016a; Rossi, 2017).
- Boceprevir is indicated for the treatment of chronic hepatitic C genotype 1. It is one of the early protease inhibitors, and while effective, resistance was shown to develop early. It is indicated for use in combination with peginterferon-alfa and ribavirin, at an adult dose of 800 mg 3 times a day orally. Adverse effects associated with boceprevir include anemia and dyguesia (Kwo and Vinayek, 2011; Rossi, 2017; Rowe and Mutimer, 2011)
- Paritaprevir is used in combination with ritonavir, ombitasvir, and dasabuvir with or without ribavirin for the treatment of hepatitis C. The concentration of paritaprevir is increased when it is combined with ritonavir (which inhibits the metabolism of paritaprevir by CYP450 3A4), and this is the sole purpose of ritonavir in this combination as it has no impact on the hepatitis C virus. Paritaprevir is available in combination packs with ritonavir, ombitasvir, dasabuvir, and ribavirin. This treatment regimen is effective in treating genotype 1b infection and may also be used for genotype 1a infection if patients have not previously received treatment and do not have cirrhosis (although ribavirin will be needed in this case for optimal response). The combination treatment with five medications is an effective treatment option; however, caution is needed before recommending use to ensure drug interactions and contraindications are avoided (Anon, 2016b; Rossi, 2018).
- Simeprevir is indicated for hepatitis C genotypes 1 and 4 and is used in combination with perginterferon alfa and ribavirin. It may also be used in combination with sofosbuvir for genotype 1a (Dhawan, 2018). The adult dose is 150 mg orally once daily (Rossi, 2017).

Sofosbuvir is a HCV polymerase inhibitor and inhibits NS5B polymerase, which has a key role in the replication of the virus. It is indicated for the treatment of genotypes 1, 2, 3, and 4 as combination treatment. It may be used in patients with hepatocellular carcinoma and awaiting liver transplantation to prevent recurrence of infection (Dhawan, 2018).

HCV NS5A inhibitors include daclatasvir, ledipasvir, and ombitasvir. They work by inhibiting NS5A, which is important for viral RNA replication (Dhawan, 2018; Rossi, 2018).

- Daclatasvir is indicated for chronic hepatitis C genotypes 1 and 3 in combination with sofosbuvir. It may also be used in combination with ribavirin depending on the genotype and other patient factors, such as whether cirrhosis is present or post liver transplantation. The recommended dose for adults is 60 mg orally once a day, with dosage adjustment required if used in conjunction with strong CYP3A4 inhibitors or moderate CYP3A4 inducers (Dhawan, 2018; Rossi, 2018).
- Ledipasvir is used in combination with sofosbuvir as oral treatment for genotypes 1, 4, 5, or 6. Treatment is available as a combination tablet, with the recommended dose for adults being 1 tablet once a day (containing ledipasvir 90 mg and sofosbuvir 400 mg) (Dhawan, 2018; Rossi, 2018).
- Ombitasvir may be used in combination with paritaprevir and ritonavir for genotype 4 infection without cirrhosis. This combination may also be used with dasabuvir for genotype 2 infection (Dhawan, 2018).
- Elbasvir is a HCV NS5A inhibitor and is indicated to be used in combination with grazoprevir (a HCV NS3/4A protease inhibitor) for treating genotypes 1 and 4 infection, with or without ribavirin. Research has found that response to therapy was high in patients who had previous unsuccessful treatment with peginterferon/ribavirin, and that adding ribavirin to the combination treatment improved response. The most common side effects associated with this treatment were fatigue, headache, and nausea, with anemia also being a common adverse effective when ribavirin was also part of the treatment regimen. There is potential for drug interactions as both elbasvir and grazoprevir are partially metabolized by oxidation (mainly by CYP450 3A). Strong inducers of CYP3A are contraindicated for use in combination with elbasvir and grazoprevir. Elbasvir/grazoprevir is available as a tablet containing 50 mg elbasvir and 100 mg grazoprevir, and is taken at a recommended dose of 1 tablet daily (Anon, 2017; Dhawan, 2018).

Dasabuvir is a non-nucleoside NS5B RNA-dependent polymerase inhibitor that suppresses viral replication. It may be used in combination with ombitasvir/paritaprevir/ritonavir for genotype 1 infection and may also be used in patients with compensated cirrhosis or concurrent infection with HIV (Dhawan, 2018).

Other Antivirals

Ribavirin

Ribavirin is indicated for the treatment of hepatitis C and also respiratory syncytial virus (RSV). It is an antiviral nucleoside analogue (Dhawan, 2018; Rossi, 2018).

Ribavirin impairs RNA and DNA synthesis, which in turn inhibits viral replication. When used to treat hepatitis C infection, ribavirin has been shown to have an effect on the virus and/or the host and the host's immune response to the virus. Ribavirin treatment may lead to an early increase in mutation of the hepatitis C virus; however, this appears to be transient. When used as part of combination therapy for hepatitis C, the risk of mutation has not been shown to be increased. When used to treat RSV ribavirin has been shown to inhibit RSV particle release and RSV gene expression by epithelial cells in the airway that are infected and reduce IL-8 secretion, IL-8 mRNA expression, and nuclear factor-kappa B activation (Martin and Jensen, 2008; Rossi, 2018).

As monotherapy, it has little impact on the hepatitis C virus, however, is much more effective when used in combination with interferon-alfa. The recommended dose depends on which treatment it is used in combination with. When taken orally ribavirin has a rapid absorption, with time to reach maximum concentration being approximately 1.5 h, and has rapid distribution and prolonged elimination. Despite its extensive absorption, its absolute bioavailability is approximately 50%, which is likely due to first-pass metabolism. It takes approximately 4 weeks to reach steady state after multiple dosing and due to slow elimination the half-life after multiple dosing is approximately 298 h. Ribavirin is mainly cleared renally and often accumulates in patients with renal dysfunction. It is not cleared effectively with hemodialysis (Dhawan, 2018; Glue, 1999; Martin and Jensen, 2008; Rossi, 2018).

When taken orally, the most significant adverse effect of ribavirin is hemolytic anemia, which is commonly seen in patients taking interferon plus ribavirin for hepatitis C infection. Factors that can influence haemolysis include the amount of interferon used, platelet level prior to treatment and haptoglobin phenotype. Hemoglobin decrease has also been associated with lower creatinine clearance at baseline, higher baseline hemoglobin levels, and greater age. Reduced bone mineral density has also been seen with ribavirin use; however, there has been conflicting results. Other potential adverse effects include reticulocytosis, decreased CD4 cell count in people with HIV infection (which is reversible), insomnia, irritability, fatigue, dizziness, nausea, and sweating (Martin and Jensen, 2008; Rossi, 2018).

Peginterferon Alfa

Peginterferon alfa is indicated for the treatment of hepatitis B and C. The formulation of peginterferon alfa leads to a drug with better pharmacokinetics and a more convenient dosing schedule compared to conventional interferon alfa. Peginterferon alfa-2a is given as a subcutaneous dose of 180 μg once a week in adults for 48 weeks for chronic hepatitis B infection (Lau et al., 2005; Medscape, 2018c; Rossi, 2018).

Research has found that when used for the treatment of hepatitis Be antigen (HBeAg) positive chronic hepatitis B, peginterferon alfa-2a when given either as monotherapy or in combination with lamivudine was more effective than using lamivudine alone in leading to HBeAg seroconversion or hepatitis B DNA levels below 100,000 copies/mL (Lau et al., 2005). When used in patients with chronic hepatitis C and cirrhosis, peginterferon alfa-2a given at a dose of 180 μg once a week subcutaneously has been found to be an effective treatment dose (Heathcote et al., 2000).

Adverse effects associated with interferon alfa include pyrexia, fatigue, headache, myalgia, and psychiatric disorders such as depression (Lau et al., 2005; Rossi, 2018).

Prevention

Prevention strategies for viral infections will depend on the infection. Vaccines are available for a number of viral infections (e.g., HPV, varicella zoster, herpes zoster, influenza, hepatitis A and B). Other general prevention strategies include practicing good hygiene, such as using a condom if infections can be transmitted sexually, covering sores and cuts, avoid sharing eating and drinking utensils, discarding used tissues properly, washing hands regularly, covering mouth and nose when coughing or sneezing, and regularly cleaning and disinfecting surfaces that are touched.

Role of Pharmacists in Optimizing Antiviral Treatment

As medication experts, pharmacists have many opportunities to contribute to optimal management of viral infections and use of antiviral medicines. This includes education and counseling of patients to ensure treatment is taken correctly and only when required, referring patients for management by a medical practitioner where required, and optimizing the dosage and safety of antiviral medicines. The scope of pharmacists' involvement in the prevention and treatment of viral diseases will depend on their practice setting.

Role of Community Pharmacists in Managing Viral Presentations

Pharmacists working in primary care settings have numerous opportunities to be involved in managing and optimizing treatment of viral infections. This can range from counseling and education of the public, supplying antiviral medicines, and providing immunization services to prevent viral infections.

Upper respiratory tract infections (URTIs) are often viral in origin; however, despite this antibiotics are commonly prescribed for these infections (Zoorob et al., 2012). One study in England found that 41% of acute cough presentations, 82% of bronchitis cases, and 88% of rhinosinusitis presentations were prescribed an antibiotic (Pouwels et al., 2018). While various factors may contribute to this high rate of antibiotic prescribing, one Australian study found that the main reason for inappropriate prescribing was to meet patient expectations (Fletcher-Lartey et al., 2016). This highlights the important role that pharmacists can play in educating patients about treatment for URTIs such as influenza. Key points that pharmacists can highlight to patients with influenza include:

- Antibiotics do not treat viral infections, which is the cause of the many URTIs. Antibiotics can cause side effects and also increase the risk of resistance developing when used inappropriately. Do not expect that your doctor will prescribe you antibiotics.
- Treat the symptoms (e.g., paracetamol can be used to treat fever, headache, and aches and pains).
- Drink plenty of fluids to avoid dehydration.
- Rest until the infection has cleared, particularly if very unwell (Dolin, 2018).

Receiving the annual influenza vaccine is an important prevention strategy against influenza and associated complications. Pharmacists have a key role in educating patients on the benefits of the influenza vaccine, dispelling myths associated with the vaccine, and answering patient questions. In some countries, pharmacists can administer the influenza vaccine to patients, playing an additional crucial role in increasing vaccination rates against influenza. Research has reported that offering pharmacist-administered influenza vaccinations has increased the accessibility of immunization leading to higher uptake rates. A Canadian study reported that patients were satisfied with the service they received from pharmacists administering the vaccination, and 18% of patients had not received the influenza vaccine the previous year (Poulose et al., 2015). An Australian study also found high patient satisfaction with pharmacist-administered influenza vaccines (Burt et al., 2018).

Topical and oral antiviral medicines (e.g., famciclovir) for the treatment of cold sores are available without a prescription from pharmacists in certain countries. Having treatment available without a prescription increases the accessibility for the patient, particularly when treatment is recommended when symptoms first occur. Pharmacists have a responsibility to discuss with the patient their request to ensure that the supply is appropriate, provide education to the patient to ensure that the medicine is taken correctly, as well as provide general advice on the management of cold sores. Pharmacists must also ensure that the treatment is being used for the approved indication and not for other indications (e.g., genital herpes) (Cunningham et al., 2012). If the requested treatment is inappropriate, pharmacists should discuss with the patient what the particular medicine is indicated and approved for and provide advice on the most appropriate management of the presenting condition (e.g., referral to a medical practitioner for further review and management).

Patients will often seek advice of their pharmacist on symptoms they are experiencing, and pharmacists are in a position to provide recommendations on the most appropriate treatment or when the patient should see another health professional such as a medical practitioner. Pharmacists can play a key role in facilitating early review and treatment for particular viral infections (e.g., herpes zoster) to optimize management of the infection and reduce the risk of complications.

Role of Hospital Pharmacists in Managing Viral Presentations

Pharmacists working in acute care settings may be more likely to encounter different viral presentations compared to pharmacists working in primary care, and the focus of their role may be different. Nevertheless, pharmacists in this setting have a vital role in contributing to optimal use of antiviral medicines.

Management of hepatitis C carries with it a number of complexities, including identifying and managing potential drug–drug interactions, as well as managing adverse effects and providing patient education. Pharmacists, as medication experts, have a crucial role to play in this area. Pharmacists have a role to play in reviewing prescribed treatment to ensure dosing is correct and recommending any adjustments based on renal or hepatic function, identifying and managing potential drug–drug interactions (including potential interactions with nonprescription medicines), providing patient education and managing adverse effects that may arise. A study in the United States found that the pharmacist was a key member of the interdisciplinary team and played a crucial role in identifying and managing potential drug–drug interactions (Langness et al., 2017).

As ganciclovir is carcinogenic, it should be handled using hazardous drug precautions. Staff handling and administering ganciclovir may not be aware of this risk or the precautions needed when handling this medicine. Pharmacists can therefore play a key role in educating staff on the risks associated with handling ganciclovir, and hazardous drug precautions that should be taken (Rossi, 2018). These include

- Only staff appropriately trained should handle hazardous medications.
- Staff must use approved equipment and clothing when handling hazardous drugs.
- Drug must not come into contact with the skin, mucosal, or serosal areas when preparing or administering the drug.
- Skin contact, aerosolization of powder into the air, and cross-contamination with other medicines must be avoided, and strategies should be implemented to facilitate this.
- Staff must refer to local policies or guidelines available on safe handling of hazardous drugs (Rossi, 2018).

Ganciclovir is the active metabolite of valganciclovir; therefore, any adverse effect associated with ganciclovir can also be applied to valganciclovir. Valganciclovir tablets and oral solution should therefore also be handled with caution. The manufacturer recommends that the tablets should not be broken or crushed and that contact with skin or mucous membranes with broken or crushed tablets, powder, or solution should be avoided. Reconstitution of the solution should be done with caution, and inhalation avoided. It is also recommended to use gloves when reconstituting the solution and the outer surface of the bottle and cap and table should be wiped after reconstitution (Roche Products Limited, 2008; Roche Products Pty Limited, 2018). Pharmacists have a key role in ensuring safety of both themselves and other staff when handling these medicines.

Dosage adjustments of antiviral medicines may be required based on patient factors such as renal or hepatic function. Pharmacists have a key role to play in reviewing prescribed doses and making recommendations for dosage adjustments where required to support the quality use of medicines and optimize safety. In addition, monitoring of certain parameters (e.g., complete blood count, liver enzymes) may be required with the use of certain antiviral medicines. Pharmacists can provide education to other health professionals on the requirements of monitoring and the intervals for when this monitoring should occur and can follow-up on this to ensure required monitoring is being carried out (Jiang et al., 2014).

Monitoring for potential adverse effects is another key role pharmacists can play in optimizing the use of antiviral medicines. Pharmacists can play a key role in providing advice for when a presenting symptom may be due to an adverse effect and then make recommendations for how this can be managed. Pharmacists also play an essential role in providing education to patients about their medicines, which includes potential side effects that may be experienced and what to do if these occur. This role is relevant to pharmacists working in both community and hospital pharmacy settings (Olea et al., 2018).

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Nutritional Anemias

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Learning Objectives

1. Describe the epidemiology and etiology of vitamin B_{12} and iron deficiency anemias.
2. Describe the clinical presentation and diagnosis of vitamin B_{12} and iron deficiency anemias.
3. Describe the pharmacological and nonpharmacological management and monitoring of vitamin B_{12} and iron deficiency anemias.
4. Describe the role of the pharmacist in the health-care team's management and monitoring of vitamin B_{12} and iron deficiency anemias.
5. Describe the pharmacist's role in the interprofessional team with respect to the management of vitamin B_{12} and iron deficiency anemias.

Take Home Messages

- Anemia is a common condition, affecting around one-third of the population globally. Iron and vitamin B_{12} deficiencies are two causes of "nutritional anemias," and iron deficiency is the most frequent cause of anemia worldwide.
- The clinical signs and symptoms of iron and vitamin B_{12} deficiency and related anemias are not specific, and laboratory investigations are required to confirm a diagnosis. Once a diagnosis is made, it is critical to establish the underlying cause of iron or vitamin B_{12} deficiency, as this determines the therapeutic strategy. Close monitoring of patients undergoing treatment is critical to ensure that the correct diagnosis is made, and lifelong therapy is required for some patients.
- Oral iron therapy is the most common strategy to correct iron deficiency anemia; however, parental therapy is indicated in some cases. Intramuscular hydroxycobalamin infusion is the most frequently used therapeutic strategy to correct patients with clinical vitamin B_{12} deficiency; however, the use of high-dose oral supplementation is increasing. Ensuring dietary adequacy of iron and vitamin B_{12} is an important measure to prevent recurrent deficiency for patients without severe malabsorptive causes of deficiency.
- Pharmacists have an important role to play in the inter-professional team in the management of patients presenting with iron and vitamin B_{12} deficiencies, ranging from subclinical deficiency to anemia. They are an important first contact for patients with mild deficiencies to ensure that they undergo appropriate hematological investigations to obtain a correct diagnosis before supplementation begins. Compliance with therapy and interactions with supplementation can be a challenge, particularly with oral iron therapies, and pharmacists have the potential to significantly improve therapeutic outcomes through adequate patient counseling with respect to management of side effects and maximizing absorption.

Introduction to Anemia

Anemia is a condition where either the number of red blood cells or their oxygen-carrying capacity is inadequate to meet an individual's physiologic needs. The term "nutritional anemia" was first defined in a 1968 World Health Organization technical report as "a condition in which the hemoglobin content of the blood is lower than normal as a result of a deficiency of one or more essential nutrients, regardless of the cause of such deficiency" (WHO Scientific Group, 1968).

Anemia was estimated to account for 9% of the total global disability burden from all conditions in 2010 (FAO, 2017), and affected approximately 27% of the world's population in 2013 (Kassebaum et al., 2016). Population groups most vulnerable to anemia include infants and young children, adolescents, and women of reproductive years. The burden of anemia comes with a range of consequences that vary at different life stages—in children anemia is associated with poor cognitive outcomes, or with poor birth outcomes in pregnancy such as low birth weight, prematurity, as well as maternal and perinatal mortality (Balarajan et al., 2011). More importantly, the consequences of anemia are not limited to the individual, but have wide-reaching societal and economic impacts across low-, middle-, and high-income countries.

Globally, the top three causes of anemia are considered to be iron deficiency, hemoglobinopathies, and malaria, with iron deficiency as the leading cause (Kassebaum et al., 2016). Although this chapter will be focusing on 'nutritional anemias' it is important to recognize that there are a range of causes and classifications within the wider context of anemias.

Chapter Focus

This chapter will focus on iron and vitamin B_{12}, which are two micronutrients that contribute to distinct forms of anemia. Iron is an essential component of hemoglobin, myoglobin, and cytochromes and is required for the oxygen transport and cellular respiration (Anderson and McLaren, 2012). Vitamin B_{12} plays a central role in the folate/methionine cycle and DNA synthesis, and is therefore required for erythropoiesis (Moll and Davis, 2017; Reynolds, 2006).

The remainder of this chapter will outline the epidemiology, etiology, diagnosis, management, and future projections of nutritional anemias relating to iron and vitamin B_{12} deficiencies.

Anemia Epidemiology

The global prevalence of anemia was estimated to be 27% in 2013 (Kassebaum et al., 2016), and iron deficiency remains the most common cause (Kassebaum et al., 2016). However, it is important to note that the data regarding the epidemiology of anemia are relatively unreliable, as it is often ascribed to iron deficiency regardless of its true cause.

Globally, the most vulnerable population group is children aged 0–5 years, followed by adolescence, women (particularly during pregnancy), and older adults (de Benoist et al., 2008; Stevens et al., 2013; WHO, 2017). This reflects the fact that each of these groups experiences a greater physiologic demand for iron, and is therefore more susceptible to deficiency. Childhood and adolescence are periods of rapid growth and development with elevated demands for iron, as is pregnancy to meet the needs of the fetus, placenta, and expanded maternal blood volume (Stevens et al., 2013). Women of reproductive years are particularly vulnerable to deficiency secondary to menstruation, which is compounded by the fact that diets are typically low in bioavailable iron in women across many low- and middle-income countries (Torheim et al., 2010). The elderly are also considered to be an at risk group, and although the prevalence and etiology of anemia among this group has not been well characterized (WHO, 2017), this is projected to become a substantial burden in the future due to the increasing proportion of older adults in the population (Patel and Guralnik, 2007).

Etiology of Nutritional Anemias

Nutritional anemias result when the intake of certain nutrients is inadequate to meet the demands for red blood cell and hemoglobin (Hb) synthesis (Balarajan et al., 2011). Deficiency of iron and vitamin B_{12} both contribute to the development of anemia due to their distinct roles in erythropoiesis, though there are easily distinguishable changes that occur to the shape, size, and color of the red blood cells in the case of either deficiency. Microcytic anemia occurs with iron deficiency, where the red blood cells are smaller with a reduced hemoglobin content, while megaloblastic anemia occurs in the case of vitamin B_{12} deficiencies where red blood cells are enlarged (WHO, 2017). However, anemia is a late stage of these micronutrient deficiencies and there are sequential changes in status that occur before a diagnosis of anemia is made, and not all deficiency states will reach anemia, yet may require pharmacological intervention (WHO, 2017).

Iron Deficiency

The etiology of iron deficiency anemia (IDA) is multifaceted and depends on an individual's age, medical condition, comorbidities, and concomitant therapies. Common examples of factors involved in the etiology of iron deficiency and IDA are outlined in **Table 1** (Lopez et al., 2016).

Table 1 Factors contributing to the development of iron deficiency and iron deficiency anemia

Cause	*Example*	*Comment*
Inadequate dietary intake	• Vegetarian or vegan diets • Complementary foods in infancy	This is rarely the sole cause of iron deficiency anemia
Blood loss	• Digestive tract: colonic and gastric carcinoma, inflammatory bowel disease • Parasites (hookworm, malaria) • Ulcers • Surgery • Hemodialysis • Nonsteroidal anti-inflammatory drugs	
Malabsorption	• Celiac disease • Gastrectomy • *Helicobacter pylori* • Gut resection, bypass gastric surgery • Atrophic gastritis or bacterial overgrowth • Proton-pump inhibitors, H2 antagonists, achlorhydria • Interaction with nutrient components	
Association with anemia of chronic disease	• Chronic heart failure • Cancer • Chronic kidney disease • Rheumatoid arthritis • Obesity • Inflammatory bowel disease	
Genetic disorders	• Iron-refractory iron deficiency anemia	

Table 2 Factors contributing to vitamin B_{12} deficiency

Cause	*Example*	*Comment*
Inadequate dietary intake	• Vegan diets or diets relatively low in animal-based foods (meat, poultry, seafood, dairy, eggs)	Maternal diets that are strictly vegetarian or vegan during pregnancy or lactation can lead to inadequacy in infants. Most common cause of subclinical deficiency
Food-bound cobalamin malabsorption	• Gastric resection • Proton pump inhibitor use • Persistent infection with *Helicobacter pylori*	This occurs when there is a release of cobalamin from its binding proteins in food and occurs in states of gastric dysfunction or reduced gastric acid secretion
Malabsorption	• Pernicious anemia (loss of intrinsic factor) • Ileal resection • Gastric resection • Chron's disease • Celiac disease • Metformin • Oral contraceptive pill	Factors that may lead to clinical deficiency and anemia
Infection	• *Helicobacter pylori* • *Giardia lamblia*	
Inherited disorders	• Imerslund- Gräsbeck syndrome • Hereditary intrinsic factor deficiency • Transcobalamin deficiency	

Table 3 Major distinctions between clinical and subclinical vitamin B_{12} deficiency

	Clinical deficiency	*Subclinical deficiency*
Phenotype	Clinical disease Biochemical changes[a]	No clinical findings Biochemical changes[a]
Role of malabsorption	Major causative role	Mild or no role
Prognosis and cause	Usually progressive	Usually static or fluctuating Rarely progresses to clinical deficiency
Need for therapy	Mandatory	Unknown
Prevalence	Very low (<0.1% in adults, 1%–2% in elderly)	Higher than clinical deficiency

[a]Elevated methylmalonic acid and homocysteine can be significant in clinical deficiency, but mild elevations may also occur in subclinical deficiencies.

Vitamin B_{12} Deficiency

As with IDA there are a number of factors contributing to the development of vitamin B_{12} deficiency and associated anemia, with major causes and examples outlined in **Table 2** (Carmel, 1995, 2000, 2013).

It is important to distinguish subclinical vitamin B_{12} deficiency from clinical deficiency, as these are two distinct conditions, as summarized in **Table 3** (Carmel, 2013). Vitamin B_{12} turnover is very small, and as depletion is rare, transiently poor intake or changes in absorption does not have a clinically relevant impact on body stores. Clinical deficiency however results from more significant depletion of body stores, such as in the case of failed cobalamin internalization with pernicious anemia, and has the potential to progress to megaloblastic anemia (Carmel, 2013).

Clinical Presentation of Nutritional Anemias

Iron Deficiency

Patients with IDA may present with symptoms associated with a range of anemias, only some of which are associated with specific signs of iron deficiency. Clinical features depend on the severity of deficiency, the patient's age, comorbidities, and speed of onset, and some patients may even remain asymptomatic (Lopez et al., 2016).

As Hb concentration falls, oxygen-carrying capacity is compromised, resulting in the classic symptoms of anemia—fatigue, shortness of breath, and diminished work capacity (WHO, 2017). Other symptoms that result from hypoxic functioning include exertional dyspnea, vertigo, headaches, tachycardia, and a cardiac systolic flow murmur. In more severe cases, patients may present with dyspnea at rest, angina pectoris, and hemodynamic instability (Moll and Davis, 2017). Symptoms ranging from common through to rare IDA are summarized in **Table 4**.

Table 4 Clinical presentation of iron deficiency anemia

Very frequent	*Frequent*	*Rare*
Pallor of the skin, conjunctivae, and nail beds	Dry and rough/damaged skin or hair, alopecia	Hemodynamic instability
Fatigue	Atrophic glossitis (inflammation of the tongue)	Syncope (fainting)
Dyspnea (shortness of breath)	Restless leg syndrome	Koilonchydia (spoon-shaped fingernails)
Headaches	Cardiac murmur	Plummer-Vinson syndrome (esophageal webs)
Angular stomitis	Tachycardia	Pica (urge to consume nonnutritive items, e.g., dirt, starch, raw pasta)
Chelitis (inflammation and small cracks in the corners of the mouth)	Neurocognitive dysfunction	
Reduced work capacity	Angina pectoris	
	Vertigo	

Vitamin B_{12} Deficiency

As with IDA, patients with macrocytic anemia due to vitamin B_{12} deficiency will present with general symptoms of anemia such as fatigue. However, the defining feature of clinical vitamin B_{12} deficiency is unexplained neuropsychiatric symptoms, which tend to be myelopathic or neuropathic in nature (e.g., numbness and tingling in the hands and feet). Additional symptoms of vitamin B_{12} deficiency might include poor memory, confusion, depression, and difficulty in maintaining balance. In pediatric cases, signs of a vitamin B_{12} deficiency include failure to thrive, developmental delays, and impaired movement. However, as with iron deficiency, many of these symptoms are not specific and may result from a number of medical conditions besides vitamin B_{12} deficiency (Carmel, 2013).

Diagnosis of Nutritional Anemias

A diagnosis of anemia is made when Hb concentrations fall below established cutoff values, which are summarized in **Table 5**. It is important to note that although the World Health Organization recommends these guidelines, the values used still vary across laboratories and countries. Other blood measures that may be used for diagnostic purposes include hematocrit, mean cell volume, blood reticulocyte count, blood film analysis, or Hb electrophoresis, though these are less frequently used (World Health Organization, 2011).

Iron Deficiency

To confirm that the anemia is caused by iron deficiency, additional measures of iron status are required. The hematological tests used in the diagnosis of iron deficiency and IDA are summarized in **Table 6** (Goddard et al., 2011; Pasricha et al., 2010; World Health Organization, 2001).

Summary of the Diagnosis of Iron Deficiency Anemia

The World Health Organization recommends the use of Hb in combination with serum ferritin for the diagnosis of iron deficiency and IDA (World Health Organization, 2004). Typically, investigations will include a complete blood count, reticulocyte count, and serum iron indices, and the underlying cause should be established in all patients during diagnosis. **Fig. 1** summarizes the steps involved in the investigation and management of IDA.

Table 5 Recommended hemoglobin (g/L) cutoff values for the diagnosis of anemia

	Anemia			
Population group, age	*No anemia*	*Mild*	*Moderate*	*Severe*
Children, 6-–59 months	≥110	100–109	70–99	<70
Children, 5–11 years	≥115	110–114	80–109	<80
Children, 12–14 years	≥120	110–119	80–109	<80
Nonpregnant women, 15 years and older	≥120	110–119	80–109	<80
Pregnant women	≥110	100–109	70–99	<70
Men, 15 years and older	≥130	110–129	80–109	<80

Table 6 Summary of laboratory tests used to confirm iron deficiency anemia

Test	*Cutoff value*	*Rationale and advantages*	*Disadvantages*
Serum ferritin	<12–15 μg/L Thresholds of 100 μg/L have been suggested for chronic kidney disease or 200 μg/L for patients undergoing dialysis	• Measures total iron body stores • Most powerful test for iron deficiency • Highly sensitive	• Affected by inflammation and liver disease • Investigations should also include C-reactive protein
Serum soluble transferrin receptor	N/A	• A measure of the intensity of erythropoiesis and demand for iron • Useful to differentiate IDA from anemia of chronic disease • Not affected by inflammation	• Lacks standardization • Not routinely conducted
Transferrin saturation	<16% <20% in the presence of inflammation	• Inexpensive • Well established	• Low specificity • Wide diurnal variation
Mean cell volume	<80 fL	• Widely available	• Microcytosis can also occur in other causes of anemia (e.g., thalassemia) • May be normal at early stages of iron deficiency anemia

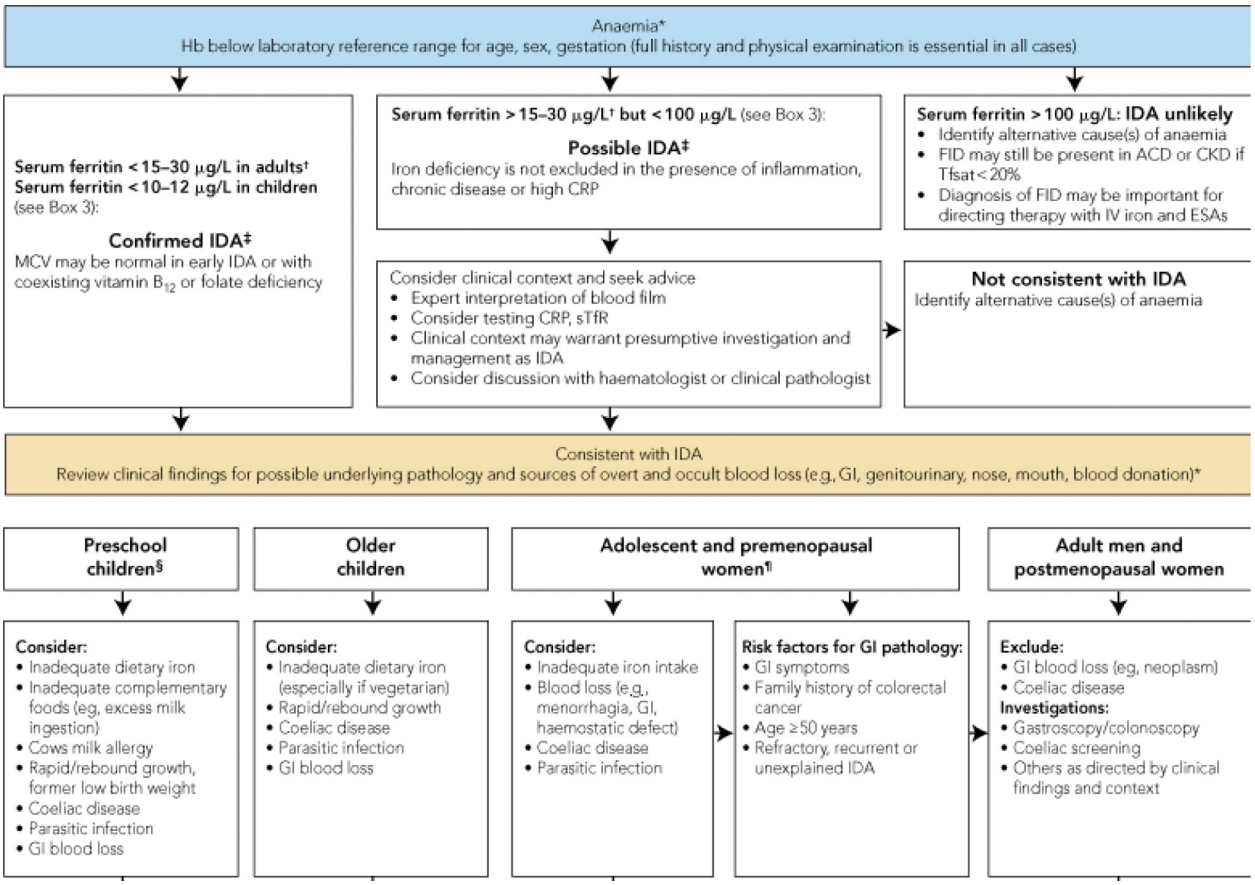

Figure 1 Summary of the tests used to investigate and confirm iron deficiency anemia. *Source: Figure reproduced from Pasricha et al. (2010).*

Table 7 Summary of laboratory tests for the investigation of vitamin B_{12} deficiency

Test	*Finding*	*Notes*
Full blood count	• Characteristic finding of clinical deficiency is macrocytic anemia	• Macrocytosis and anemia will not always be present in individuals with clinical deficiency • Leucopenia and thrombocytopenia may also be present
Blood film	• Hypersegmented neutrophils (defined as >5% of neutrophils with 5 or more lobes) • Oval macrocytes	• Not sensitive or specific in early cobalamin deficiency (Westerman et al., 1999)
Mean cell volume	• Elevated	• Not a specific indicator of vitamin B_{12} deficiency. Other causes should be excluded (e.g., alcohol excess or drugs) (Galloway and Hamilton, 2007). • Neurological impairment can occur in individuals presenting with normal values, and the absence of an elevated mean cell volume should not exclude further cobalamin testing (Healton et al., 1991).
Anti-intrinsic factor antibody Note that all patients suspected of pernicious anemia should be tested.	• Positive	• Identifies patients requiring lifelong cobalamin replacement. • Can be helpful in identifying the cause for those with an unclear cause of deficiency

Vitamin B_{12} Deficiency

As with IDA, further investigation is required to diagnose vitamin B_{12} deficiency. **Table 7** summarizes the hematological tests used for the initial investigation of vitamin B_{12} deficiency (Carmel, 2000; Carmel and Sarrai, 2006; Devalia et al., 2014).

A summary of laboratory tests used to confirm a diagnosis of vitamin B_{12} deficiency are summarized in **Table 8** (Devalia et al., 2014; Heil et al., 2012; Hvas and Nexo, 2006; Hvas et al., 2001). It is important to note that there is no gold standard test available, and each test has its own advantages and disadvantages, as outlined in **Table 8**.

Table 8 Summary of laboratory tests used to diagnose vitamin B_{12} deficiency

Test	*Cutoff value Clinical deficiency*	*Advantage Subclinical deficiency*	*Disadvantage*	
Serum total vitamin B_{12}	<150 ρmol/L in adults	Not defined	• Easily accessible • Cheap	• Does not reflect cellular status • Functional cobalamin deficiency can occur with normal serum concentrations • Falsely low results during pregnancy and folate deficiency • Variation in reference ranges • Sensitivity and specificity uncertain
Plasma homocysteine	>15 μmol/L		• High sensitivity • Functional marker of deficiency	• Poor specificity (also elevated with folate and vitamin B_6 deficiency, and with renal impairment) • Influenced by lifestyle factors (smoking, alcohol intake, coffee consumption) • Special procedure for sample handing is required • Limited value when used alone.
Plasma methylmalonic acid	Between 0.27 and 0.75 μmol/L in adults	Not defined	• Functional marker of deficiency • High sensitivity	• Concentrations also elevated with renal impairment and small bowel bacterial overgrowth. • Greater specificity than homocysteine, but specificity is still debatable. • Not easily accessible • Expensive
Plasma holo-transcobalamin	<32 ρmol/L has been suggested		• The active fraction of total cobalamin • Expected to have high sensitivity	• Further research required to evaluate its clinical utility • Specificity not yet known.

Summary of the Diagnosis of Vitamin B_{12} Deficiency

Suboptimal vitamin B_{12} levels may occur with nonspecific symptoms and no anemia, while patients with classical clinical features of deficiency may have serum cobalamin levels that lie within a normal range. A range of laboratory tests should be used to determine an underlying functional or biochemical deficiency (Devalia et al., 2014). Total serum B_{12} is the most practical and least expensive measure at a population-level, while methylmalonic acid and homocysteine assays offer greater sensitivity this is offset by being more expensive. It is also important to note that universally accepted cutoffs to define deficiency are lacking other than for serum total vitamin B_{12}. Folate status should also be measured in individuals with suspected deficiency given the close interrelationship between their metabolism.

Of note, it has been suggested that early diagnosis may not be worth the risk of over-diagnosing subclinical deficiency, particularly as this is likely to remain metabolically and clinically stationary for a number of years, and treatment benefits are not yet clear (Carmel and Sarrai, 2006).

Management of Iron Deficiency Anemia

As with the diagnosis of IDA, clear clinical practice guidelines for its treatment are still unavailable. Historically, the guidelines for treatment of iron deficiency have been based on perceptions of safety and efficacy, rather than on evidence-based research.

Pharmacological Management

Oral Therapy

Oral iron therapy remains the preferred therapy for the treatment of iron deficiency as opposed to intravenous infusion as it is safe, generally adequate for most patients, cost-effective, relatively well-tolerated, and associated with less burden for the patient and health-care provider.

Oral iron therapy preparations

The two main forms of supplemental iron available are ferrous and ferric preparations. Ferrous iron salts are the most efficiently absorbed form, and there are a number of preparations available, including ferrous fumarate, ferrous sulfate, and ferrous gluconate. Although ferrous fumarate has the greatest absorption, ferrous sulfate and ferrous gluconate are the preferred oral preparations, and both are relatively inexpensive with good bioavailability (Goddard et al., 2011; Lopez et al., 2016; New Zealand Formulary, 2018).

Ferric bisglycinate is the only ferric preparation available. It is an enteric-coated, delayed-release supplement that is generally well-tolerated with fewer gastrointestinal complaints than the ferrous solutions. However, ferric bisglycinate is not often recommended due to significantly lower absorption than ferrous iron salts. For infants and young children, oral therapies are also available in drop, syrup, or bead form to facilitate ease of supplementation and dose titration (New Zealand Formulary, 2018).

Additional over-the-counter preparations include polysaccharide iron complexes, ferric citrate, ferrous ascorbate, ferrous succinate, carbonyl iron, and heme iron polypeptide. These do not differ significantly in their effectiveness or side effects and all are relatively inexpensive and widely available (Auerbach and Adamson, 2016).

Dose of oral iron therapy

The dose of elemental iron used to treat IDA depends on the patient's age, estimated severity of deficiency, and the urgency with which it needs to be corrected. Generally, the recommended dose in adults is 100–200 mg/day for three months (Auerbach and Adamson, 2016; Schrier and Auerbach, 2018), and for children is 3 mg/kg of body weight per day (up to 60 mg/day). This is most easily achieved for children with the use of ferrous sulfate liquid (elemental iron of 6 mg/mL) at doses of 0.3–0.45 mL/kg/day. This may be increased to an initial dose of 0.9 mL/kg/day split into 2–3 doses per day in cases of severe deficiency (Melbourne TRCH, in press; New Zealand Formulary, 2018). After the deficiency state has been corrected, oral iron should be continued for three months to ensure that stores are adequately replenished (New Zealand Formulary, 2018).

For individuals with reduced iron stores but have not yet developed IDA, the approach to therapy should be individualized according to their etiology and severity of deficiency. It has been recommended to replace iron stores in these patients as it is likely to improve symptoms they may be experiencing, and failure to treat is likely to lead to the development of IDA (Schrier and Auerbach, 2018).

Intravenous Therapy

Historically, replacement strategies have been used with caution due to their risk for fatal anaphylactic reaction. However, this risk is now exceedingly low with the wide removal of high-molecular-weight iron dextran from the market. It is important to note that although the key advantage of intravenous therapy is the rapid replacement of iron, the rate at which Hb increases does not actually differ between intravenous and oral iron (Auerbach et al., 2008).

Indication for Intravenous Therapy

In adult and pediatric cases where oral supplementation is not tolerated or effective, iron may be replaced through intravenous infusion. The main indications for parental iron therapy include the following:

1. Malabsorption secondary to anatomic or physiologic conditions (e.g., gastric resection, atrophic gastritis, or celiac disease);
2. Intolerance to gastrointestinal side effects of oral therapy;
3. Ongoing blood loss that exceeds the capacity of oral iron;
4. Coexisting inflammatory states that interfere with regular iron homeostasis (Lopez et al., 2016; Maslovsky, 2005).
   Note that intravenous therapy is not recommended for pregnant women (especially in the first trimester), as evidence is lacking to support its safety and use during pregnancy and should be used cautiously in people with an immune or inflammatory condition (e.g., asthma or rheumatoid arthritis) as they may have a higher risk of allergic reaction (Agency, 2013).

Intravenous Preparations and Dose

There are number of standard iron preparations available for use, including iron sucrose, sodium ferric gluconate, ferric carboxymaltose, iron isomaltoside, ferumoxytol, and low-molecular-weight iron dextran (Lopez et al., 2016), though the availability of each does vary between countries. These are equally effective in treating iron deficiency, and the major differences between the preparations include cost, formulary and purchasing agreements, and the number of visits required to administer a full dose (Auerbach and Deloughery, 2016).

Iron carboxymaltose is the preferred preparation in most settings, as it can deliver up to 1000 mg of iron in 15 min and has an excellent safety profile (Baird-Gunning and Bromley, 2016). However, if a larger dose of iron is required in a single sitting, iron polymaltose may be the preferred preparation, though this may take up to 5 h for complete infusion of up to 2500 mg (Baird-Gunning and Bromley, 2016).

The dose of iron administered depends on whether the goal is to treat anemia or to fully replace iron stores. The dose is generally calculated using the Ganzoni formula, which is based on the patient's body weight, current and target Hb level, and iron stores. A fixed dose of approximately 1000 mg is often sufficient to treat anemia and provide additional storage iron, while not causing iron overload (Schrier and Auerbach, 2018). Iron infusions are typically carried out in secondary care; however, some general practice clinics have started to offer this treatment to patients. During the infusion, patients must be closely monitored to observe for any adverse effects that may develop particularly allergic reaction.

Summary of Pharmaceutical Management of Iron Deficiency

Oral supplements have a benefit over parenteral therapies for a number of reasons and are generally the preferred choice because they are cost-effective, eliminate the potential for infusion reactions, and they are the only form of iron supplementation available to patients from resource-poor settings. However, parenteral therapies are appropriate in certain cases, such as for patients who are unable to tolerate gastrointestinal side effects of oral therapy, those with severe or ongoing blood loss, and those with severely impaired absorption.

Nonpharmacological Management

Dietary Intervention

Indication for Dietary Intervention

In cases of mild deficiency (please refer to **Table 5** for definitions), dietary intervention should be considered before pharmacological strategies are required. While increasing dietary intake alone will not be adequate to treat IDA, increasing iron consumption and optimizing its absorption are valuable strategies in the secondary prevention of iron deficiency once iron levels are restored.

Bioavailability of Dietary Iron

The two forms of dietary iron are heme and non-heme. In the heme form, iron is complexed as ferrous iron (Fe^{2+}) in Hb, this is present in animal-based foods, including meat, poultry, and seafood. In the non-heme form, iron is complexed as ferric iron (Fe^{3+}), and this is present in plant-based foods, such as vegetables, cereals, cacao, and dried fruit, as well as in fortified foods (Food and Nutrition Board, 2001). Neither form has particularly high bioavailability, though heme iron is relatively greater with estimates of 12%–25% compared to <5% bioavailability of non-heme iron (Food and Nutrition Board, 2001).

Including sources of heme iron should be encouraged given its more efficient absorption; however, there are techniques that can improve the absorptive capacity of non-heme iron as summarized in **Table 9**. It can be challenging to avoid all foods containing polyphenos, phytates, and oxalates, though it has been suggested that this can be countered by including a source of ascorbic acid with the meal. However, with easily isolated nutrient components (e.g., tea or coffee), it is best to leave a space of 1–2 h between these and a meal rich in dietary non-haem iron (Hurrell and Egli, 2010). When appropriate, dietary advice should be sought for how this can be managed effectively without compromising overall dietary adequacy (Hurrell and Egli, 2010).

Table 9 Factors influencing non-haem iron absorption

Factor	*Effect*	*Examples/recommendations*
Ascorbic acid	Positive	• Citrus fruits (e.g., glass of orange juice) • Dark green leafy vegetables • Bell peppers • Strawberries • Kiwifruit Ascorbic acid supplements
Meat, fish, and poultry	Positive	
Phytates	Negative	• Whole grains • Cereals • Soy • Nuts • Legumes
Oxalates	Negative	• Spinach and other leafy greens • Nuts • Grains • Legumes
Calcium	Negative	• Dairy products • Calcium supplements
Polyphenols	Negative	• Vegetables and fruit • Cereals • Legumes • Tea • Coffee • Wine

Infants

Breast milk contains highly bioavailable iron, but this is not in sufficient amounts to meet the needs of infants older than 4–6 months (Baker and Greer FR, 2010). For this reason, some guidelines suggest that infants who are exclusively or primarily breastfed from the age of 4 months onward are given prophylactic daily iron supplements (1 mg/kg) until they begin to eat iron-containing complementary foods, such as iron-fortified cereals or pureed meats (Baker and Greer FR, 2010). As infants and younger children have a lower overall dietary intake, meeting iron requirements from natural food sources alone is challenging, and food-based strategies should also include the consumption of fortified foods (Baker and Greer FR, 2010).

Blood Transfusion

A universally accepted threshold for transfusing red blood cells in patients with IDA is unavailable. Guidelines sometimes specify certain Hb values as an indication to transfuse; however, the patient's clinical condition and symptoms should be an essential part of making this decision (Murphy et al., 2001). There are a number of adverse outcomes associated with transfusion, such as fluid overload, and a range of immunological and infectious events. Accordingly, blood transfusions are not recommended to correct iron deficiency unless the individual has severe IDA that compromises end-organ function, such as cardiac failure, or where IDA is complicated by severe, acute ongoing bleeding (Pasricha et al., 2010). Transfusion has been indicated for pregnant women with Hb levels below 6 g/dL due to the risk of impaired fetal oxygenation, which can result in low amniotic fluid volumes, fetal cerebral vasodilation, and fetal death (Acog, 2008). The goal of blood transfusion is to restore Hb to a safe, but not necessarily normal range (BPACNZ, 2013).

Management of Vitamin B_{12} Deficiency Anemia

Pharmacological Management of Vitamin B_{12} Deficiency

For patients presenting with classical megaloblastic anemia, there is a clear treatment pathway, while patients with low vitamin B_{12} concentrations of unknown significance pose a challenge for treatment. Management of these patients is based on clinical judgment, as the benefits of replacing vitamin B_{12} in those with subclinical deficiency remain unknown.

Intramuscular Injection

Standard clinical practice for the treatment of vitamin B_{12} deficiency in many countries is intramuscular replacement with hydroxocobalamin at a dose of 1 mg. This is administered three times per week for 2 weeks, or every second day for those patients with

neurological involvement until no further improvement is seen. Thereafter, maintenance intramuscular replacement is given either 3-monthly for life for those with cobalamin malabsorption secondary to failure of intrinsic factor, or 2-monthly for patients with neurological involvement (Devalia et al., 2014).

Hydroxocobalamin is preferred over cyanocobalamin as it is retained in the body for longer and can therefore be administered less frequently. It is generally well-tolerated, though some side-effects may be experienced including itching, chills, fever or hot flushes, exanthema, nausea, and dizziness (Carmel and Sarrai, 2006).

Oral Therapy

High-dose oral cyanocobalamin (1000–2000 mg dose) is available for use in several countries, and also widely available on the Internet. Although only a small fraction of a large dose is absorbed via passive, intrinsic factor-mediated absorption, this is adequate to meet requirements for most individuals. It has been suggested that this strategy is as effective as intramuscular injections and have the additional benefits of fewer visits to medical centers, which can relieve health-care costs and reduced discomfort that is associated with injections (Vidal-Alaball et al., 2005). However, oral cyanocobalamin is contraindicated in individuals with poor absorptive capacity, particularly in those with pernicious anemia.

Lower dose oral cyanocobalamin (50 μg dose) is also widely available and can improve serum B_{12} and biochemical markers in borderline cases, and the role of this treatment in those with subclinical deficiency is under active research. Careful consideration should be taken if low dose supplements are prescribed, as this strategy risks suboptimal treatment of latent and emerging pernicious anemia, and possible inadequate treatment of neurological symptoms (Devalia et al., 2014).

Nonpharmacological Management

As with iron deficiency, the long-term strategy recommended for the control of vitamin B_{12} deficiency is the consumption of a diet that meets recommendations.

However, dietary intervention to correct vitamin B_{12} deficiency is more limited than in the case of iron, as vitamin B_{12} is predominantly found in animal-based foods, including shellfish, red meats, fish, poultry, dairy products, and eggs, though it can also be found in some fortified plant-based products, such as fortified nutritional yeast, breakfast cereals, or non-dairy milks (Institute of Medicine, 1998). Individuals following vegetarian or vegan diets may have difficulties in obtaining adequate vitamin B_{12} through diet alone, and those on a vegan diet in particular should be recommended to consider pharmacological intervention. There are some claims of adequate vegan alternatives to fortified foods or supplements, such as algae (e.g., spirulina, nori, or chlorella), mushrooms, or barley grass. However, the concentrations are either inadequate to meet an individual's requirements (mushrooms) or are vitamin B_{12} analogs (algae). Only chlorella and nori contain true vitamin $B_{12,}$ though the content is largely dependent on the growing conditions of the microorganisms, and is not considered an adequate source of plant-based dietary vitamin B_{12} (Watanabe et al., 2014). Those with severe malabsorption as the underlying cause of deficiency will also require supplementation, as diet alone will not be sufficient to meet their physiologic requirements.

Summary of Vitamin B_{12} Management

High-dose oral and intramuscular injection routes appear to be equally effective in the replacement of vitamin B_{12} in those with adequate absorptive capacity. Intramuscular injection with hydroxocobalamin remains the preferred choice, but moving to oral supplementation in the future may have additional benefits in terms of cost and comfort. A treatment pathway for patients presenting with borderline deficiency or unclear clinical symptoms remains a challenge for health professionals, and clinical guidelines are unavailable.

Monitoring and Measuring of Iron and Vitamin B_{12} Deficiency

Any treatment prescribed for the correction of iron or vitamin B_{12} deficiency should also include a strategy for measuring an individual's response.

Iron Deficiency

Although standard recommendations for monitoring iron status following supplementation have not been established, it is expected that Hb concentration should improve by approximately 1 g/L, per day and be approximately 20 g/L higher after 3–4 weeks of supplementation (New Zealand Formulary, 2018). However, completely restoring iron stores with a subsequent improvement in Hb and hematocrit usually takes around 4 months. For children with IDA, it is recommended that ferritin and reticulocyte response is checked four weeks after treatment is commenced (Melbourne TRCH, in press). As iron overload can be fatal in children, regular iron studies are necessary when high-dose therapy is used in pediatric patients (Melbourne TRCH, in press).

If the patient is managing iron deficiency through oral therapy, there are a number of reasons as to why they might not be responsive to therapy, as summarized in **Table 10**, which should be investigated to determine whether intravenous therapy is appropriate.

Table 10 Causes of non-responsiveness of iron status to iron therapy

Cause	*Notes*
Inadequate iron intake	• Patient not complying with supplementation. • Patient taking a supplement with insufficient iron concentration
Inadequate iron absorption.	• Intestinal disorders (e.g., celiac disease, inflammatory bowel disease) • Impaired gastric acid secretion • Gastric or intestinal bypass procedures • *Helicobacter pylori* persistence • Coexisting inflammation • Concomitant consumption of inhibitors of iron absorption
Ongoing iron losses or requirements that exceed the dose of supplementation or absorptive capacity	• Recurrent or undiagnosed gastrointestinal blood losses (e.g., malignancy, peptic ulcer) • Other sources of recurrent blood loss (e.g, menorrhagia, or inherited bleeding disorder)
Coexisting condition that interferes with bone marrow response to supplementation	• Concomitant vitamin B_{12} or folate deficiency • Coexisting bone marrow disease
Incorrect diagnosis of anemia	• Anemia of chronic disease or renal failure • Hemoglobinopathy

Once Hb and red cell indices have returned to a normal range, these parameters should be monitored at regular intervals. It has been recommended that iron status markers and full blood counts are taken monthly for the first 3 months, and then every 3 months for a year after Hb concentrations have returned to a normal range (Goddard et al., 2011).

Vitamin B_{12} Deficiency

There is no consensus regarding how the treatment effect of cobalamin supplementation should be monitored. Although patients may experience increased energy levels in the first 24 hours following treatment, the hematologic response will only begin several days later. It has been suggested that reticulocytes should be checked 1 week after treatment is initiated, Hb after 1–2 months, and mean corpuscular volume should have returned to normal by 8 weeks after intervention. Homocysteine and methylmalonic acid levels are expected to normalize during the first week of treatment, and if not this would suggest an incorrect diagnosis. Cobalamin and holo-transcobalamin measures are not informative as these will increase with cobalamin treatment, regardless of its therapeutic effectiveness (Carmel, 2008). Neurologic improvement should be observed within the first week and tends to be complete within 6–12 weeks, though this follows a less predictable course (Healton et al., 1991).

Follow-up every 1–3 years is suggested for all patients with an unknown cause or without hemodynamic compromise and should include clinical reevaluation in conjunction with cobalamin and methylmalonic acid or homocysteine assays (Carmel, 2008). Incomplete response to treatment should alert clinicians to consider other causes of anemia and/or neurological disease. Residual neurologic disability is estimated to affect 6% of patients with neurologic symptoms and is likely to persist if it still remains after 6–12 months of treatment (Healton et al., 1991).

Role of the Pharmacist in the Management of Nutritional Anemias

Role in the Health-Care Team

Pharmacists have the potential to play an essential role in the management of patients with anemia, as they have the expertise to take on the following roles:

1. *Initial screening of patients for iron/vitamin B_{12} deficiency or anemia and collection of clinical information.* It is essential for pharmacists to have a good understanding of the etiology, clinical signs and symptoms, course of disease, and management of anemia. When an individual begins to experience symptoms of fatigue and ill health, they will often first seek advice from a pharmacist on supplementation options. This provides the pharmacist with an ideal opportunity to look for early warning signs of anemia and make a timely referral to physicians as required. The pharmacist should consider the patient's duration of fatigue, previous history of nutrient deficiencies, lifestyle factors (questions regarding diet, work, or social stresses) medication, and supplement use in their collection of clinical information.
   Although pharmacists working in a general practice or in hospitals have access to patient health records, community pharmacists do not yet have this opportunity. Similarly, general practitioners do not have access to pharmacy records, and any medicines or over the counter supplements purchased by a patient at community pharmacies remain unknown. Providing community pharmacists access to patient records would allow them to check the relevant medical history and hematological results of customers who present to community pharmacists complaining of symptoms of fatigue. In turn, this could help prevent

inappropriate use of supplements, which as previously mentioned might mask or delay the treatment of underlying conditions, further delaying appropriate hematological investigation and management if symptoms are temporarily alleviated by an over the counter supplement.

2. *Referral if medical assistance or input from other health-care providers is required*. If a nutritional anemia or deficiency is suspected that requires further investigation to diagnose, patients should be promptly referred through to their medical provider with detail of relevant clinical information.
   However, depending on the primary care system in place, there are barriers for direct referral of patients between health professionals. For example, if a patient presents at a pharmacy with symptoms and a clinical history that would suggest benefit from a referral to a dietician that has not been acted upon by a physician, the pharmacist often has little option other than the traditional route of referral to the general practitioner first.
3. *Therapy regime management and modification*. Managing polypharmacy is where a pharmacist's expertise plays an essential role in the multidisciplinary approach to a patient's care. Their extensive pharmaceutical knowledge should contribute to considerations that take place regarding each patient's optimal medication regimen, particularly when comorbidities and polypharmacy are involved as clear clinical guidelines are not yet available for nutritional anemias.
   This would involve ensuring that medicines are used appropriately, and are stopped when no longer appropriate, and to consider opportunities for lifestyle changes or non-medical therapies.
4. *Taking lead in the development of guidelines for the management and monitoring of nutritional anemia or deficiency*.
   Pharmacists, alongside other health professionals, should advocate for and develop guidelines for the management of nutritional anemias. This is particularly important for subclinical nutritional deficiencies, as guidelines are currently unavailable, and early identification and treatment can either prevent later disease development if managed correctly or can have a detrimental effect if underlying conditions are masked.
5. *Simple dietary recommendations* Pharmacists should be able to provide simple information on how to improve dietary intake and/or bioavailability of iron and vitamin B_{12}. This should include rich sources of iron or vitamin B_{12} (please refer to nonpharmacological management section) and factors that might enhance (e.g., ascorbic acid) or inhibit (tannins in tea and coffee, oxalates, phytates) iron absorption. If the patient is interested in further dietary information, refer them to a registered dietician or nutritionist who can assist in tailored advice.

Counseling in Pharmacologic Management of Nutritional Anemias

Providing patient education has the potential to significantly improve patient outcomes through enhanced advocacy and compliance with treatment regimens. Pharmacists are encouraged to take adequate time to counsel their patients through face-to-face interviews and provide patients with educational brochures that summaries the information provided. Counseling should outline goals of Hb recovery, cover management of side effects, how to maximize absorption from their oral supplement, lifestyle modifications, and possible drug interactions.

This may be challenging for the pharmacist to thoroughly complete; however, as prescribing and management discussions are still routinely performed with their general practitioner or specialists in the case of nutritional anemias. Accordingly, pharmacists have more limited opportunities to see patients in a primary care setting as part of a practice team and direct contact with the patient is often brief, not always desired, and has little scope for a detailed consultation (Tarn et al., 2006).

Counseling in the Management of Iron Deficiency

Gastrointestinal Side Effects to Oral Iron Therapy

Oral iron supplementation is associated with a number of common gastrointestinal side effects, which pose a barrier to the adherence of oral iron therapy (Cancelo-Hidalgo et al., 2013). The pharmacist should take care to explain each of the possible side effects and provide advice on how to manage these symptoms. Gastrointestinal symptoms are often-dose related, and though there is little evidence to recommend a specific strategy, the approaches to improve compliance outlined in **Table 11** may be suggested by the pharmacist (Goddard et al., 2011; Lopez et al., 2016; Pasricha et al., 2010). Patients should also be advised to contact their general practitioner or specialist if symptoms persist.

Enhancing Absorption of Oral Iron Supplements

Pharmacists should counsel all patients on how to maximize absorption from their oral iron supplement. The following advice should be provided:

1. Avoid nutrient components that can reduce the absorption of iron (please refer to **Table 9** for details).
2. Take oral iron between meals
3. Bioavailability of iron is enhanced under acidic conditions, and supplements should be taken alongside a source of ascorbic acid (e.g., a glass of orange juice). Although ascorbic acid does enhance absorption, patients should be made aware that this does also increase the frequency of gastrointestinal side effects.

Table 11 Common gastrointestinal side effects to oral iron therapy and approaches to management of symptoms.

Side effect	*Approach to manage symptom*
Epigastric discomfort Flatulence and bloating Nausea and vomiting Black/green or tarry stools	1. Taking supplements with meals, though this will reduce absorption by up to 40%. 2. Taking the prescribed dose at bedtime 3. Dividing the total prescribed dose into smaller doses 2–3 times per day. Note this may require the use of a lower-dose iron preparation (e.g., ferrous sulfate liquid), as controlled release preparations should be swallowed whole. 4. Prescribing the lowest effective dose 5. Intermittent dosing schedules (e.g., from every second day to once weekly). 6. Changing oral preparations to a reduced dose of elemental iron (e.g., switching from ferrous sulfate to ferrous fumarate) 7. Slow release preparations are often recommended (however, there is inadequate evidence to support this strategy).
Black discoloration of teeth (liquid supplementation)	If liquid ferrous sulfate is prescribed, recommend patients to dilute the liquid preparation with water, drink this through a straw, and follow with a glass of water to reduce dental discoloration (Australian, in press)
Constipation	1. Prescribing the lowest effective dose of oral iron or prescribing an intermittent dosing regimen if constipation is dose-related. 2. Gradually increasing dietary fiber. Patients should be warned that this can initially increase abdominal distention and flatulence. 3. Gradually increasing fluid intake 4. Light physical exercise 5. Advising patients to attempt to defecate soon after waking and postprandially. 6. Soluble fiber supplements (e.g., Metamucil) or osmotic laxatives (e.g., Movicol) are often recommended to prevent iron-induced constipation; however, it should be noted that these may require adequate dietary fiber intake in order to be effective and should therefore be used with caution

Drug Interactions

Oral iron supplementation can reduce the absorption of other medicines, and patients should be advised to take the following preparations at least two hours apart from oral iron supplements (Baird-Gunning and Bromley, 2016);

1. Tetracyclines (e.g., doxycycline, minocycline)
2. Quinolones (e.g., ciprofloxacin, moxifloxacin, norfloxacin)
3. Antacids containing aluminum, magnesium, and calcium.
4. Calcium supplements and calcium-rich foods (milk and other dairy products)

Administration of iron should also be spaced apart from drugs that might reduce its absorption, including oral bisphosphonates, levodopa, carbidopa, methyldopa, and thyroid hormones. An increase in gastric pH will also reduce the absorption of oral iron, which should be considered when a patient is prescribed proton pump inhibitors and antacids (Baird-Gunning and Bromley, 2016). Oral zinc and iron products have been shown to reduce each other's relative bioavailability (Lynskey and Machin, 2012).

Counseling in the Management of Vitamin B_{12} Deficiency

A common misuse of cobalamin is as a cure for fatigue and other nonspecific symptoms. Education of the patient around use of cobalamin supplements helps to prevent patients from ceasing treatment once they achieve symptomatic improvement, which typically precedes adequate hematological improvement.

Drug Interactions

Vitamin B_{12} supplements have the potential to interact with certain medications, while some medications might negatively affect an individual's vitamin B_{12} status. Some common examples are provided below, and patients should be advised on these as appropriate:

1. Proton pump inhibitors—interfere with vitamin B_{12} absorption from food by slowing the release of gastric acid into the stomach (Howden, 2000).
2. H2 receptor antagonists—interfere with vitamin B_{12} from food by slowing the release of hydrochloric acid into the stomach (Force and Nahata, 1992).
3. Metformin—may reduce the absorption of vitamin B_{12} through a number of mechanisms (Buvat, 2004).

Advances in the Management of Nutritional Anemias

Therapeutic Advances

There is ongoing research in the development of new therapeutic strategies for the treatment of nutritional anemias, and pharmacists with active research roles have a critical role in this. Pharmacists should be involved in leading the decision of how to implement

these into guidelines, and close collaboration is required between scientists, clinical investigators, and health professionals to deliver optimal therapies to the greatest number of patients worldwide.

An example of this is the discovery of the potential to target the hepcidin-ferroportin system as a therapeutic strategy. Ferroportin is a membrane transporter that stimulates the uptake of iron by intestinal epithelial cells and the egress of iron from macrophage. Hepcidin is a small peptide secreted by the liver and binds ferroportin to stimulate its degradation, leading to reduced intestinal absorption of iron and subsequent accumulation within the reticuloendothelial system. Downregulating hepcidin in patients with IDA could enhance uptake of iron and its release from reticuloendolothelial stores (Ganz and Nemeth, 2011; Sankaran and Weiss, 2015). Although hepcidin is not upregulated in all cases of IDA as it is in anemia of inflammation or anemia of chronic disease, patients presenting with these concomitant conditions may also benefit from such treatment, though this would require accurate investigation into the underlying cause of patients with IDA, and further research to determine the benefit of this therapeutic strategy in patients where chronic disease or inflammation is not the primary cause of anemia. There have been different approaches to target various regulatory steps of the hepcidin pathway in an attempt to pharmacologically control its expression. This includes hepcidin-sequestering agents (antibodies, anticalins, and aptamers), inhibitors of the BMP/SMAD or IL-6/STAT3 pathways, inhibitors of hepcidin transduction, or ferroportin stabilizers (Poli et al., 2014; Sun et al., 2012).

Liposomal oral iron preparations may provide relief to gastrointestinal side effects in the future and are under evaluation. These preparations consist of iron encased in a phospholipid coat containing ascorbic acid and prevent direct contact between the intestinal mucosa and iron (Pisani et al., 2015).

Pharmacy-Managed Clinics

There is an opportunity for better integration of the pharmacist in the management of patients with nutritional anemias in the setting of a pharmacist-managed clinic (PMC), which is an example of effective pharmacist–physician collaborative practice. These have been shown to improve patient outcomes across a range of clinical settings worldwide, and beneficial effects have consistently been reported with respect to cost-effectiveness, patient adherence to and knowledge about pharmacotherapy, and therapeutic outcomes (Aspinall et al., 2012; Snider et al., 2012; Vivian, 2002; Wallgren et al., 2012). Accordingly, PMCs have emerged as models that provide superior patient outcomes and are also associated with a reduced economic burden to primary health care (Armor et al., 2010; Gupta et al., 2015).

Recent studies have investigated the effect of clinical pharmacists actively managing outpatients with renal anemia, and it was found that having pharmacists actively involved was associated with improved therapeutic outcomes (Ohnishi et al., 2011). Following this, a randomized control trial was recently conducted in Jordan, where the role of clinical pharmacists in the management of adult patients diagnosed with IDA was investigated in an outpatient setting. It was found that having the input of clinical pharmacists improved these patients' outcomes. This improvement related to a number of interventions from the pharmacist, including patient counseling, which was conducted face to face in private and in simple layman's language, the provision of pamphlets to simplify this educational material and to assist in remembering instructions, good rapport was also developed between patients and clinical pharmacists where patients were able to ask diverse questions about drug information, patients were also able to call the clinical pharmacist and ask any questions they might have relating to IDA, drug interactions, laboratory tests, or the date of follow-up visits. From the perspective of the clinical pharmacist, an improvement in patients' knowledge of IDA and the importance of therapy was observed, which translated to increased compliance with therapy. As patients were comfortable with providing information to their pharmacist, pharmacists were then able to better recommend individualized iron therapy regimens. A high proportion of the pharmacist's recommendations were then accepted by physicians due to the collaborative relationship that had been built, and physicians were able to ask drug information questions relating to IDA and other medications and conditions. These collaborative relationships lead to positive clinical outcomes with respect to the patient's health status, with three new cases of coeliac disease diagnosed. This study highlights the importance of the clinical pharmacist's role in outpatient settings for the treatment of IDA and the benefit of physician–pharmacist collaborations (Tahaineh and Khasawneh, 2018).

Although further research in this field is required, it is foreseeable that clinical pharmacists will have a more closely integrated role in the collaborative care of outpatients with nutritional anemias, particularly in the primary care setting, with ongoing monitoring and dynamic treatment strategies provided by the pharmacist. The development and implementation of pharmacist-managed anemia programs is predicted to lead to enhanced patient awareness and education, alongside close monitoring and evaluation of the efficacy of treatment, translating to improved clinical outcomes for the patient, as well as helping to relieve the heavy burden on physicians in the primary setting through better use of other health professionals. However, further education of pharmacists would be required, with possible change in the delivery of curriculum if such models are to have widespread implementation in the future. Clear guidelines would need to be in place for PMCs, which could be universally adapted across various clinical settings. Guidelines should include the purpose, background, required knowledge and skills of pharmacists, the pharmacist's roles, the steps in patient education and counseling process, content, and documentation.

Intravenous Therapy

In more recent years, there has been an increasing use of intravenous therapies in the community. For example, iron carboxymaltose has been made available for dispense in the community by PHARMAC in New Zealand, and infusion can be performed in general practice clinics rather than hospital inpatient or outpatient settings. Wider implementation of this has the potential to positively affect hospital services as there would be a reduced hospital pharmaceutical expenditure and demand on hospital

infusion clinics, while also allowing the patient to receive therapy closer to their homes (Pharmac, 2017). However, this does require a concerted effort between hospital and community physicians and pharmacists to ensure that such programs are rolled out effectively.

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Clinical Pharmacy Considerations in Special Population: Drug Dose Adjustment in Hepatic Impairment

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Learning Objectives

- Describe the pathophysiology of liver disease and how to assess the severity of liver disease.
- Understand the pharmacokinetic alterations in patients with chronic liver disease with respect to medication use.
- Understand the pharmacodynamic alterations in patients with chronic liver disease with respect to medication use.
- Provide a clinical perspective on dosage adjustment and medication use in hepatic impairment.

Introduction

The liver plays a major role in medication absorption, distribution, metabolism, and clearance. In clinical practice, both the pharmacokinetic and the pharmacodynamic properties of medications are equally important. This chapter aims to outline some pharmacokinetic principles related to medication dosing, pharmacodynamic considerations of medication use, and some general principles of medication dosing in liver disease.

Pathophysiology of Liver Disease

Liver disease can be acute or chronic in nature. Chronic liver disease will lead to cirrhosis and portal hypertension, and in this group of patients, medication dosing adjustment is of more relevance (Lewis and Stine, 2013). The common etiologies of chronic liver disease can be numerous: alcoholic liver disease, nonalcoholic fatty liver disease, viral hepatitis, and rarer forms including hereditary diseases such as Wilson's disease.

Dosing adjustment of medications is required in liver cirrhosis, due to an array of pathophysiological changes in the liver that may influence medication pharmacokinetics (Le Couteur et al., 2005). Cirrhosis is a process whereby the normal liver parenchyma is converted to abnormal nodules, leading to a reduction in hepatic blood flow. These changes lead to the development of portal hypertension and reduction in the number and activity of the functional cells of the liver (hepatocytes) (Le Couteur et al., 2005). Ultimately, this will cause the manifestation of several complications including esophageal varices, variceal bleeding, ascites, encephalopathy, and hepatorenal syndrome, which all contribute to changes in the pharmacokinetic parameters and pharmacodynamic effects of medications. Cholestasis also occurs as a consequence of liver disease, where there is impairment in the secretion of bilirubin due to intrahepatic and extrahepatic processes that lead to the development of lesions in the biliary tract (Zollner and Trauner, 2008). Liver cirrhosis can affect multiple organs—most notably the kidneys, resulting in hepatorenal syndrome. This causes severely impaired renal function, in which medication doses will require adjustments for renal impairment in addition to hepatic impairment.

Assessing Liver Function

The term liver function test (LFT) is a misnomer. The best indices of impaired hepatic metabolic capacity are elevated bilirubin, low serum albumin, and coagulopathy (raised international normalized ratio, prothrombin time or ratio) (Bollinger, 2017). This impairment reflects in the function of the liver to synthesize protein, coagulation factors, and the ability to metabolize medications. An elevated non-differentiated serum bilirubin may indicate hemolysis and/or cholestasis. The presence of cholestasis may indicate impaired elimination of medication excreted into the bile ducts (Limdi and Hyde, 2003). The liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST) may indicate hepatocyte injury but have limited use for medication dosing in hepatic impairment (Limdi and Hyde, 2003). Unlike serum creatinine for renal function, there is no single biochemistry marker available to measure liver function.

There are two commonly used liver disease classification scores to assess the severity of liver disease: the Child-Turcotte-Pugh (Child-Pugh) score and the Model for End-Stage Liver Disease (MELD) score. The Child-Pugh score has been used to estimate the prognosis of patients with liver cirrhosis. The parameters included in the scoring include serum concentrations of bilirubin, albumin, the prothrombin time, and the presence of hepatic encephalopathy and ascites (Pugh et al., 1973). The MELD score was intended to gauge prognosis of patients awaiting liver transplantation. This score may be more accurate in assessing severity of liver disease, as it only takes into account objective biochemical markers as opposed to potentially subjective assessments of encephalopathy and ascites (Malinchoc et al., 2000).

In reality, pharmaceutical manufacturers often use the Child-Pugh score to make dose adjustment recommendations in patients with liver disease. However, the reasons for this preference are unclear. The recommendations are usually conservative and are likely based on pharmacokinetic modeling instead of real-world patient based data. Thus, it is critical for the pharmacist to use their clinical judgment and advise the treatment team on how best to manage the patient's medications, in the context of their liver disease.

Pharmacokinetic Alterations in Chronic Liver Disease and Considerations in Medications Use

Hepatic Clearance

In clinical practice, the use of hepatic clearance is impractical and very time consuming to offer significant benefit. Moreover, hepatic extraction of medications is not a pharmacokinetic parameter that is readily available in common and easily accessible references. Thus, this chapter will only introduce the key equations and the underlining principles in relation to alterations in pharmacokinetics. Hepatic extraction is how efficient the liver is at eliminating a medication, depending on blood flow (Johnson and Thomson, 2008).

Hepatic clearance (CL_H) is defined as the volume of blood from which medication is removed completely by the liver per unit time. It is thus a function of hepatic blood flow (Q_H) and the hepatic extraction ratio (E_H) of the medication (Johnson and Thomson, 2008):

$$CL_H = Q_H \times E_H$$

Since E_H also depends on liver blood flow, the intrinsic clearance of the unbound medication (CL_{int}), and the fraction of the unbound medication in the blood (fu), the following important equation for CL_H can be derived:

$$CL_H = Q_H \times \frac{fu \times CL_{int}}{Q_H + fu \times CL_{int}}$$

This equation is based on a pharmacokinetic model most frequently used to describe the relationship between hepatic medication clearance and the three primary determinants of hepatic elimination: blood flow, medication binding in the blood, and the intrinsic clearance (activity of enzymes and transporters) (Johnson and Thomson, 2008). Medications can be categorized according

to how efficiently the substance is removed from the circulation by the liver via the extraction ratio. There are three categories for the extraction ratio:

1. High extraction ratio ($E_H > 0.7$)
2. Low extraction ratio ($E_H < 0.3$)
3. Intermediate extraction ratio ($0.3 < E_H < 0.7$)

In clinical practice, these equations may be of limited use, but their implications in medication dosing needs to be appreciated. The hepatic clearance of highly extracted medications approaches and becomes limited by liver blood flow:

$$E_H > 0.7, \text{ i.e., } Q_H \ll fu \cdot CL_{int} \rightarrow CL_H \cong Q_H$$

This means that these medications are so well metabolized, that there is a lower oral bioavailability. Note that there is little difference in intrinsic clearance between healthy and diseased individuals, irrespective of the enzymatic and transporter capacity activity of the liver (i.e., CL_{int}) (Verbeeck, 2008). This is because secondary diseases from portal hypertension (such as esophageal varices and portosystemic shunting) have the most impact on the clearance of orally administered medications. Therefore, this would mean that these medications would bypass "first-pass" metabolism. A common example of this in practice is the dosing of morphine with a hepatic extraction of 0.76 (Delcò et al., 2005), which is considered as a highly extractable medication. In liver cirrhosis, the oral bioavailability of morphine can be increased to 100% from around 50% in normal patients (Hasselström et al., 1990). The dose should be conservative (at least half of the normal dose), due to its many-fold increase in oral bioavailability. Therefore, the dose will need to be titrated carefully as per individual patient response. The potential for adverse effects will be elevated due to the increased risk of accumulation. This may lead to constipation and sedation, both of which can precipitate and exacerbate hepatic encephalopathy (Lewis and Stine, 2013). The starting and maintenance dose of these highly extractable medications should be reduced.

On the other hand, medications may be poorly extracted and their hepatic clearance is mainly affected by intrinsic hepatic clearance:

$$E_H < 0.3, \text{ i.e., } Q_H \gg fu \cdot CL_{int} \rightarrow CL_H \cong fu \cdot CL_{int}$$

These medications have a low extraction ratio and tend to have higher oral bioavailability (≥70%) as they are not extensively metabolized by the liver. The clearance of these medications is more reliant on the activities of enzymes and transporters such as cytochrome P450 (CYP450) enzymes. However, these medications are less affected by liver cirrhosis as they already have a relatively high oral availability and do not depend on hepatic blood flow, which means the presence of portosystemic shunts is unlikely to affect these medications (Delcò et al., 2005). Therefore, medications with a low extraction ratio can generally be started at a normal dose if a rapid response is required, while their maintenance dose should be reduced.

The last class of medications is those with intermediate extraction ratios of between 30% and 70% (e.g., calcium channel blockers, statins and amiodarone). Clearance is both determined by blood flow across the liver and intrinsic clearance. Thus, both the maintenance dose and the starting dose should be at the lower range of normal.

In summary, it is generally accepted in clinical practice that medications with a high extraction ratio or low oral bioavailability, should have their starting dose reduced by half, while medications that have a low extraction ratio or high oral bioavailability should have their starting dose reduced by a quarter. See **Table 1** for some examples of drugs with high and low extraction ratios (Sloss and Kubler, 2009).

Absorption

Gastrointestinal dysfunction has often been observed in patients with liver disease and in particular those with cirrhosis. It has been shown that cirrhotic patients have delayed gastric emptying (Chander et al., 2013; Kalaitzakis, 2014). In clinical practice, it is recommended to avoid slow release or modified release preparations in this group of patients. The use of modified release medications in these patients would likely lead to further delay in medication release, causing difficulty in predicting response and potential toxicity.

Table 1 Examples of medications with high and low extraction ratios (Sloss and Kubler, 2009)

High extraction ratio medications	*Low extraction ratio medications*
Antipsychotics, e.g., haloperidol	NSAIDs
Calcium channel blockers	Warfarin
Morphine	Paracetamol
Antidepressants	Phenytoin
Beta-blockers (some), e.g., propranolol	Amiodarone

Table 2 Bioavailability of certain medications in non-cirrhotic patients compared with patients with cirrhosis

Medication	*Bioavailability in non-cirrhotic subjects*	*Bioavailability in cirrhotic subjects*	*Fold increase*	*Reference*
Carvedilol	0.19	0.83	4.4	Neugebauer et al. (1988)
Labetalol	0.33	0.63	1.9	Homeida et al. (1978)
Metoprolol	0.50	0.84	1.7	Regårdh et al. (1981)
Midazolam	0.38	0.76	2.0	Pentikainen et al. (1989)
Morphine	0.47	1.00	2.1	Hasselström et al. (1990)
Propranolol	0.36	0.60	1.7	Branch et al. (1977)

As suggested above, the bioavailability of many medications will be elevated in hepatic impairment. This increase is a result of changes in hemodynamics, such as portosystemic shunting due to portal hypertension. This will cause the flow-limited medications to have a reduced clearance leading to a significant increase in serum level. Transjugular intrahepatic portosystemic shunt (TIPS) can be used for the management of complications related to cirrhosis. This is a nonselective portosystemic shunt aimed at reducing portal hypertension. It minimizes the risk of variceal bleed and recurrence of ascites. The presence of TIPS can substantially elevate the oral bioavailability of flow-dependent medications such as midazolam (Chalasani et al., 2001). This allows the medication to bypass presystemic hepatic first-pass metabolism, which is a major determinant of oral bioavailability. See **Table 2** for some examples of changes in oral bioavailability of medications between non-cirrhotic patients and patients with cirrhosis.

Medication Distribution

Ascites and edema are common complications of liver cirrhosis and this will increase the volume of distribution for hydrophilic medications. Consequently, the loading dose of a medication may need to be increased for a rapid effect to be observed (Delcò et al., 2005). Edema and ascites do not affect the elimination of medications, so the maintenance dose should not require alteration (Delauter et al., 2000). However, the protein binding profile of medications may affect distribution around the body. A low level of albumin may increase distribution and the free serum level of medications (Delcò et al., 2005). Medications with a high protein binding profile (>90%) and a narrow therapeutic index (e.g., phenytoin), should be monitored for their free serum level to minimize risks of toxicity.

Renal Dysfunction in Liver Disease

A large number of medications are primarily excreted via the kidneys. Therefore, renal function must also be evaluated to determine medication dosing. It is difficult to evaluate renal function in patients with cirrhosis, since their serum creatinine poorly represents renal function. This is due to a poor nutritional status resulting in muscle atrophy, impaired synthesis of creatine, and the dilutional effect of edema and ascites on serum creatinine (Figueiredo et al., 2000). A study was published by Francoz et al. (2014) comparing various methods of calculating renal function to actual measured renal function in patients with liver disease. The paper examined the following methods of calculating renal function: Cockcroft-Gault, Modified Diet in Renal Disease-4 (MDRD-4), MDRD-6, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). It showed that most methods of calculating renal function tended to overestimate the glomerular filtration rate (GFR) by as much as 25 mL/min. The most accurately calculated GFR was via the MDRD-6 method. It provided the truest estimate of renal function in a patient with liver disease (Francoz et al., 2014). Ideally, if hospital resources are available, all patients on the waiting list for liver transplant should have a measured renal function. This will enable optimal dosing of medications that are primarily eliminated renally, thereby minimizing the risk of toxicity.

Metabolism

Medication metabolism mainly occurs via the liver through enzymatic activities of the sinusoidal and canalicular transporters (Liu and Pang, 2005; Pang et al., 2009). This determines the important parameter of hepatic intrinsic clearance (CL_{int}). Medication metabolism usually involves two phases in the liver. The first phase involves reactions such as hydrolysis, oxidation, and reduction. These reactions are reliant on the CYP450 class of enzymes. The second phase involves the attachment of molecules, via glucuronidation and acetylation. Besides inactivation of medication, changes in metabolism will affect "pro-drugs." "Pro-drugs" are medications that require metabolism to be active, and some are heavily reliant on the CYP450 enzymes. In patients with liver disease, these medications will have a decrease in effect due to failure to convert to active metabolites (e.g., codeine conversion to morphine).

In chronic liver disease, there is a decrease in enzymatic activity and hence, metabolism of medications. This is related to a loss of hepatocytes and impaired function of existing cells. In a study by Frye et al. (2006), a validated cocktail approach was used to study the effect of liver disease on multiple CYP450 enzymes. It was shown that the CYP450 enzymes had a progressive

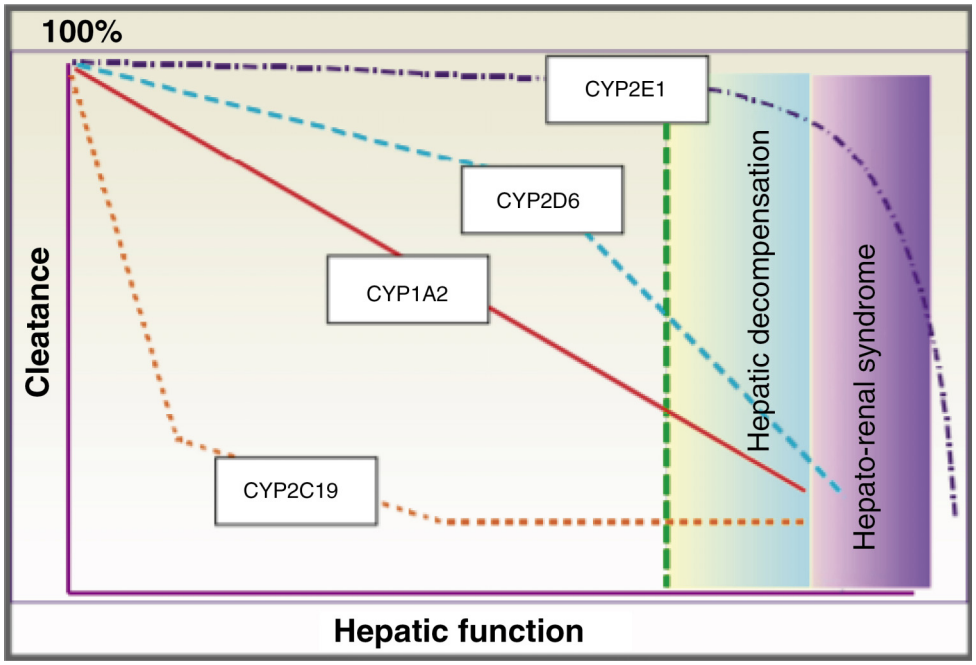

Figure 1 Sequential progressive model of hepatic dysfunction. The ordinate shows how plasma clearance, starting at 100% when hepatic function is normal, decreases for substances eliminated predominately by metabolism via individual CYP450 isoforms in the liver. *Source: Reprinted with permission from the American Society for Clinical Pharmacology and Therapeutic from Frye, R.F., Zgheib, N.K., Matzke, G.R., Chaves-Gnecco, D., Rabinovitz, M., Shaikh, O.S., Branch, R.A., 2006. Liver disease selectively modulates cytochrome P450—mediated metabolism. Clin. Pharmacol. Ther. 80 (3), 235–245.*

nonuniform reduction in activity (Frye et al., 2006). The authors proposed that a "sequential progressive model of hepatic dysfunction" may better quantify the loss in activity of liver enzymes with respect to the severity of liver disease (Fig. 1). According to this model:

- CYP2E1 activity is maintained mostly throughout the liver disease until decompensation and end-stage.
- CYP2D6 and CYP1A2 have a more gradual decline over the course of the disease with CYP2D6 showing more resilience earlier on in the progression of liver disease.
- CYP2C19 appears to sharply decline at the earlier stages of chronic liver disease.

The largest subset of the CYP450 enzymes is the CYP3A family. They are the main enzymes responsible for metabolizing more than 50% of medications commonly prescribed (Verbeeck, 2008). In a clinical study involving midazolam as a CYP3A probe, it was shown that the activity of CYP3A activity decreases with the severity of liver disease (Albarmawi et al., 2014). The authors demonstrated that patients with Child-Pugh Class A had similar midazolam clearance as the control group (non-cirrhotic patients). Conversely, compared to the control group, the clearance in patients with Child-Pugh Class B was decreased to 23% and only 14% in those with class C. This study demonstrates that CYP3A enzyme metabolism decreased with the severity of live disease. There was also a good correlation of results between using the Child-Pugh and MELD scores which suggests that either scores can be used interchangeably as a marker for metabolic CYP3A capacity (Albarmawi et al., 2014). Finally, phase two reactions such as glucuronidation have conflicting data on how they are affected in liver disease. It is generally accepted that medications that only depend on phase two reactions remain largely unaffected and are preferred in patients with liver disease (Lewis and Stine, 2013). Examples include mycophenolate, lorazepam, and lamotrigine (Marcellin et al., 2001; Parker et al., 1996).

Pharmacokinetic-Related Cases

PK Case 1

A 45-year-old female patient with a history of liver cirrhosis due to chronic alcoholism was admitted to the hospital with refractory ascites. Her biochemistry was mostly unremarkable, except mild hyponatremia that was thought to likely be due to dilutional effects of ascites. TIPS was decided as an appropriate procedure to manage her ascites.

- Patient current medications include: spironolactone 400 mg daily, furosemide 80 mg twice daily, and carvedilol 6.25 mg twice daily.
- Postoperatively, the patient was prescribed oral morphine 10 mg as required every 4 h for pain and regular paracetamol.

Commentary/expert opinion

TIPS is a nonspecific shunt to alleviate portal pressure. Once inserted, medications would bypass first-pass metabolism and greatly increase in bioavailability (Chalasani et al., 2001). As per **Table 1**, morphine bioavailability will effectively double, so starting dose should be half of normal.

There are two important tasks that the pharmacist must complete in this case. The first is to calculate the GFR in a patient with cirrhosis using the MDRD-6 equation and consider if morphine is appropriate since morphine elimination is heavily dependent on renal function (Micromedex, 2018). Second, if the patient has adequate renal function, the clinical pharmacist should recommend changes to the oral morphine dose to be 5 mg as required every 4 h and titrate as needed. However, if morphine was deemed inappropriate (poor renal function) and opioids are still required, fentanyl is preferred due to its shorter half-life and inactive metabolites, thereby minimizing the chance of accumulation (Lewis and Stine, 2013). Regarding her other medications, carvedilol bioavailability may also increase due to bypassing first pass metabolism (see **Table 2**). Her diuretic oral bioavailability is unlikely to change. However, once TIPS has been inserted, portal pressure should normalize and her ascites should resolve over time. Thus, the need for continuing her carvedilol and diuretics should be reviewed.

PK Case 2

Patient with liver cirrhosis on ribavirin for the treatment of hepatitis E was admitted to the hospital with a myocardial infarction requiring percutaneous coronary intervention with stenting. In view of elevated prothrombin ratio (1.3), cardiology team started the patient on clopidogrel instead of ticagrelor, with aspirin. As the clinical pharmacist you have been asked to review the patient.

Commentary/expert opinion

First, identify that clopidogrel is a "pro-drug" and is activated via the CYP450 enzymes. CYP2C19 plays a key role in the biotransformation of clopidogrel to its active form (Micromedex, 2018). As per **Fig. 1**, CYP2C19 has a steep decline in its metabolizing function at the earliest stages of liver cirrhosis, which means it is unlikely that the patient will receive an effective dose of clopidogrel, thereby increasing the risk of stent thrombosis. Ticagrelor, however, is not reliant on biotransformation to be active but produces an active metabolite via CYP3A4-3A5 (Micromedex, 2018). Thus, it would produce a more reliable antiplatelet effect compared to clopidogrel. The clinical pharmacist should involve the treatment team to weigh up the increased bleeding risk and stent thrombosis, which may lead to another episode of myocardial infarction.

PK Case 3

A patient was admitted to the hospital due to acute alcoholic hepatitis, with a history of alcoholic cirrhosis and is started on the alcohol withdrawal scale. The patient has deranged LFTs with a gamma-glutamyl transferase (GGT) of more than 4 times the upper limit. The medical team started the patients on diazepam for withdrawal.

Commentary/expert opinion

As the clinical pharmacist, you should first assess the severity of the patient's liver disease and confirm that the liver is cirrhotic from past medical histories. Once confirmed, the use of diazepam should be queried given that diazepam has a long half-life and is metabolized by CYP3A4 to active metabolites (Micromedex, 2018). Diazepam metabolism in a patient with cirrhosis will be significantly impaired as per previous discussions, depending on the severity of the patient's liver disease, extending the half-life of diazepam and its metabolites. So an alternative benzodiazepine that is metabolized via an alternative pathway and produce inactive metabolites should be considered. Lorazepam and oxazepam should be considered as alternatives, given that both are metabolized via phase two reactions (glucuronidation) and produce inactive metabolites (Lewis and Stine, 2013). Other considerations that the pharmacist should have are the dose conversion between diazepam to either lorazepam or oxazepam, and the particular withdrawal scale tailored to the severity of the signs of withdrawal.

Understand the Pharmacodynamic Alterations in Chronic Liver Disease Patients with Respect to Medication Use

Sedatives and Opioids

Patients with chronic liver disease are more sensitive to the effects of sedatives, anxiolytics, and opioids. Various mechanisms have been proposed: greater permeability of the blood-brain barrier, increased GABAergic tone and increased number of GABA receptors (Caputo et al., 2011). Both sedatives and opioids may precipitate hepatic encephalopathy and subsequent liver decompensation. Opioids may further contribute to decompensation by causing constipation. This will then impair the excretion of toxins, which may lead to the development and worsening of encephalopathy (Verbeeck, 2008). It is recommended to wean off all chronic sedatives, especially benzodiazepines (when possible). Further sedatives should be avoided in the future. Prior to prescribing and administering opioids and sedatives, the presence of hepatic encephalopathy must be excluded.

It is important that the clinical pharmacist is aware of the symptoms of hepatic encephalopathy and liver decompensation. Insomnia is a possible consequence of mild to moderate hepatic encephalopathy and the use of sedatives would only cause further deterioration, while being ineffective in treating insomnia (Ferenci, 2018). The clinical pharmacist should also be aware of agents traditionally not considered to be sedatives, but may still have sedating and central nervous system effects. Such medications include

the phenothiazine class of medications and antiemetics such as cyclizine, which can be sedating and constipating. It is best to avoid these classes of medications or use sparingly in patients with liver disease.

Nephrotoxics and Antihypertensives

These include the likes of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), alpha blockers, nonselective beta blockers, and nonsteroidal anti-inflammatory medications (NSAID). Diuretics, including loop diuretics and aldosterone antagonists such as spironolactone, are common therapies in patients with liver disease for the management of ascites. However, the use of these agents should still be closely monitored to minimize the risk of hypotension and kidney injury as these medications will decrease intravascular volume. The risks and benefits of continuing diuretics should be weighed against the need for ongoing paracentesis for the management of ascites.

Both the American and European international guidelines on the management of ascites recommend caution with the use of ACEI and ARB in patients with ascites and cirrhosis (EASL, 2010; Runyon and AASLD, 2009). The main blood pressure support in a cirrhotic patient is mediated by the renin-angiotensin-aldosterone system and is activated to maintain blood pressure and autoregulate renal perfusion (Vlachogiannakos et al., 2001). Thus, if an ACEI is on board, patients will be at risk of experiencing severe hypotension and deterioration in renal function. The European guideline has suggested the avoidance of alpha-blockers in patients with ascites which have been shown to increase sodium and water retention (EASL, 2010).

Evidence from observational studies have shown that nonselective beta-blockers should be avoided in patients with recurrent ascites (Sersté et al., 2010) and spontaneous bacterial peritonitis (Mandorfer et al., 2014). The beta blocker would likely cause hypotension and decrease in renal perfusion, leading to increased patient mortality. Thus, nonselective beta blockers should be used with caution in selected patients. The current American and European guidelines predate the observational studies and thus have not incorporated them into their recommendations. However, many centers have adopted the recommendation into their usual practice.

NSAIDs should be avoided in patients with cirrhosis as they increase sodium retention and further vasoconstrict afferent arterioles in the nephrons. This causes deleterious effects on renal function and ascites (EASL, 2010; Runyon and AASLD, 2009). NSAIDs should also be avoided in patients with esophageal varices. NSAIDs can affect platelet aggregation leading to bleeding and rupture of varices that may be life threatening (Yoshida et al., 2013).

Pharmacodynamic-Related Cases

PD Case 1

The general medicine house officer has started oral tramadol at 100 mg every 6 h for a patient complaining of nonspecific pain, admitted with mild alcoholic hepatitis. The patient is a chronic alcoholic with liver cirrhosis. The patient biochemistry results are all normal with an albumin of 32 g/L, slightly elevated bilirubin (68 μmol/L) and INR 1.6. There are no signs of encephalopathy.

Commentary/expert opinion

In this case, the pharmacist should question whether tramadol is an inappropriate agent to be used at this stage of alcoholic hepatitis, given that the patient may be withdrawing from alcohol. The patient will be at risk of seizures and tramadol may further lower the seizure threshold. The dose of tramadol in the context of liver disease should also be queried. Depending on the resources available, the starting dose for immediate-release tramadol may vary between 25 and 50 mg every 6 h to every 12 h (Lewis and Stine, 2013). Thus, the starting dose should be decreased to 50 mg. The main monitoring required for tramadol is nausea, constipation, changes in mental state, and sedation.

The clinical pharmacist should also have an understanding on how liver cirrhosis affects how tramadol act. Tramadol is extensively metabolized in the liver via CYP2D6 producing O-desmethyl-tramadol which is the main metabolite responsible for tramadol's opioid activity (Micromedex, 2018). Tramadol itself is more responsible for the neurochemical effects on serotonin and noradrenaline receptors. As per **Fig. 1**, CYP2D6 decreases in function with worsening of liver disease. Thus, in liver cirrhosis, tramadol may have a reduced opioid effect with an increased serotonergic and noradrenergic effects due to reuptake inhibition, similar to that of venlafaxine—an antidepressant (Reeves and Cox, 2008).

PD Case 2

A patient was admitted with acute hepatitis due to hepatitis B virus, with mild encephalopathy—receiving treatment with lactulose. The patient has developed intractable nausea and is unable to maintain daily intake of nutrition. In addition, the patient received both intravenous ondansetron and metoclopramide with little improvement.

Commentary/expert opinion

There are a limited number of options to use for the treatment of intractable nausea due to local hospital restrictions, with remaining therapies including dexamethasone, droperidol, and chlorpromazine. It is up to the clinical pharmacist to decide which of the remainder is appropriate for this patient. They must weigh up how the medication may interact with patient's liver disease and treating the nausea. Dexamethasone, in this case would be contraindicated, since it would further suppress the immune system and

allow breakthrough proliferation of the hepatitis B virus as we are attempting to suppress viral replication via oral treatment (Reddy et al., 2015). Chlorpromazine has a wide range of activities targeting multiple receptors that mediate vomiting response. It is however, anticholinergic and histaminergic causing sedative effects. These central acting effects will likely worsen encephalopathy and thus should be avoided (Lexicomp, 2018).

Droperidol would be the agent of choice in this case even though it is centrally acting due to its dopamine antagonism in the chemoreceptor trigger zone (Sandoz, 2010). Droperidol does not have anticholinergic effect, thus it has less chance of precipitating encephalopathy. The usual dose for droperidol would be 0.625–1.25 mg up to every 6 h; but given the acute liver decompensation and droperidol being extensively metabolized by the liver, it would be advisable to start with half the usual dose at 0.3125 mg every 6 h.

PD Case 3

A patient was admitted to the hospital with sepsis likely due to spontaneous bacterial peritonitis (SBP) and was started on empiric therapy of intravenous cephalosporin. Patient continued to be febrile after 24 h, and the team considered adding in an aminoglycoside to broaden the antimicrobial coverage. The patient currently has signs of decompensation, including encephalopathy and ascites. However, patient's biochemistry is mostly unremarkable, with normal serum creatinine but low albumin, and deranged LFTs of three times the upper limit.

Commentary/expert opinion

In this case, the clinical pharmacist needs to appreciate the degree of decompensation. It is likely that the normal serum creatinine is unlikely to reflect the patient's true normal renal function and that other parameters such as urine output and serum urea should also be assessed. A number of factors mentioned above may contribute to this uncertainty such as dilution due to ascites and likely decreased perfusion due to refractory ascites (Francoz et al., 2014). Thus, the patient would be at high risk of acute kidney injury and nephrotoxic effects of aminoglycoside (Molitoris, 2018). The clinical pharmacist should advise an alternative antibiotic that is less nephrotoxic and would provide similar antimicrobial coverage to aminoglycosides depending on regional microbial sensitivity.

A Clinical Perspective on Dosage Adjustment and Medication Use in Hepatic Impairment

In general, rarely, do manufacturer data sheets provide clear guidance on dosage adjustment in varying severities of liver disease (Spray et al., 2007). Most references would only provide general guidance in nonspecific hepatic impairment, without considering the differences between non-cirrhotic and cirrhotic patients. The severity of cirrhosis (MELD or Child-Pugh scores) is not usually taken into consideration. However, in the event that a medication data sheet does offer clear dosing guidance in the context of liver disease, this would be a good starting point.

As a clinical pharmacist reviewing patients' medication therapy, there are a few main points to consider:

- The pharmacist should elicit a clear history of the patient's liver disease, including the presence and severity of cirrhosis and portal hypertension.
- The pharmacist should independently evaluate the severity of the patient's cirrhosis, by calculating the MELD or Child-Pugh score to estimate the impairment of hepatic clearance of medications.

Portal hypertension would normally indicate the presence of varices, which leads to medication bypassing first pass metabolism. Note that if patients only have LFT derangement with no history of cirrhosis, then medication adjustment is not necessary, although the pharmacist will need to investigate if the LFT derangement is caused by the medications due to hepatotoxicity.

In a patient with an acute worsening of liver cirrhosis, for example, when the patient deteriorates to category B from A based on Child-Pugh grades, the pharmacist should search for formal recommendations on dose adjustment of medication either in the literature or as recommended by the manufacturer where available. Otherwise the pharmacist should use other resources to check the pharmacokinetic characteristics of the medication to determine if, and to what extent, acute liver decompensation will affect medication metabolism. The extraction ratio, oral bioavailability, metabolizing pathways and excretion should all be considered by the pharmacist to determine if the current therapy will require any immediate intervention. Therefore, the pharmacist needs to have sound knowledge on these aspects and be familiar with the resources that are useful in determining the relevant parameters.

The clinical pharmacist may also be required to review long-term medications in a patient with stable and chronic liver disease. It is important that the clinical pharmacist has a clear history of when each medication was started, the duration of therapy, indication, and risk of hepatotoxicity. Medications that may be hepatotoxic should be stopped to prevent further liver injury. Similarly, medications that have narrow therapeutic indices and are highly protein bound (e.g., phenytoin), would have an increased free serum concentration over time, due to decreased albumin which can lead to toxicity. In these instances, the pharmacist should request free serum levels of the medication (when available) and undertake therapeutic drug monitoring. If the serum concentration measurement is not available, then an alternative agent that is not affected by protein binding and liver disease should be considered. In any case, advising the team on expected response rates and adverse effects related to medication accumulation is of clinical benefit.

Conclusion

There is a profound complexity in dose adjustment of medications in hepatic impairment due to the interplay of pharmacokinetic and pharmacodynamic parameters of medicines in chronic liver disease. The important question may not necessarily be about dosing, but rather, the appropriateness in the first place. For example, if the medication has the potential to be hepatotoxic or nephrotoxic. In most cases, following the cautionary dosing of "start low and go slow" is recommended.

Useful Links and Further Readings

- Interactive Clinical Pharmacology: http://www.icp.org.nz/index.html
- Drugs and the liver—a guide to drug handling in liver dysfunction by North-Lewis, Penny. First Edition, Pharm Press, 2008.
- Assessing hepatotoxicity of medications—Livertox: https://livertox.nih.gov/

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Clinical Pharmacy Considerations in Special Populations: Geriatrics

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Learning Objectives

- Describe risks factors for medication-related adverse effects in older people, including physiologic and prescribing.
- Describe the atypical presentation of medication-related adverse effects in older people, particularly as they relate to functional changes.
- Discuss the role, tools available and related evidence for pharmacists in medication management for older people.

Take Home Messages

- The population globally is aging and with it the number of medications taken.
- Older people are at increased risk of adverse events from medications due to a variety of factors, including changing physiology, polypharmacy, and use of potentially inappropriate medications.
- Polypharmacy and the use of potentially inappropriate medications is exacerbated by the prescribing cascade, in which a medication-related adverse effect is misdiagnosed as another condition and treated with a new prescription, increasing the number of medications, potential adverse effects, and potential for drug interactions.
- Pharmacists provide care to older patients in a variety of settings, including community pharmacy, ambulatory clinics, long-term care, specialized geriatric clinics, general acute care units, and specialized geriatric units.
- Pharmacist-led interventions, as well, as collaborative work on interprofessional teams, have been found to improve medication use in older adults in these diverse clinical practice settings.

- Medication management, most often referred to in the literature as general pharmacist clinical intervention or as medication review, has been shown in a variety of clinical settings to improve medication use and patient outcomes, as well as having cost benefits.
- A variety of tools are available to assist pharmacists in identifying potentially inappropriate medications for reassessment and potential discontinuation in older people, including the Beers Criteria, the Drug Burden Index, the Medication Appropriate Index (MAI), STOPP/START, and STOPPFrail.
- Pharmacists offer a variety of supports around medication adherence, which includes devices, such as dossettes or specialized packaging, as well as, therapeutic optimization to minimize dosing frequency.
- Pharmacists are aware of the potential changes in hearing, vision, dexterity and cognition when providing medications to older people and assist in finding solutions to allow the safe and effective use of medications when age-related changes impair abilities (e.g. decreased dexterity requiring easy open medication vials).

Introduction

The world's population is aging. In 2013, it was estimated that 12% of the world's population was 60 years of age or older (Hohl et al., 2017a). In North America, adults 65 years of age and older represent approximately 16% of the Canadian and 13% of the US population, respectively (Heuberger and Caudell, 2011; Holmes et al., 2006). Similar trends are observed in Europe, Asia, and the Pacific Region (Marshall et al., 2013; Steinman et al., 2011). Over the next 40 years, the proportion of older individuals is projected to double, representing 25%–30% of the world's population (Hohl et al., 2017a).

Aging is associated with the onset of a number of chronic diseases often treated with medications, the result of which is older persons using more medications compared to younger individuals. Across multiple international jurisdictions it is estimated that persons 65 years of age and older account for one-third to half of recipients of all prescribed medications and almost two-thirds of prescription drug costs (Canadian Institute for Health Information, 2016; Craftman et al., 2016; Duerden et al., 2013; Qato et al., 2008; Wastesson et al., 2018).

The use of multiple medications is referred to as polypharmacy, which can be either appropriate or problematic (Marcum et al., 2012a). Appropriate polypharmacy refers to use of multiple medications for complex or multiple conditions where medications have been optimized according to best evidence and demonstrate benefit to the patient (Marcum et al., 2012a). In contrast, problematic polypharmacy occurs when medications do not provide the intended benefit and/or cause harm (Marcum et al., 2012a).

Problems associated with polypharmacy include nonadherence, inappropriate medication use, drug–drug or drug–disease interactions and adverse drug events (Hajjar et al., 2007). Nonadherence is important as it can be associated with therapeutic failure or adverse drug withdrawal events (Marcum et al., 2012b). Clinically important drug–drug and drug–disease interactions are more likely to occur as the number of medications increases (Doan et al., 2013; Hanlon et al., 2017). These interactions can also cause serious adverse drug events (Gnjidic and Johnell, 2013; Hanlon et al., 2011; Juurlink et al., 2003). Likewise, use of potentially inappropriate medications are associated with an increased risk of adverse drug events (Hudhra et al., 2016; Walsh et al., 2016).

Adverse drug events are common in older adults and are an important contributor to morbidity and mortality (Herr et al., 2015; Hohl et al., 2001; Maher et al., 2014). Moreover, adverse drug events can present atypically as disease exacerbation, cognitive decline, falls, functional decline or urinary incontinence resulting in their being overlooked as medication-related effects (Corsonello et al., 2009, 2014; Hilmer et al., 2009; Onder et al., 2018; Peron et al., 2011). This can sometimes lead to use of another medication to manage the condition without recognizing that it has been caused by a drug, often referred to as the "prescribing cascade" (Rochon and Gurwitz, 2017a).

Perhaps the most challenging aspect of caring for older patients is finding the appropriate balance between the benefits and potential harms of medications. As the medication experts on the health care team, pharmacists have an important role to play in ensuring the safe and effective use of medications among this growing population, regardless of their practice setting, for example, community pharmacy, long-term care, acute care.

Medication Use in Older Adults

Polypharmacy

Polypharmacy refers to the use of multiple medications, although a standard definition has not been agreed upon. It is frequently defined based on a specific threshold for the number of medications, ranging from 5 to 10, that a person is taking (Gillette et al., 2015; Hajjar et al., 2007). Defining polypharmacy based on number of medications alone is now being questioned as it does not address the issue of medication appropriateness (Gillette et al., 2015; Hanlon and Hajjar, 2018). The World Health Organization defines polypharmacy as "the administration of an excessive number of drugs" or "the administration of many drugs at the same time" (WHO Centre for Health Development, 2004). This has been expanded by some to include therapeutic duplication, use of more medications than clinically indicated, use of ineffective medications, use of potentially inappropriate medications and drug–drug interactions (Bushardt et al., 2008; Fulton and Allen, 2005; Gillette et al., 2015).

Despite the lack of a standard definition for polypharmacy, review of the literature demonstrates three consistent themes regarding medication use in older adults: (1) Medication use is high in older adults, (2) inappropriate use of medications is common, and (3) polypharmacy increases the risk of medication-related harms.

Medication Use

Firstly, medication use is high in persons 65 years of age and older on an international basis. A recent review of Canadian publicly funded drug programs found that, on an annual basis, approximately 66% of persons 65 years of age and older were prescribed five or more drug classes, 26% prescribed at least 10 and 8% prescribed 15 or more (Canadian Institute for Health Information, 2016). These data are consistent with that observed in other jurisdictions. A large European study, across 11 countries, found that half of the study population (mean age 72 years) were taking six or more medications on a daily basis (Fialova et al., 2005). A second European study in six countries observed 39% of patients receiving home care were using five or more medications concurrently and 23% were using ten (Giovannini et al., 2018). Data from the United States demonstrated an increase from 31% to 36% of an older population using five or more medications concurrently between the years of 2005 and 2011 (Qato et al., 2016).

Medication use is even higher in the nursing home setting. Among Canadian seniors residing in nursing homes, 48% were prescribed 10 or more drug classes, with an average of 9.9 drug classes in 2016 (Canadian Institute for Health Information, 2016). The European SHELTER study found that almost half of long-term care residents were prescribed between five and nine medications and approximately one in five were prescribed ten or more medications (Onder et al., 2013). In the US Nursing Home Study, 40% of long-term care residents were prescribed nine or more medications (Dwyer et al., 2010).

Prescription drugs, over-the-counter products, vitamins, and natural health products all contribute to medication use in older persons. Medication classes commonly used by older community dwelling adults include statins, ACE inhibitors, diuretics, beta-blockers, antiplatelets, and oral antihyperglycemic agents (Canadian Institute for Health Information, 2016; Morgan et al., 2012b; Qato et al., 2016; Quinn, 2017). Self-medication with over-the-counter medications, vitamins and supplements is also common among older adults living in the community. Thirty to thirty-eight percent of prescription drug users report use of over-the-counter agents and 46%–64% report the use of vitamins, herbal products or supplements (Morgan et al., 2012a; Qato et al., 2016). Analgesics (acetaminophen and NSAIDs), antacids, laxatives, and vitamins are reported most frequently (Goh et al., 2009; Qato et al., 2016). Common supplements used included fish oils and glucosamine (Goh et al., 2009; Loya et al., 2009; Qato et al., 2016). Patterns of prescription drug use are somewhat different for residents of long-term care facilities with higher use of antidepressants, antipsychotics, and opioids, although cardiovascular medications (statins, ACE inhibitors, and beta-blockers) are frequently prescribed to this population as well (Canadian Institute for Health Information, 2016; Dwyer et al., 2010; Onder et al., 2012).

Multiple factors are associated with medication use in older persons; including age, gender, presence of chronic diseases, number of health care visits and multiple prescribers (Alldred et al., 2016; Castioni et al., 2017; Hovstadius and Petersson, 2012; Niclos et al., 2018). Among these, age and comorbidity are most frequently identified (Duerden et al., 2013; Hovstadius and Petersson, 2012). As people age, they develop more chronic diseases, resulting in application of disease-based guidelines and increasing numbers of medications prescribed (Canadian Institute for Health Information, January 2011; Department of Health (UK), 2001; Federal Interagency Forum on Aging-related Statistics, June 2016; Wehling, 2011). Guidelines commonly recommend multiple drugs for management of a single condition, resulting in numerous drugs being added to the therapeutic regimen. The impact of guidelines on the number of drugs is more pronounced in those with multiple comorbidities as they see different specialists for each individual condition and have medication prescribed for each disease accordingly (Wehling, 2011). Primary care providers are often hesitant to change or discontinue medications initiated by other prescribers, especially if started by a specialist or during hospital admission, causing the overall number of medications to increase over time (Anthierens et al., 2010). Yet the generalizability of disease specific guidelines in an older, frail population are questionable as this group is usually excluded from clinical trials on which guidelines are based (Bourgeois et al., 2017; Cherubini et al., 2011; Dodd et al., 2011; Konrat et al., 2012). Furthermore, guidelines tend to focus primarily on longevity rather than symptom control without consideration of the time to benefit in the context of life expectancy. This can result in the addition of medications without adequate thought given to the potential benefits of drug therapy versus the risk of medication-related harms based on patient specific factors (Cox et al., 2011; Holmes et al., 2006).

Inappropriate Medication Use

One study of older ambulatory adults found that 16% had a therapeutic duplication, 55% were taking medication without a clear clinical indication, and 30% were taking medications that were ineffective (Rossi et al., 2007). A second study showed that 57% of American veterans were taking at least one medication that was not effective, not indicated or a therapeutic duplication (Steinman et al., 2011). In the nursing home setting up to one-third of residents are prescribed at least one medication that is not clinically indicated (Brulhart and Wermeille, 2011; Silva et al., 2015; Stuijt et al., 2008). Among hospitalized patients, 30% were discharged with at least one medication without a clear indication with 25% of these started during hospitalization (Hajjar et al., 2005).

Rates of potentially inappropriate medication use in older adults vary depending on the population studied and the criteria used to define inappropriate use. Both explicit and implicit criteria are available. Beers, STOPP, and STOPPFrail are examples of explicit criteria whereas the Medication Appropriateness Index (MAI) represents implicit criteria (see "Medication Review" section below for more details on these criteria) (American Geriatrics Society, 2018; Hanlon and Schmader, 2013; Lavan et al., 2017; O'Mahony et al., 2015). Regardless of the clinical setting or the criteria used, the more medications that are taken the more likely a potentially inappropriate medication will be used (Buck et al., 2009; Fialova et al., 2005; Hanlon et al., 2004a; Hudhra et al., 2016). Likewise,

potentially inappropriate medication use, regardless of criteria used, is associated with adverse drug effects and other medication-related harms (Hudhra et al., 2016; Lund et al., 2010; Walsh et al., 2016).

Medication-Related Harms and Adverse Drug Events

Adverse drug events occur frequently in older adults, in outpatient, hospital and long-term care settings (Handler et al., 2006; Maher et al., 2014; Parekh et al., 2018). Adverse drug events are reported in up to 35% of outpatients and 40% of hospitalized seniors (Maher et al., 2014). Furthermore, up to 50% of older adults will experience an adverse drug event upon discharge from hospital (Parekh et al., 2018). In the United States, it is estimated that adverse drug events are responsible for over 3.5 million physician visits, 1 million emergency department visits and 125,000 hospital admissions per year (Office of Disease Prevention and Health Promotion, 2018). Within acute care settings, adverse drug events are estimated to account for one in three hospital-related adverse events and increased length of hospital stay by almost 5 days (Office of Disease Prevention and Health Promotion, 2018). Medications commonly reported as causing adverse drug events include anticoagulants, antihyperglycemic agents, corticosteroids, NSAIDs, opioids, psychotropic medications, and drugs with significant anticholinergic effects (Hanlon et al., 2014; Maher et al., 2014; Onder et al., 2018).

Most adverse drug events in older adults are preventable and result from an exaggeration of the pharmacologic effect of a medication rather than being idiosyncratic in nature. Age-related physiologic changes contribute to the vulnerability of older adults to adverse drug reactions. Reduced elimination of some medications increases both the peak and duration of effect (Reeve et al., 2017; Sera and McPherson, 2012). Changes to receptors may enhance sensitivity to certain agents (Reeve et al., 2017; Sera and McPherson, 2012). Frailty may also play a role as declining functional reserves and impaired homeostatic mechanisms can render an older person more susceptible to the pharmacologic effect of some medications (Hubbard et al., 2013; Reeve et al., 2017).

However, the most important risk factor for adverse drug events is the number of medications that someone is taking. A study of older veterans found that the odds of being hospitalized for an adverse drug event was increased almost three-fold (OR 2.85, 95% CI 1.03–7.85) for those taking five to eight medications and almost four-fold (OR 3.90, 95% CI 1.43–10.61) when nine or more medications were taken (Marcum et al., 2012a). In the long-term care setting, residents taking nine or more medications had twice the odds (OR 2.33, 95% CI 1.54–3.52) of experiencing an adverse drug event in comparison to those taking fewer drugs (Nguyen et al., 2006). Many adverse drug events are related to drug–drug or drug–disease interactions.

The greater the number of medications the higher the probability of a clinically important interaction occurring (Hanlon et al., 2017; Maher et al., 2014). Drug–disease interactions often present atypically as geriatric syndromes (cognitive impairment, falls, and urinary incontinence) or functional decline and may not be recognized as being medication-related (Onder et al., 2018).

Medication Use and the Physiologic Changes of Aging

Normal aging is associated with physiologic changes that alter the pharmacokinetics (absorption, distribution, metabolism, and renal elimination) and pharmacodynamics of medications. These changes contribute to the risk of medication related harms in older adults.

Drug Absorption

Several age-related changes with potential to impact the oral absorption of medications have been reported. These include increased gastric acidity and reductions in gastrointestinal motility, splanchnic blood flow and the surface area of the intestinal mucus membrane (Hubbard et al., 2013). However, recent studies have demonstrated that such changes may not occur in fit or robust older adults (Hubbard et al., 2013). Furthermore, there is little data evaluating the effect of these changes on drug absorption in frail, older individuals (Hubbard et al., 2013).

Drug interactions may be the most important consideration with respect to oral absorption of medications, as administering multiple medications at the same time increases the potential of one drug affecting the absorption of another. For example, administration of L-thyroxine with antacids, calcium and iron supplements, or proton pump inhibitors may impair the absorption of this agent, leading to a poor therapeutic response (Skelin et al., 2017). Likewise, absorption of quinolone antibiotics may be reduced by concomitant use of calcium or iron supplements, resulting in therapeutic failure (Lomaestro and Bailie, 1991). Drug disease interactions may also play a role. Decreased blood flow to the gastrointestinal tract secondary to congestive heart failure can result in poor absorption of some agents used to treat the condition, such as furosemide, compromising the therapeutic response (Delafuente, 2008).

Distribution

Three age-related changes have the potential to alter drug distribution in older adults: (1) reduction in total body water; (2) increase in body fat with a corresponding decrease in lean body mass; and (3) reduction in serum albumin (Delafuente, 2008; Hubbard et al., 2013; Reeve et al., 2017).

Total body water is estimated to decrease by 10%–15% with aging, affecting the distribution of hydrophilic medications such as gentamicin or lithium. This can result in higher serum concentrations in an older adult compared to a younger person given the same dose, thereby increasing the risk of toxicity (Turnheim, 2003). Likewise, a reduced lean body mass will also result in higher serum concentrations of some medications, such as digoxin (Delafuente, 2008). Conversely, increased adipose tissue affects the distribution of lipophilic agents, such as amiodarone or diazepam (Turnheim, 2003). While peak serum concentrations of these agents may be lower, duration of effect can be prolonged as the drug will be stored in the fat tissue, prolonging the half-life (Delafuente, 2008; Turnheim, 2003).

Many medications bind to the serum protein, albumin, which has been shown to decrease by 5%–15% with aging, with further reductions related to frailty (Delafuente, 2008). For highly protein bound medications, such as phenytoin, this can result in an increase in the pharmacologically active unbound drug relative to the inactive bound portion. In most cases, the increased levels of unbound drug are accompanied by an increase in elimination through normal metabolic or renal pathways without any clinically important differences in therapeutic response or toxicity (Reeve et al., 2017). However, for some narrow therapeutic index medications, such as phenytoin, serum concentrations of total drug may fall within the normal range but patients may be exhibiting signs and symptoms of toxicity as total concentrations do not accurately reflect serum concentrations of unbound drug (Delafuente, 2008).

Metabolism

The liver, which functions as the primary site for metabolic elimination of most medications, undergoes a number of age-related changes, although their impact on therapeutic effect and toxicity remains unclear (Delafuente, 2008). Important changes involve reduction in hemoperfusion which affects the bioavailability of some medications subject to high extraction during the "first pass" through the liver (Klotz, 2009). With reduced liver blood flow, less drug is extracted resulting in greater bioavailability and higher serum concentrations (Klotz, 2009). Examples of high extraction drugs with greater bioavailability in older adults include beta-blockers, such as labetalol and propranolol (Klotz, 2009).

Metabolism of low extraction medications is dependent on the amount of metabolizing enzymes present in the liver (Turnheim, 2003). Phase II or conjugation type metabolism is generally not affected by the aging process but some age-related changes to Phase I type metabolism, via the Cytochrome (CYP) P450 system, have been reported (Delafuente, 2008; Turnheim, 2003). Metabolism via the CYP 2D6, CYP 3A4, and CYP 2C9 is generally thought not to be different in older adults, whereas metabolism via CYP 1A2 and CYP 2C19 may be reduced, although the clinical importance of this remains to be determined (Delafuente, 2008).

Elimination

Numerous studies demonstrate that renal function declines with normal aging, related to fewer functioning renal glomeruli, reduced renal blood flow and tubular function (Delafuente, 2008; Hubbard et al., 2013; Turnheim, 2003). On average, creatinine clearance is estimated to decline by 1 mL/min per annum beginning at age 40, requiring that medications predominantly eliminated by the kidney undergo dosage reduction in older adults (Bell et al., 2013; Delafuente, 2008). Presently, the Cockcroft-Gault equation remains the most widely used tool for renal drug dosing in older individuals (Bell et al., 2013; Delafuente, 2008).

Prescribing Cascade

The prescribing cascade may exacerbate issues around medication inappropriateness and polypharmacy. A prescribing cascade is considered to begin when an adverse drug reaction to a previously prescribed medication is misidentified as a new medical condition and a new medication is prescribed to treat the new "medical condition" (Rochon and Gurwitz, 1997). A commonly described example, is the prescribing of a nonsteroidal anti-inflammatory drug that causes an increase in blood pressure that leads to the prescribing of an antihypertensive medication (Rochon and Gurwitz, 1997). An expanded prescribing cascade has recently been proposed that also includes the treatment of the new "medical condition" with nonprescription medications (which may be initiated by the patient) or the use of a medical device (e.g. pacemaker device insertion to treat bradycardia from a drug interaction) (Rochon and Gurwitz, 2017b). Clinicians must keep in mind the prescribing cascade and consider all new signs and symptoms as possibly caused by current therapy. This also serves as a reminder of the importance of reviewing all medications and supplements when reviewing a patient's therapy, as there may be nonprescription medications or supplements being taken that can be causing the symptoms.

Role of Pharmacist

Practice Settings

Pharmacists provide care for older people in a variety of settings, including community pharmacies, outpatient clinics, acute care hospitals, geriatric rehabilitation units, assisted living and long-term care facilities. Reviews of the evidence have shown that pharmacist interventions, regardless of practice setting, reduced the occurrence of drug related problems in the elderly (Hanlon et al., 2004b).

In the community pharmacy, pharmacists see older people in the pharmacy on a regular basis with studies from the United Studies showing that an estimated 55% of adults visit a pharmacy in any given week, 58% in Ireland visit more than once a month and a study from the United Kingdom finding that 70% of those 65–74 and 67% of those 75 and over collecting a prescription from the pharmacy in the previous month, giving the pharmacist many opportunities to review medications (Boardman et al., 2005; Grabenstein et al., 2002; Steyer et al., 2004; The Pharmaceutical Society of Ireland). The identification and management of drug-related problems in older adults by community-based pharmacists have been associated with decreased medication-related problems, including, therapeutic duplication and decreased number of medications used, as well as some indications of improved clinical and economic outcomes (Nkansah et al., 2010; Vinks et al., 2009; Westerlund and Marklund, 2009). In many community-based pharmacy settings, additional medication management services also include formal medication reviews, which have been shown in a review of systematic reviews to result in a range of benefits for clinical outcomes (Jokanovic et al., 2017).

In long-term care, pharmacists provide a variety of clinical services, including regular medication reviews (often 2–4 times per year), family care conferences, and consultations with the interprofessional team. Pharmacists are often charged with keeping statistics on medication use and ensuring formulary medications are used. Pharmacists in long-term care settings have been shown to improve care through identification and resolution of medication-related problems (Pepe et al., 2018; Thiruchelvam et al., 2017a).

In acute care, clinic and rehabilitation settings pharmacists often review older people's medications on admission and then offer further recommendations during rounds (which may be daily or several times per week) with the team and through chart notes. Their involvement has been shown to improve medication use, including decreased medication errors, improved monitoring of potential drug interactions and decreased use of potentially inappropriate medications (Cortejoso et al., 2016; Komagamine and Hagane, 2017).

As members of interprofessional teams, pharmacists are the medication experts, providing medication recommendations for optimal patient care. Studies have shown that the addition of a pharmacist on the team results in improvement of chronic disease management and quality use of medicines (Chisholm-Burns et al., 2010; Tan et al., 2014).

Preventing Adverse Drug Reactions

A key role for pharmacists in the care of older people is in preventing adverse drug reactions (ADRs). Due to a variety of reasons, older people are at greater risk of adverse reactions to medications, even at appropriate doses. It is estimated that ADRs occur 10%–35% annually in community-dwelling adults and that nearly 9% of hospital admissions are due to ADRs in older adults (Gray et al., 1999, 2018; Oscanoa et al., 2017). Active monitoring for adverse effects should take place in all clinical settings (Steinman et al., 2011). Pharmacists can play a key role in this active monitoring by regularly reviewing the medications of their older patients to ensure that adverse reactions are not experienced. It may not be obvious that an adverse reaction is related to a medication, as another medication has been prescribed to treat the adverse reaction, which is then not apparent (prescribing cascade), but adds to pill burden and potential for further adverse reactions. Medication reviews are often the mechanism for finding and preventing adverse drug reactions with varying levels of evidence seen in each clinical setting.

Medication Reviews

Pharmacists lead medication management efforts through a variety of interventions. One of the most studied is medication reviews, which can be performed in a variety of settings. Medication reviews has been defined as "a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of drug-related problems (DRPs) and reducing waste" (Clyne et al., 2008).

Medication reviews in community settings have been shown in an overview of 31 moderate to high quality systematic reviews to improve medication management, including identification and resolution of drug-related problems, and some studies also showed improvement in surrogate markers for chronic disease management and improvements in the number and appropriateness of medications (Jokanovic et al., 2017). The same overview also found improvements reported in medication adherence and quality of life for those completing a medication review with a pharmacist (Jokanovic et al., 2017).

A systematic review from 2017 of the impact of medication reviews on medication use in residential aged care facilities (also known as long-term care) included 20 studies (Thiruchelvam et al., 2017b). Of those 8 of the 12 clinical trials were pharmacist-led medication reviews and the remaining four were team-based reviews and 8 of the 10 observational studies were pharmacist-led medication reviews with 2 being team-based reviews (Thiruchelvam et al., 2017b). The review found reductions in the number of medications prescribed, reductions in inappropriate medications, and reductions in adverse outcomes (e.g. deaths, hospitalization) in the groups that received medication reviews (Thiruchelvam et al., 2017b).

Medication reviews are often not completed or studied as a separate component of medication management in hospital, compared to community and long-term care and are often imbedded within general medication management services. Many studies have instead focused on medication reconciliation, which is generally considered a technical function and not extensive like a medication review, although it may be a component of a medication review (Mekonnen et al., 2016). Despite this, a recent study conducted in Canada found that early in-hospital medication review in the emergency department reduced hospital-bed utilization in high-risk patients under 80 years of age compared to those who did not receive medication review (Hohl et al., 2017b). Unfortunately, the benefits were not seen in those over 80 years of age (Hohl et al., 2017b). A study form Ireland found that pharmacist-led medication reviews in hospital prevented adverse drug events and benefited females and those 65 years of age and older the most (Kearney et al., 2017).

A variety of tools exist to assist pharmacists in identifying the medications that may be most harmful during medication reviews. A few are summarized below.

Beers Criteria

The Beers Criteria was first published by the American Geriatrics Society (AGS) in 1991 as a list of potentially inappropriate medications to use in older adults (Beers et al., 1991). Publication of the 2018 update is pending (American Geriatrics Society, 2018). In the interim, the 2015 version is the current version being used (By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015). The Beers Criteria presents a list of medications where the risk of harm outweighs potential

benefits (American Geriatrics Society, 2018). It also lists high-risk drug–drug interactions to avoid and identifies agents requiring renal dosing adjustments (American Geriatrics Society, 2018). The various iterations of the Beers Criteria have been found to be helpful in reducing inappropriate medication usage through identification of medications associated with health issues, such as confusion, falls, and mortality that can be avoided when prescribing or considered for stopping (By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015).

STOPP/START and STOPPFrail

First published in 2008 as a screening tool for reviewing medications in older people with a list of criteria for medications that may be inappropriate and reviewed with consideration to STOPP (Screening Tool of Older Persons' Prescriptions) and criteria for potentially indicated medications that should be reviewed for consideration to START (Screening Tool to Alert doctors to Right Treatment) (Gallagher et al., 2008). The tool was updated to add in additional evidence-based criteria and remove any obsolete criteria with version 2 being published in 2014 (O'Mahony et al., 2015). STOPP criteria includes medications that present a high risk relative to benefit in older adults, increase the risk of falls, clinically important drug–drug and drug–disease interactions as well as common therapeutic duplications (O'Mahony et al., 2015). STOPPFrail is similar to STOPP but incorporates frailty and life expectancy (Lavan et al., 2017). STOPP/START has been validated and used in a variety of settings, including community practice, acute care and long-term care, and in several jurisdictions (including Europe, Asia, and North America) (Hill-Taylor et al., 2013). The strongest evidence for benefits of its use are in acute care and long-term care settings, where it has been shown to reduce use of potentially inappropriate medications, reduce falls, and decrease length-of-hospital stay and costs (Hill-Taylor et al., 2016; O'Mahony et al., 2015). Evidence for its usefulness in community practice are not as strong, with one study finding that most drug-related problems identified during a medication review not being associated with STOPP/START criteria (Verdoorn et al., 2015).

Comparisons of STOPP/START and Beers

The Beers Criteria, STOPP, and STOPPFrail criteria are grouped by organ system and provide explanation as to why a particular medication is considered to be potentially inappropriate (American Geriatrics Society, 2018; Lavan et al., 2017; O'Mahony et al., 2015).

A study published in 2016 compared Beers 2003, Beers 2012, STOPP/START version 1, and STOPP/START version 2 in reviewing patient medications in an acute geriatric medicine unit and found STOPP/START version 2 resulted in the greatest reduction of medications (Boland et al., 2016). A study published in 2018 compared Beers 2015 with STOPP version 2 to assess frequency and factors associated with potentially inappropriate medication use, as well as patients' satisfaction (Sakr et al., 2018). More potentially inappropriate medications were identified with Beers 2015 criteria compared to STOPP criteria, but noted that Beers is less specific, as it does not take the patient's clinical condition into consideration (Sakr et al., 2018). Patient satisfaction was increased with the absence of potentially inappropriate medications, regardless of the tool used (Sakr et al., 2018).

Drug Burden Index

The Drug Burden Index (DBI) is an evidence-based risk assessment tool developed to measure the cumulative exposure to anticholinergic and sedative medications commonly used in older adults (Hilmer et al., 2007). DBI score has been found in many studies across many countries (Australia, Canada, Finland, the Netherlands, New Zealand, UK, and US) to be associated with poorer physical function, reduced quality of life, frailty, falls, and hospital readmission (Kouladjian et al., 2014). DBI may be used to target medications that may be considered for discontinuation.

Medication Appropriateness Index

The Medication Appropriateness Index guides clinical judgment through the use of ten questions about clinical indication, therapeutic duplication, medication effectiveness given patient specific factors, dosing and duration of therapy, practicality of directions, drug–drug and drug–disease interactions as well as cost considerations (Hanlon and Schmader, 2013). Higher MAI scores have been significantly associated with unscheduled ambulatory or emergency department visits, hospital admission, and lower quality of life (Hanlon and Schmader, 2013).

Once potentially inappropriate medications are identified, a planned approach to decreasing doses and/or discontinuing medications can be planned.

Screening and Monitoring

Pharmacists frequent encounters with patients in the community offer many opportunities to screen for potential health issues, such as dementia. A community pharmacist with regular interaction with an older person can often notice changes in cognition before it is apparent to other care providers who may see the patient less often. Pharmacists in community may then screen these individuals using validated tools, such as the Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Tombaugh and McIntyre, 1992). The MMSE was developed as a brief screening tool to assess the severity of cognitive impairment and document change over time (Tombaugh and McIntyre, 1992). The MoCA was also developed as a brief screening tool, but with a focus on identifying those with mild cognitive impairment that may have scored within the normal range on the MMSE (Nasreddine et al., 2005). If the practice setting and skillset of the pharmacist allow, a comprehensive geriatric assessment may also be performed (Rockwood et al., 1998). Results can be used to follow up with the primary care provider. Ongoing

monitoring may be performed by the pharmacist to ensure any medications started, such as cholinesterase inhibitors, are meeting the goals of therapy. Pharmacists in other settings may also use these tools for screening and monitoring; however, it is more likely that other team members may be completing the tests or that the pharmacist has a specialized role, such as in an ambulatory geriatric clinic, in which it is part of their usual practice to use these screening tools.

Economic Considerations

Many older people are on fixed budgets due to limited pensions and government supports. Despite many jurisdictions providing some insurance coverage to older people, not all do, and when they do there are often co-payments and medications that are not covered. Pharmacists should have an understanding of the funding supports for older people in their jurisdiction, so they can serve as an advocate for older people by ensuring that medications used are not only safe and effective, but also acceptable financially.

Dosing/Formulations

Dexterity decreases with age and with many conditions, such as osteoarthritis. Ensuring that medication supplies are provided in a way that is usable by the patient, such as easy open vials and accessible multidose packaging, is an important component of medication management. Counseling on the importance of keeping medications that are not in safety formats (e.g. child-resistant safety vials) away from children and pets is a crucial component of easy access medication packaging.

Some older people will have difficulty swallowing, so consideration for alternate formulations (e.g., liquid, dissolvable) and specialty compounding must be considered. When splitting or crushing tablets, use drug information resources available to ensure it is safe and that a controlled-release mechanism is not altered. The same with opening capsules, ensure the capsule is not required for appropriate drug delivery (e.g. delayed release).

Adherence Aids

A variety of options can be used to assist in adherence. Creating medication calendars that patients can mark off each day may assist some people. Others may be more tech savvy and benefit from alerts on smartphones. Frequently multidose, multidrug packaging is used, such as blister packages and refillable dosettes. Ensuring that patients and caregivers understand how to use the packaging is important and often missed. Automatic refills and refill reminders may also assist with adherence.

Another way to improve adherence is simplifying medication regimens, ideally to once-daily dosing, as more frequent dosing is associated with decreased adherence (Claxton et al., 2001; Coleman et al., 2012). When possible, choose medications with less frequent dosing and if appropriate dose at the same time, for example if all medication are dosed once daily, give them at the same time, such as the morning, unless they must be spaced due to a potential drug interaction or a medication must be given at bedtime. Regular medication reviews and deprescribing should also assist in streamlining the medication regimen and minimizing pill burden.

Communication

Many older people have hierarchical views on healthcare and will see the physician's orders as more important than pharmacist recommendations. It is key to communicate in a professional manner that does not undermine other professionals, while still ensuring the appropriate medications are used and dosages adjusted if necessary. Making it clear that the pharmacist is part of the care team and works closely with the physician or other primary care provider to ensure optimal medication use may improve acceptance of medication changes.

Some older adults may have low levels of education and health literacy. Ensuring they understand how to properly use medications and know when to follow up with the pharmacist and/or other primary care provider may take additional communication strategies. Avoid asking questions like "Do you have any questions?" and "Do you understand?", as these closed-ended questions will often prevent further communication. Additional notes on medications may be required to assist in understanding instructions on use, such as adding images to vials, like a rising sun for morning and a moon for bedtime.

Older adults have declining vision and may require larger font sizes on printed materials. Other strategies such as use of magnifying glasses, pictorial labels, different textures and shapes of containers, and audible labels may also help (Smith and Bailey, 2014). Clear verbal communication is crucial to ensure understanding. Recorded messages around medication use and instructions may also be useful.

Decreased hearing is also common with aging. Many older people find coping strategies for loss of hearing, such as reading lips. When possible, be aware if there is a "good ear" and "bad ear" and try to position yourself on the "good ear" side. If they prefer to read lips, then ensure you enunciate well, face them straight on, and avoid looking away.

Older adults with cognitive impairment and early dementia may have diminished capacity, but are still able to care for themselves and make decisions. They may require more discussion and time to comprehend instructions. Keep this in mind during communications.

It is also important to keep in mind that older people often share medications with friends, family, and acquaintances. A 2014 systematic review summarized 19 studies from 9 countries and found 5%–51.9% of people (children to older adults) borrowed

prescription medications and that 6%–22.9% loaned prescription medication to someone else (Beyene et al., 2014). This reinforces the significance of pharmacists providing clear communication to all patients, including their elderly patients, about the importance of prescription medications being intended for an individual patient and not taking from others or loaning to others.

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Further Reading and Resources

American Geriatrics Healthcare Professionals Publications & Tools: https://www.americangeriatrics.org/publications-tools
The Beers Criteria: https://geriatricscareonline.org/ProductAbstract/beers-criteria-pocketcard/PC001
STOPP/START Toolkit: Supporting Medication Review. NHS. https://www.networks.nhs.uk/nhs-networks/nhs-cumbria-ccg/medicines-management/guidelines-and-other-publications/Stop%20start%20pdf%20final%20Feb%202013%20version.pdf/view

Clinical Pharmacy Considerations in Special Population: Pediatrics

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Learning Objectives

At the end of this chapter, the reader should be able to:

- Describe the physiology of the developmental stages of the pediatric population and how this influences pharmacokinetics;
- Explain off label and unlicensed medicine use for children;
- Recall the importance of formulations with respect to pediatrics;
- Describe the role of the pharmacist in caring for pediatric patients.

Take Home Messages

- The field of pediatrics covers a vast and diverse population, ranging from extremely premature neonates born from around 23 weeks gestation and weighing less than 1 kg, to adolescents approaching adulthood, who on occasion may weigh over 100 kg.
- Significant changes to pharmacokinetic parameters occur as a child develops from birth to adolescence. The three principle contributors to pharmacokinetic variability are size, maturation and organ function. Maturation and organ function primarily

affect children under two years old, whereas in children over two years old, size is the main factor differentiating a child from an adult.

- Dosage forms are particularly important in the pediatric population and need to be able to cater to vastly different sized patients, as well as being suitable for administration to developmentally diverse patients. A lack of licensed products continues to hinder the safe and effective use of medicines in children, and manipulation of products designed for adults is often required to enable the treatment of children.
- Excipients should not be considered inert components of medications. The ability of infants and children to metabolize and eliminate excipients may differ from adults, and thus the potential for toxicity or other unintended effects on the child should be considered when formulation is being selected, especially where multiple medications are used.
- In pediatric practice, the child must be cared for in the context of their family situation, with care taken to provide information, education and advice to both child and parent in line with the age and developmental stage of the child. Information and advice may also need to be provided to those who provide care and/or education to the child. As the child matures, their increasing autonomy should be respected and competence to consent to their own treatment considered.
- With the ongoing increase in professional roles available to pharmacists, pediatric-centered roles are emerging in vaccination, health promotion, primary health care and education, as well as more advanced clinical roles, including prescribing.

Introduction

The phrase "children are not small adults" has become an apt yet somewhat cliché statement when discussing medication for children. It refers to the fact that the pharmacokinetic and pharmacodynamic response to a medication in a child cannot be predicted by extrapolating adult data alone. Children differ to adults in size, body composition, bodily function, sensory maturity, and drug handling ability. Significant variation exists even within the pediatric population. The term pediatric encompasses neonates through to adolescents, with distinct physical, metabolic, and psychological differences across this age range. Further, the spectrum of diseases is broad, ranging from mild self-limiting illnesses to fatal disease, including those seen exclusively in children through to genetic disorders that present during childhood, as well as many of the same conditions seen in adults.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E11 classification divides the pediatric population into neonates (covering preterm and full term newborn infants from birth to 27 days old), infants and toddlers (28 days to 23 months), preschool children (2–5 years), school children (6–11 years), and adolescents (12 up to 16 or 18 years, depending on region) (European Medicines Agency, 2001). In practice, preschool and school children are generally combined and adolescent dosing often mirrors that of an adult. This classification system is aimed at the pharmaceutical industry to rationalize medicine licensing in children. However, many medicines are not licensed for use in children, resulting in nearly 70% of children hospitalized in both Europe and the United States (US) receiving at least one unlicensed or off-label medicine during a hospital stay (Conroy et al., 2000; Yang et al., 2011). Where a medicine is used in this way, safety, quality, and efficacy cannot be assumed and pharmacists have an important role in ensuring that the medication is appropriate for a patient given the limited information available. In 2007, the European Union (EU) introduced a Pediatric Regulation with the view of improving the health of children up to 18 years of age by supporting the development and accessibility of medicines for children and improving data available regarding their use. The Pediatric Regulation offers incentives for manufacturers to investigate drug development for children prior to marketing authorization of new drugs. However, there are ethical, technical, and practical challenges involved in conducting pediatric clinical trials, which perhaps explains why only three pediatric use marketing authorizations have been granted in the ten years since inception of the Regulation in 2007 (Tomasi et al., 2017). Similarly, the US Food and Drug Administration (FDA) have the Best Pharmaceuticals for Children Act (last amended 2007). The US and EU represent large pharmaceutical markets for newly developed drugs and have the potential to influence the global pharmaceutical industry.

This chapter will explore pertinent considerations for a pharmacist with regard to medicines use in children. These include dosage form, dosing and off label medicine usage. Specific conditions will not be discussed in detail. The pharmacist plays a vital and varied role in ensuring children receive effective medicines that are also safe. The role of the pharmacist will be discussed in detail later on in this chapter.

An Overview of the Pediatric Population

A normal pregnancy is considered to be 40 weeks from the first day of the last menstrual period and a baby born before 37 weeks gestation is defined as preterm. Births at less than 28 weeks are classed as extremely preterm, but as most infants born from 25 weeks onwards respond well to initial stabilization in the delivery suite they routinely receive neonatal intensive care in well-resourced settings. Resuscitation is not usually performed in neonates born at less than 23 weeks gestation as they rarely survive long enough to be discharged from hospital and may have overwhelming disability. Given the significant maturation that occurs across this gestational period, the developmental differences between patients at birth can be significant.

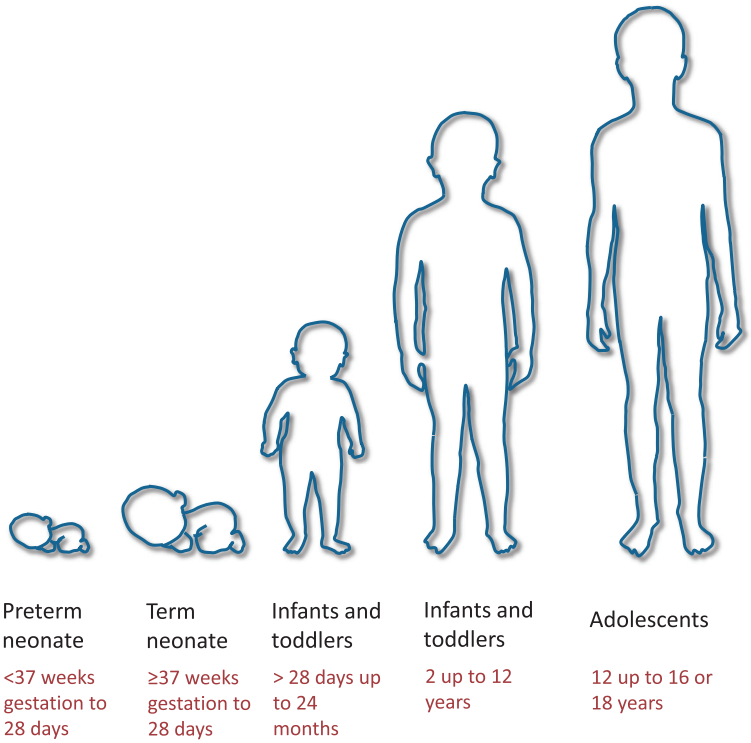

Figure 1 Developmental age groups for drug dosing.

Physiology

Significant physiological changes occur throughout childhood as organ systems develop and mature, particularly during the first 12 months of life and then again at puberty. Although puberty involves marked physiological changes, there is limited impact on drug handling. Developmental changes in the first 12 months of life have the most significant implications for drug therapy as these changes affect the pharmacokinetics of drugs. Different doses (e.g., mg kg^{-1}) or dosing intervals may be required, and adverse effects may be more prevalent if these changes are not taken into account. Additionally, some drugs may not be effective for all age groups. For example, sucrose is an effective analgesic for minor procedures in neonates (though the optimal dose has not been identified), but is ineffective in older children (Stevens et al., 2013). The age brackets that are often considered pharmacologically important for drug dosing are shown in Fig. 1.

Pediatric vital signs are considerably different to adult values and change with age. These changes are outlined in Table 1.

The transition from fetus to neonate involves substantial cardiovascular changes triggered by aeration of the lungs. Before birth, lungs are filled with fluid and gas exchange takes place across the placenta. Blood bypasses circulation to the lungs, instead being shunted from the aorta to the left pulmonary artery via the ductus arteriosus. Within minutes of birth, aeration of the airways and gas exchange region of the lungs takes place as a result of the hydrostatic pressure gradient created when the neonate first inhales.

Table 1 Pediatric normal vital signs according to age

Age	*Heart rate (beats per minute)*	*Blood pressure (mm Hg)*	*Respiratory rate (breaths per minute)*
Premature	120–170	55–75/35–45	40–70
0–3 months	100–150	65–85/45–55	35–55
3–6 months	90–120	70–90/50–65	30–45
6–12 months	80–120	80–100/55–65	25–40
1–3 years	70–110	90–105/55–70	20–30
3–6 years	65–110	95–110/60–75	20–25
6–12 years	60–95	100–120/60–75	14–22
12+ years	55–85	110–135/65–85	12–18

Source: Reprinted from Hartman, M.E., Cheifetz, I.M., 2016. Pediatric emergencies and resuscitation. In: Kliegman, R., Stanton, B., St Geme, J., Schor, N. (Eds.), Nelson Textbook of Pediatrics, 20th ed., with permission from Elsevier.

Initiation of breathing involves the interaction of biochemical, neural, and mechanical factors (Alvaro and Rigatto, 2012), triggering a decrease in pulmonary vascular resistance and subsequent increase in pulmonary blood flow. After birth, the ductus arteriosus is no longer required and generally closes within two days. This significant rearrangement in circulation is essential for survival and results in a circulatory system that mirrors that of an adult. The transition can be difficult for preterm neonates, whose lungs are immature, and lung injury can result from mechanical ventilation. Sometimes, the ductus arteriosus does not close, a condition called patent ductus arteriosus. When medical treatment is required to close this duct, nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin or ibuprofen are often the first choice. More recently, paracetamol has been reported to be an alternative option with fewer side effects (Dang et al., 2013; Dowd et al., 2018). If these medical treatment options are contraindicated or unsuccessful, then a surgical procedure may be required.

Pharmacokinetic Changes

An understanding of pharmacokinetics is essential in determining the dose needed to achieve the target concentration of a medicine for therapeutic effect. In children, the three principal contributors to pharmacokinetic variability are size, maturation, and organ function. Maturation and organ function primarily affect children under two years old, whereas in children over two years old size is the main factor differentiating a child from an adult (Anderson and Holford, 2013). Changes in pharmacokinetic parameters that occur throughout childhood are detailed below.

Absorption

Absorption describes the distribution of a drug from site of administration into the plasma and is a fundamental step prior to drug action for all routes of administration except intravascular, when drug is delivered directly into the systemic circulation. Three factors that influence drug absorption and are different in pediatrics compared with adults are gastrointestinal (GI) function, blood flow to the site of administration and skin permeability.

The surface area of the GI tract is proportionately larger in infants compared with adults, which can lead to varied drug absorption that cannot be directly predicted from adult data. Gastric emptying time is unpredictable and irregular in neonates, although this may be due to food type as opposed to age (Bonner et al., 2015). Variation in gut microflora and high levels of beta-glucuronidase add to the variability of oral absorption. It is well reported that the gastric pH is neutral at birth, but information regarding the maturation of pH over this neonatal period is contradictory (Yu et al., 2014). Premature neonates have a relatively higher gastric pH due to reduced acid secretion by the immature gastric mucosa. This can lead to higher absorption of acid labile drugs such as penicillin and reduced absorption of weak acids such as phenobarbitone. By the age of 12, the structure and function of the GI tract is comparable to that of an adult.

Absorption (particularly from the intramuscular route) is affected by blood flow at the administration site. While neonates have reduced muscle blood flow and contractions, there is also a rich supply of capillaries so intramuscular absorption may be higher in infants than in older pediatric patients (Anderson, 2017). Rectal absorption also depends on blood supply, which varies depending on placement of the dosage form (usually suppository or enema) within the rectum. Rectal absorption can therefore be difficult to predict in children, particularly in neonates.

Neonates have thin, permeable skin and throughout childhood the epidermis is hydrated and perfused more so than in adults. The surface area to body volume ratio in neonates and young children is also greater than in adults. This facilitates higher systemic absorption of topically applied drugs than occurs in adults, including of topical steroid creams, and this may lead to systemic effects and toxicity.

Distribution

Drug distribution in pediatrics is influenced by differences in body composition, low levels of plasma proteins, and maturity of physiological barriers such as the blood brain barrier. These factors change as a child grows and alter the distribution of a drug in the body. Bodyweight alone may vary by over 100-fold in the pediatric population. Premature neonates can be born as young as 23 weeks gestation weighing less than 500 g and obese adolescents can weigh greater than 100 kg.

Neonates and infants have a lower percentage of body fat than adults with a body composition reported to be about 75% water, compared with 50%–60% in adults (Woo, 2004). Therefore, larger doses relative to body weight of water soluble drugs (such as gentamicin) and lower doses of lipid soluble drugs (such as diazepam) are often required (Conroy, 2003). One measure of size is body weight, which is often used to calculate pediatric drug doses. However, there is debate around whether this is appropriate (Anderson and Holford, 2017; Young and Korotzer, 2016), particularly as body weight is not directly proportional to pharmacokinetic parameters. Further, as childhood obesity becomes more endemic (Skinner et al., 2018), body composition and drug lipophilicity are becoming increasingly important considerations. Doses should be capped (usually at the adult dose) for any given drug, even if the child's body weight suggests otherwise based on pediatric weight-based dosing.

Serum albumin, alpha-1-acid glycoprotein and total protein concentrations are lower than adults in the first year of life, resulting in lower levels of plasma protein binding and higher levels of the free drug. This means that lower total drug concentrations may be necessary to avoid drug toxicity and have the same effect seen in older children and adults. However, there is still considerable debate in the literature on whether changes in protein binding result in sufficient changes in free drug concentration to cause clinically significant adverse effects, if drug clearance is unchanged. In the neonate and especially the preterm neonate, reduced drug clearance is often seen and it may be this effect that dominates so that dose reduction is required (Anderson, 2017). Adult levels of albumin are

observed from about 12 months of age (Suggs, 2000). Protein binding is further altered in neonates due to increased competition from bilirubin and free fatty acids. In neonates, the blood brain barrier has higher permeability, which can lead to an increase in drug distribution to the brain and enhanced central nervous system effects at equivalent mg kg^{-1} doses.

Metabolism

Drug metabolism occurs via enzymatic reactions, mostly in the liver. Neonates have immature livers, so cannot metabolize foreign substances as well as children and adults. By the time a child is a year old, liver enzyme activity has increased such that the rate of drug metabolism is typically higher than adults, which can lead to a shorter plasma half-life for drugs primarily eliminated by hepatic metabolism. This is most likely due to their larger size of the liver relative to the body. Metabolic pathways mature at different rates, so the predominant pathway may differ with age. For example, glucuronidation is reduced in neonates, which can lead to accumulation of drugs that are metabolized via this pathway. Sulfation is higher in neonates than older children and adults (Miller et al., 1976). As a result, paracetamol is primarily metabolized by sulfation in neonates rather than glucuronidation, but the sulfation pathway is more easily saturated. To overcome these issues, paracetamol doses used in neonates are lower than in infants and older children (Anderson et al., 2000). Chloramphenicol accumulates in neonates as it cannot be efficiently glucuronidated, leading to toxicity known as "Grey Baby Syndrome" with symptoms including cyanosis, abdominal distension, vomiting, cardiovascular collapse, irregular respiration, and in some cases death (Mulhall et al., 1983).

Excretion

Elimination of most drugs or their metabolites occurs in the kidneys through glomerular filtration, active secretion and tubular secretion. Only free drug is filtered by the glomerulus and excreted. Neonates have reduced renal excretion due to functionally immature kidneys, leading to a longer half-life for drugs excreted primarily via this organ. Elimination rate rapidly increases after the first week of life as glomerular filtration rate (GFR) increases (**Fig. 2**). Adult parameters for GFR are reached by 9 months and tubular function matures when the infant is about 12 months old. GFR is the most useful indicator of kidney function and creatinine clearance is often used as a marker for GFR. The Schwartz equation is the most widely used formula for estimating GFR in children. It has been modified several times since it was first developed in the 1970s and uses serum creatinine, height and an empirical constant to estimate the GFR (Schwartz et al., 1976). In the first week of life, creatinine levels in the neonate reflect that of the mother, therefore, GFR is difficult to estimate. No single method for predicting pediatric drug clearance based on adult values is suitable for all drugs or all age groups (Mahmood, 2006). However, as neonates have significantly lower renal function compared with adults,

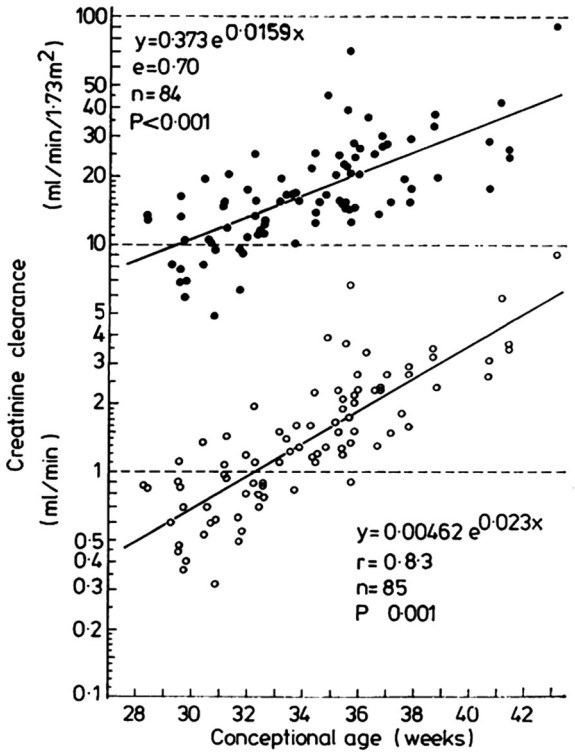

Figure 2 Creatinine clearance, corrected (closed circles) and uncorrected (open circles) for body surface area, plotted against conceptional age. In this and subsequent figures the regression statistics were calculated from x (conceptional age) expressed in days, although the axis is marked in weeks for convenience. *Source: Reprinted with permission from Al-Dahhan, J., Haycock, G.B., Chantler, C., Stimmler, L., 1983. Sodium homeostasis in term and preterm neonates. I. Renal aspects. Arch. Dis. Child. 58, 335–342.*

Table 2 Factors that influence administration of a medicine

Influence	*Explanation*
Capability	Relates mostly to age, physical development, and coordination, but also psychological development and understanding
Influence of illness	Acute illness may lead to a child being frightened and uncooperative. Vomiting may limit use of oral route. Children requiring continuing medication for long-term illnesses can be trained/persuaded to take their medicine, but to improve compliance it is ideal to have a range of dosage forms so pediatric patients and caregivers have a choice
Convenience for parent/caregivers	In addition to child preference, ease of administration for parent/caregivers requires consideration
Childcare/school	Clear instructions and route of administration are important when a medicine needs to be given at childcare facilities/school. The development of longer acting formulations may be required to avoid administration during school hours
Adolescence	As adolescents develop independence, they will often become responsible for their own medicine administration. There is a chance of rebellion where they will reject medicines previously taken and discrete, portable forms are important
Disability	Some disabilities may limit the ability for a pediatric patient to take their own medicine and limit appropriate dosage forms
Cultural differences	Acceptability of different routes of administration and taste may differ by geographical region as well as religion

Source: Committee for Medicinal Products for Human Use (CHMP), 2006. Reflection Paper: Formulations of Choice for the Paediatric Population [EMEA/CHMP/PEG/194810/2005]. European Medicines Agency, London, UK

dose adjustments are required to maintain a constant drug level and prevent overdose in the same way as adults with renal impairment. This may be achieved by decreasing the dose, increasing the dosing interval, or a combination of these two approaches. For example, the dose and frequency of gentamicin varies depending on gestational age at birth and postnatal age.

Dosage Forms for Children

When it comes to medicines for children, dosage form becomes important. The ability for a child to take a medicine is influenced by a number of factors, which are summarized in **Table 2**. Flexible dosing is required so that a single formulation may be used for a broad range of ages and bodyweight. Whereas solid oral dosage forms such as tablets and capsules are the most commonly used and desirable form in adults, many children cannot swallow these dosage forms and the strengths are often inappropriate, especially for young children. The age at which a child is able to swallow solid oral dosage forms varies considerably between children and depends on the formulation, especially tablet or capsule size. Oral liquid dosage forms offer flexible dosing and are considered easier for children to swallow. However, accurate measurement devices are needed to obtain correct dose volumes and the toxicity of excipients needs to be considered, especially in the very young neonate.

A variety of more patient centric dosage forms are being developed, which have the potential of improving dosage forms for children (Hanning et al., 2016). For more detailed descriptions of dosage forms being developed for children, the reader is referred to the additional reading section at the end of this chapter. A summary of some key advantages and disadvantages of dosage forms to consider for pediatrics are presented in **Table 3**. It is important that the pharmacist understands these dosage forms in order to explain to children and their caregivers and in some cases, prescribers, about their use.

Neonatal Considerations

Neonates in intensive care are exposed to many drugs via intravenous (i.v.), enteral, and other routes. Inserting an i.v. line into a neonate can be a significant challenge due to their small, fragile veins. Maintaining i.v. access using peripheral catheters is difficult in this population, so where prolonged i.v. access is needed, a peripherally inserted central catheter (PICC) is often placed. Placement of a PICC can be difficult and complications include infiltration, phlebitis, occlusion, leakage, effusion and edema (Colacchio et al., 2012). Alternatively, central catheters can be inserted via the umbilical vein or arteries in the first day of life, and provide relatively easy access to the central circulation for the administration of medications, fluids, and for blood sampling.

Challenges in i.v. drug delivery include flow rate, fluid volume and accuracy of volume. Typically, an i.v. fluid infusion rate of 10–20 mL h^{-1} is appropriate for a full term neonate and 3–5 mL h^{-1} for a neonate weighing less than 1 kg (Koren, 1997). Neonates often require small doses of medication, which, combined with the slow infusion rate, can mean that it takes a long time for the drug to reach the bloodstream. An example is gentamicin, where dose volume can be as low as 0.2 mL. It has been demonstrated that there is a discrepancy between the intended and actual dose of gentamicin received following infusion of low dose volumes of less than 1 mL into slow-flowing lines over 30 minutes (Sherwin et al., 2009). A proposed solution to ensure complete and timely gentamicin delivery is to inject a bolus of low-dose-volume drug solution into a slow flowing line, followed by an appropriate fluid volume to flush the drug from injection site into the patient (Medlicott et al., 2013).

The risk of error is compounded when using low dose volumes, where rounding doses and manipulation of dosage forms become essential when appropriate dosage forms are not available. Manipulation increases the risk of computational error and rounding can significantly alter the dose. Rounding should be accounted for at the point of prescribing so that the person administering the medicine (usually nurse or caregiver) is not faced with an unmeasurable volume. It is generally considered acceptable to report up to two decimal places so long as an appropriate measuring device is available and those measuring are

Table 3 Possible advantages and disadvantages of dosage forms for delivery of medicines to the pediatric population

Dosage form	*Possible advantages*	*Possible disadvantages*
Oral tablets, capsules	Commercially available Quality assured	Dose adjustment difficult Difficult for children to swallow
Oral mini tablets	Small enough for children as young as 6 months to swallow	Possible/perceived choking risk May need to take many tablets to achieve desired dose
Oral liquids (solutions, syrups, suspensions, emulsions)	Flexible dosing possible Generally considered the most appropriate option for children from birth to 8 years	Task masking and stability can be challenging Many drugs are not commercially available in this form, require extemporaneous compounding and information around this may be limited
Orodispersible/chewable dosage forms (films, tablets, wafers)	No need to swallow an intact tablet Easy to administer	Flexible dosing difficult Possible choking risk Acceptable mouthfeel and taste masking is challenging
Rectal suppositories/enemas	No need to mask the taste of drug Avoids enteral route	Not suitable for all drugs Not considered acceptable by some patient groups Variable absorption, can be erratic especially in neonates
Subcutaneous injection	Suitable when enteral route not appropriate Less invasive than i.v. or i.m.	Painful Requires frequent administration Only useful for small volumes
Intravenous injection	Fast acting Rapid response to dose titration Overcomes any problems with absorption	Requires trained personnel Increased risk of infection May be difficult to access vein Not generally suitable for long-term treatment
Intramuscular injection	Fast acting Possibility of prolonged duration of action	Painful due to lower muscle mass, reduced muscle perfusion especially in infants
Topical creams, gels, ointments	Local drug delivery Ease of administration	Higher risk of toxicity from drug and/or excipients in neonates and infants If not rapidly absorbed, may be wiped off by child
Transdermal	Long acting Painless Easy to administer	Difficult to adjust dose Absorption may be higher in neonates and young children than in older children
Inhalers	Rapid acting local drug delivery to lungs Spacer or mask can be used with metered dose inhalers to enable administration to young children	Not all devices (nebulizers, dry powder inhalers) are suitable for young children
Eye, ear, nasal drops, and sprays	Local drug delivery	Difficult to administer particularly to young children Absorption may be higher in neonates and young children

*Source: Based on Ivanovska, V., Rademaker, C. M. A., van Dijk, L. & Mantel-Teeuwisse, A. K. (2014). Pediatric drug formulations: a review of challenges and progress. Pediatrics **134**, 361–372; Klingmann, V., Spomer, N., Lerch, C., Stoltenberg, I., Fromke, C., Bosse, H. M., Breitkreutz, J. & Meissner, T. (2013). Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. Journal of Pediatrics **163**, 1728–1732 e1.*

familiar with using the device accurately. Ensuring dose accuracy in enteral syringes is difficult, with heterogeneity when using different syringe brands, sizes, and dose volumes. This highlights the importance of using the closest syringe size to the dose volume and avoiding small volumes (0.25 mL and less) (Arenas-Lopez et al., 2017).

Excipients

Recommending an appropriate pediatric formulation requires consideration of both the active pharmaceutical ingredient and the excipients. Excipients are defined as everything in a formulation other than the active drug. This includes flavoring agents, coloring agents, preservatives, suspending agents, fillers, and solubilizers. While excipients have been historically considered to be inert components of a formulation, it is now well known that excipients have their own toxicity issues, safety concerns, and potential for allergic reactions (Table 4). Excipients are important components of all medicinal products, especially for pediatric formulations where oral liquid dosage forms are often desired. Some excipients that are suitable in adult formulations may not be appropriate for pediatric use. As with active ingredients, this is often due to differences in ability to metabolize and eliminate some excipients, especially in neonates and infants. The effect of excipients can be cumulative if a patient has been prescribed more than one medicine. Combinations of excipients from all medicines need to be considered.

An open access, evidence-based Safety and Toxicity of Excipients for Pediatrics (STEP) database has been developed collaboratively between the European and United States Pediatric Formulation Initiatives. This user-designed resource is a compilation of clinical and nonclinical safety and toxicity details of excipients from various sources (European Paediatric Formulation Initiative (EuPFI), 2017; Salunke et al., 2013). The STEP database provides a useful platform to retrieve data pertaining to a particular excipient. It has application both in the development of new dosage forms and in the manipulation of existing adult formulations for children.

Table 4 Examples of excipients that are reported to have higher toxicity in pediatrics compared to adults

Excipient	*Purpose*	*Age group affected*	*Effect*	*Reference*
Benzyl alcohol	Preservative	Neonates (especially low-birth weight premature infants). Best avoided in children under three years old	Intraventricular hemorrhage, metabolic acidosis, seizures, gasping, increased mortality, cerebral palsy, and developmental delay at high levels	Brown et al. (1982), Dawson and Nahata (1991) and Shehab et al. (2009)
Benzoic acid, benzoates	Preservative, cosolvent	Neonates	May increase risk of jaundice in neonates	Committee for Medicinal Products for Human Use (CHMP) (2013)
Ethanol	Solvent	Neonates, infants	Accumulation of acetaldehyde leading to neurotoxicity, intoxication	Committee for Medicinal Products for Human Use (CHMP) (2006) and Whittaker et al. (2009)
Propylene glycol	Solvent preservative	Children under four years old and particularly preterm neonates	Reduced ability to metabolize leading to accumulation and neurotoxic effects Alcohol competitively inhibits propylene glycol metabolism, exacerbating this effect	Committee for Medicinal Products for Human Use (CHMP) (2017), Shehab et al. (2009) and Whittaker et al. (2009)

Solvents such as ethanol and propylene glycol are found in many medicinal products to improve drug solubility, including those for children. A study conducted in the United Kingdom evaluated exposure of 38 premature neonates born at less than 30 weeks gestation and weighing under 1.5 kg to ethanol and propylene glycol (Whittaker et al., 2009). Ethanol exposure was found to be 0.2–1.8 mL per week, which for such low-weight babies is the equivalent of 1–7 alcoholic units per week. European Medicines Agency (EMA) guidelines have since recommended safety limits for ethanol of 6 mg kg^{-1} day^{-1} for children younger than 6 years and 75 mg kg^{-1} day^{-1} for children between 6 and 12 years old (Committee for Medicinal Products for Human Use (CHMP), 2014). Despite this, there are products on the market that contain ethanol at concentrations above these limits for some children. An example is furosemide oral liquid, which contains up to 0.1 mL ethanol per 4 mg furosemide. According to the British National Formulary for Children (BNF-c) (BMJ Group, 2015), the recommended oral dosage of furosemide for children is 0.5–2 mg kg^{-1} every 24 hours, which depending on the formulation used can equate to up to 20 mg kg^{-1} ethanol—well above the proposed safety limits for children under six years of age. Neonates are unable to fully metabolize propylene glycol, which can lead to accumulation and toxic effects. High doses of propylene glycol have been associated with cardiovascular, respiratory and hepatic adverse events, and toxic effects on the central nervous system in newborns and infants (Lim et al., 2014). Alcohol competitively inhibits propylene glycol metabolism, thus further exacerbating this effect (Shehab et al., 2009). These excipients should be avoided where possible, particularly in neonates up to 14 days old. The FDA recommends that the total amount of propylene glycol and alcohol from all medicines are taken into consideration in pediatrics up to 6 months of age (FDA, 2011). The EMA have proposed safety limits for propylene glycol of 1 mg kg^{-1} day^{-1} in neonates up to 28 days, 50 mg kg^{-1} day^{-1} in children from 1 month to 4 years and 500 mg kg^{-1} day^{-1} for children from 5 to 17 years old (Committee for Medicinal Products for Human Use (CHMP), 2017).

When considering a dosage form for a pediatric patient, total daily sodium and fluid intake from all sources need to be considered. Administration of excessive fluid can lead to volume overload, particularly in neonates and cardiac patients. Any fluid restriction must include all medicines and nutrition. For example, a neonatal cardiac patient weighing 3.2 kg may have a maximum fluid allowance of 7.5 mL h^{-1} immediately following surgery, with medication infusions accounting for a significant portion of this (Owens and Musa, 2009). In order to meet nutritional requirements for growth, careful consideration must be given to the composition of all i.v. fluids administered. Where possible, dextrose is used as a diluent for i.v. infusions as the calories provided add to the overall caloric intake, compared with sodium chloride which has no caloric value.

Electrolytes are often included in parenteral formulations to maintain isotonicity and avoid pain, irritation and damage to tissues at the administration site. Large quantities of sodium or potassium in parenteral formulations can cause electrolyte imbalances. In most healthy neonates, the maximum recommended daily sodium intake is 3.0 mmol kg^{-1} day^{-1} according to the BNF-c (BMJ Group, 2015), with UK guidelines recommending a maximum of 400 mg (17.4 mmol) sodium per day for children up to 12 months old (Scientific Advisory Committee on Nutrition, 2003). Sodium load is also an issue in older children, where food sources must be taken into account.

Oral liquid formulations that are acidic or contain sugar can have a cariogenic effect. This is an important consideration for long term therapy and can have life-long implications. Where possible, sugar free formulations are recommended.

Off-Label Medicine Use and Manipulation of Licensed Medicines

Ideally, commercially manufactured medicines would be available for all age groups with no further manipulation required. Realistically however, the expense of developing such commercial products that are appropriate for children from preterm neonates through to adolescents may be prohibitive. Fig. 3 shows the ideal decision pathway when providing oral liquid medicines to children who are unable to swallow solid oral dosage forms. At the very least, standard concentrations and best practice guidelines

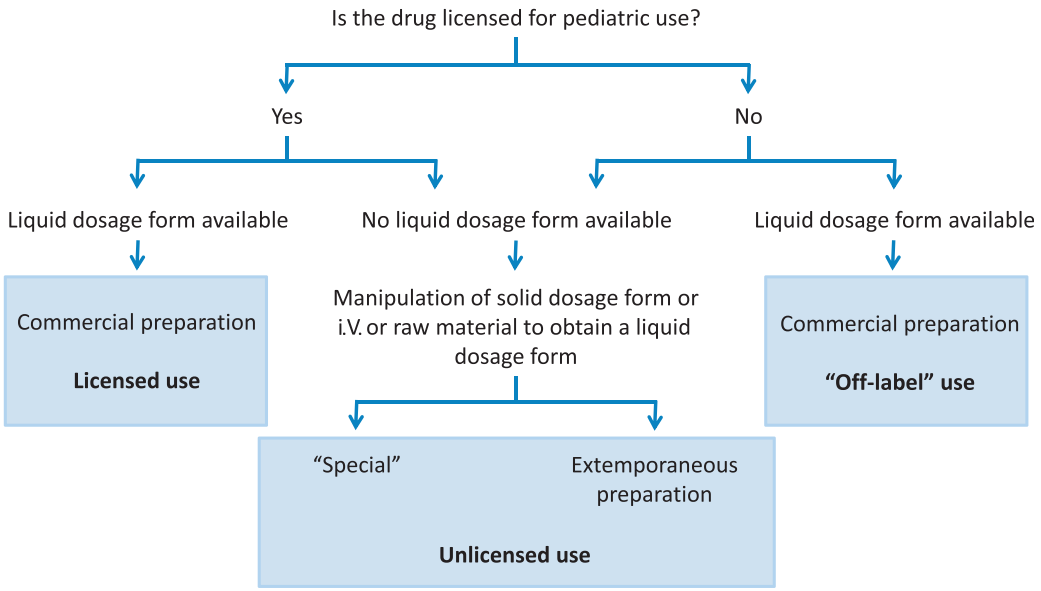

Figure 3 Decision pathway for providing oral liquid doses to children when tablets/capsules are not appropriate. *Source: Based on Standing, J.F., Tuleu, C., 2005. Paediatric formulations—getting to the heart of the problem. Int. J. Pharm. 300, 56–66, with permission from Elsevier.*

should be available at a state or national level. Indeed, there has been a move toward standardization of guidelines and formularies. Many regions have developed their own formularies including the British National Formulary for Children (BNF-c), Dutch Pediatric Formulary, New Zealand Formulary for Children (NZFc), Guida all'uso dei farmaci per i bambini (Italy), Spanish Pediamecum, and Australian Medicines Handbook for Children (AMHc). Pediatric Formularies should be evidence-based. As many medicines remain unlicensed for use in children, it is vital that the scientific background to support pediatric use is known and a risk-benefit assessment for pediatric use been performed.

Extemporaneous compounding is defined as the preparation of a therapeutic product for a patient, in response to an identified need. Medicines for pediatric patients often need to be extemporaneously compounded to produce an acceptable dosage form. Compounding generally takes place in community and hospital pharmacies, although specialist compounding facilities are available in some regions. Extemporaneous compounding has inherent risks including calculation errors, administration errors if different drug concentrations are prepared and quality concerns associated with unregulated manufacturing practice. The regulatory changes to increase the number of medicines licensed for use in children will help mitigating these risks through the availability of more evidence-based, standardized formulae.

Packaging and Compatibility of Medicines

Even packaging of medicines for children is challenging. From a practical point of view, small-volume syringes (0.1, 0.2, 0.5 mL) are difficult to label with all mandatory details as the size of the label is significantly bigger than the available surface for labeling. Ideally, all medicines will have a child resistant closure (CRC), however this may not always be possible and caregivers may need to be taught how to use them. It should be noted that these are child resistant, not child proof and care must be taken to store all medicines where children cannot access them.

Interactions between the medicine and packaging need to be considered. For example, aluminum can be leached from glass following contact with calcium gluconate solution. Accumulation of aluminum may have adverse effects on bone mineralization and neurological development in children (and adults with renal impairment). Therefore, calcium gluconate injection packed in small-volume glass containers is contraindicated for use in children younger than 18 years. Another example is amiodarone. When administering amiodarone as a continuous i.v. infusion, the administration set must be free of polyvinyl chloride (PVC) to reduce loss of amiodarone by adsorption to the PVC bag. The administration set must also be free of the plasticizer diethylhexylphthalate, or it may leach from the infusion bag into the solution, resulting in administration and potential toxicity to the child.

Where multiple medicines and fluids are prescribed, consideration must be given to the compatibility of these. For example, coadministration of ceftriaxone with calcium-containing solutions can result in particulate formation. To avoid this, ceftriaxone manufacturers advise the avoidance of any calcium-containing infusions (including intravenous nutrition), even via different infusion lines or sites, within 48 hours after the administration of ceftriaxone (AFT Pharmaceuticals, 2016). Coadministration of intravenous nutrition with any medicine using the same i.v. access is not recommended as compatibility may be problematic. Variation in the composition of intravenous nutrition formulations means published data on compatibilities is rarely available. Furthermore, potential interactions with enteral feeds must be considered. This may be particularly problematic with neonates, as they require frequent feeds, as well as those older children who are continuously tube fed.

Box 1

Vitamin K (phytonadione) is routinely given to neonates to facilitate normal clotting and prevent hemorrhagic disease until the intestinal tract acquires the bacteria necessary to synthesize vitamin K. It is given as a single intramuscular dose as soon as possible after birth, at a dose of 0.5 mg to 1 mg depending on regional guidelines.

Place of Pharmacotherapy in Children

When considering pharmacotherapy in children, risk versus benefit needs to be evaluated, particularly in young children. Recognizing when a child is ill or in pain is a complex process. Parents and caregivers often have an intimate knowledge of their child with respect to their behavior and may recognize signs of illness based on a departure from what is "normal" for their child. This concept of normality depends on the developmental stage of the child as well as a comparison to how the child usually behaves. During assessment of a child's symptoms, time is needed to determine whether they are exhibiting behaviors outside their normal range.

As with adults, the decision to prescribe medication should follow an assessment of the risk to benefit ratio for the specific patient. In pediatrics, the risks posed by a medicine may be different to those in adults and formulation and licensing considerations also need to be taken into account. Some medicines have been demonstrated to be beneficial in preventing disease, so are routinely given to children (Box 1).

Role of the Pharmacist

As in adult medicine, pharmacists are involved in many aspects of pediatric patient care. In primary care, they may advise on the management of common childhood conditions, undertake health promotion activities (including those related to vaccination, breastfeeding, and the safe use of medicines), procure appropriate formulations, dispense medicines, advise on manipulation and administration of medicines and extemporaneously compound products suitable for pediatric patients. In secondary and tertiary care settings pharmacists are involved in the provision of care including providing medicines reconciliation services, advice on the safe and effective use of medicines in individual patients or specific subgroups of pediatric patients, preparation of medicines and intravenous nutrition, the provision of medicines counseling for children, adolescents, their parents and caregivers, and the education of health care professionals. In other settings, pharmacists may work with regulatory authorities to ensure that medicines intended for children are safe and effective, or be involved in research projects that focus on the pediatric population.

However, in contrast to adult medicine where care is often focused on a single patient, pediatric care focuses on the family of which the child is a part. Decisions regarding the child's medical care are made in the context of the family, and the beliefs of the parents, while endeavoring to act in the best interest of the child.

Consent and Parental Care

Unless revoked by the courts, parents have overall responsibility for the care of their child, and are generally considered to be best placed to understand the needs of their child/children, and to make appropriate decisions in their best interests. As such, they are able to consent to medical investigations and treatment on their child's behalf until the child reaches an age where they are competent to do this themselves. However, this responsibility must be viewed in the context of the ongoing development of the child and their increasing capacity for rational decision making and autonomy, as well as the societal responsibility to protect the child from harm (Committee on Bioethics, 2016).

The right of the responsible adult (parent or caregiver) to consent to (or refuse) treatment is not absolute and is better viewed as a responsibility to represent the interests of their child rather than a right to express the caregiver's own views. In cases where the child is at significant risk of serious harm or neglect, the state (and in turn the medical system) has a responsibility to ensure that the best interests of the child are represented and that effective medical treatment is provided, regardless of the social, cultural, or religious beliefs of the parent (Committee on Bioethics, 2016). In extreme cases this may require legal advice and representation, which may result in the courts vesting the ability to provide consent in an independent guardian.

The legal framework varies by jurisdiction but in general, adults (most commonly those over the age of 18, though the legal age of majority varies by country) are presumed competent to consent unless their decisions or actions provide evidence to the contrary (Larcher and Hutchinson, 2010). The legal competence of an adolescent aged between 16 and 18 varies by jurisdiction, and may be split between different ages, with adolescents in the UK, for example, generally able to consent to treatment from the age of 16, but only able to veto treatment that will prevent serious harm or death from the age of 18 (Larcher and Hutchinson, 2010). Below the age of legal majority, a minor may provide their own consent to treatment in three broad categories (Committee on Bioethics, 2016):

- Specific exemptions for particular categories where there is concern that adolescents may not access care if parental consent is required (generally care relating to sexual health, such as contraception, and in some jurisdictions for mental health care);

- Legal emancipation—those who are considered independent of their parents (self-supporting and living separately; married or on duty with armed forces) may be considered emancipated, and have responsibility for their own decision making;
- "Mature minor" exceptions, which recognize that some adolescents are sufficiently mature and intelligent enough to understand the risks, benefits, and alternatives in a given situation, appraise these and form a well-reasoned decision. This ability is often known as "Gillick competence," following a landmark legal case in the UK in 1985 where Lord Scarman concluded "*Parental right to determine whether their minor child below the age of 16 will have medical treatment terminates if and when the child achieves sufficient understanding and intelligence to enable them to understand fully what is proposed*" (Gillick v West Norfolk and Wisbech AHA, 1985).

A child's ability to consent to or refuse treatment requires that they are able to understand the nature, purpose, and consequence of the proposed course of action. Competence is assessed in the context of the decision to be made, with decisions that entail significant risk or with potentially catastrophic consequences (e.g., accepting or refusing transplantation or chemotherapy) requiring a higher level of competence than minor decisions (e.g., deferring venepuncture, or minor surgery). With this in mind, the inclusion of the child in the decision-making process should increase over time as their maturation permits.

Counseling

In most pediatric settings, patient counseling needs to be provided for both the child being treated and their parents. Such information must be targeted appropriately as described in the subsections below.

Parents and Caregivers

In addition to standard drug information provided to adult patients (indication, possible drug interactions, duration of therapy, importance of adherence, possible adverse events, etc.), parents or caregivers need to be provided with information to enable them to accurately and safely administer the medication to their child. Pharmacists should ensure the parent has access to a suitable measuring device if required and that they know how to measure the medicine accurately using the device, and may need to provide advice on how to get the child to take the medicine. Parents also need to know how to obtain the medication (depending on the medication and the jurisdiction this may be from a standard community pharmacy, supplied directly by a pediatric hospital or manufactured on request by a specific "special products" manufacturer) and how to store it when they do obtain it. Advice on storage of the medication (use of a child-resistant closure and storage out of reach of the child) should be provided to minimize the risk of accidental overdose or poisoning (Box 2).

The Child

Children and adolescents are entitled to receive information on their treatment and medications in a form that they can understand. The information provided to the child will need to take into account the age and developmental stage of the child, their intellectual ability, and interest in the information. Tailoring the information delivery, for instance by playing games such as "memory" using medicine names and indications may be of more interest to the child patient than a typical medication counseling conversation. Toys such as dolls and medical equipment are often used to explain procedures to children and prepare them for new experiences. Adolescents in particular may have concerns relating to standing out from their peers, and these should be elicited and addressed to enhance compliance with treatment.

Virtual reality is emerging as a valuable tool in pediatric medicine, both as a distraction technique during procedures that are uncomfortable or require the child to lie still, or as a preparation technique that allows the child to experience the environment (e.g., radiology department) they will be visiting before they go there.

The Multidisciplinary Team

The multidisciplinary team plays an important role in pediatric practice. In the community setting and in rural or regional settings, care may be provided by general medical and nursing staff who care for both adult and pediatric patients. However, in the tertiary care setting, care is generally provided by specialist pediatric staff who have training and experience in pediatric patient care. In addition to team members such as medical, nursing, physiotherapy, occupational therapy, dietetics, and pharmacy often seen in the adult setting, the pediatric team works closely with those involved in the care and education of the child. Parents and/or caregivers are an integral part of the team, as are teachers and hospital play specialists.

Large tertiary children's hospitals often include a hospital school, which oversees the education of children who, due to ill-health, have experienced (or are expected to have) significant absence from their regular school. Teachers at the hospital school liaise closely with the child's usual school and their medical team to ensure that disruption to the child's education is minimized, so that academic progress is maintained as much as is possible and that reintegration into their usual school is facilitated. Education is tailored to the individual needs of each patient and may involve teaching in a hospital classroom, at the bedside, at home, or via distance methods such as online education, phone, fax, or email contact. In some cases hospital schools will also cater for the siblings of hospital patients, particularly when specialist care for one child requires the family to temporarily relocate to another area for treatment or investigations. In many cases the child does not require admission to a specific hospital school, but their ongoing care may require

Box 2

Helping Children to Take Medicines

(Best Practice Advocacy Centre New Zealand, 2014; PHARMAC et al., 2017)

- Be confident, calm, and firm, but kind, about medicine taking—the medicine needs to be given. However, if it is proving impossible to persuade the child take it, try again in about half an hour.
- If the child refuses to take the medicine, consider alternative formulations or medicines that may be available.
- Explain to the child that the medicine is to make them feel better. Reverse psychology may help—telling the child it is very special and that they can only have it once/twice/three times a day can often help!
- Sticker charts, where the child earns a sticker for each time they take their medicine and is rewarded with a treat (e.g., a trip to the park, or a toy car, etc.) after a predetermined number of stickers can be useful in rewarding and encouraging good behavior. For young children, rewards need to be frequent to be effective; older children can earn more stickers before rewards are given.
- Give the child choices where possible—having the medicine before or after their bath, what they would like to drink after the medicine, which sticker they would like for a sticker chart.
- In the hospital setting, play specialists are often a useful source of information and resources and can assist in teaching children to take medicines.
- Tablets may slip down easier with a spoonful of semisolid food—consider if the medicine can be given with apple sauce, yoghurt, or ice-cream. The jet of water obtained from a drink bottle can help carry tablets to the back of the mouth in older children.
- Capsules float on water. To teach a child to swallow capsules, have them look down at the floor. Slip the capsule into their mouth, then ask them to take a big drink of water or other fluid. The capsule should float on the liquid, and slip down as the liquid is swallowed.
- Oral liquids should be measured accurately using an oral syringe or medicine measure.
  - Babies may be wrapped gently to stop arms flailing. Use a syringe to administer medicine to the inside of the cheek (this avoids the bitter taste buds on the tongue). Administer medicine toward the back of the cheek so it dribbles down the throat rather than being spat out. Some medicines may be mixed with a little breast milk or formula, but medicines should not be mixed with bottles or large quantities of food, as if the portion is not finished the correct dose will not be given.
  - For older children, allowing them to use a straw to sip the medicine may distract them from the taste of the medicine. Follow with a small quantity of water through the straw to ensure the whole dose is given.
- If the child complains about the taste of the medicine:
  - Follow with a taste of something the child likes—breast milk, juice, or flavored sauces.
  - Encourage the child to suck an ice block before taking the medicine to numb the taste buds.
  - Encourage the child to hold their nose while taking the medicine (this also helps dull the sense of taste).
  - Consider trialing tablets or capsules instead of a liquid.
- Eye drops—have the child lie down with their head in the caregivers lap and eyes closed. Place drops in the corner of the eye near the nose, then allow child to open the eyes and blink to spread the drops.

input from, or understanding of, their condition on the part of their usual teacher and school. The pediatric team often works closely with the school to ensure the child's educational and medical needs are met.

Play is an integral part of a child's life and is how they learn. Play specialists (also known as hospital/health play specialists or child life therapists, depending on jurisdiction) provide therapeutic play and recreation programs for children of all ages in health care setting, utilizing a playroom environment and bedside play. Play activities may be used to explain investigations, tests, procedures, and treatments to children and prepare them for these, or to support their general learning and development. They also provide procedural support and distraction pre- and postoperation, at an appropriate developmental level. Play specialists also provide support to siblings and families, and can contribute to the clinical decision making process through their observations of the child and their family. From a pharmacist's point of view, play specialists can be of great value in working with children to teach them to take medications, and advising on their ability to comply with treatment options.

Vaccination

Vaccination involves the administration of an antigen to a patient in order to generate an immune response and subsequent immunological memory. The vaccine contains either attenuated (weakened) microbes, killed whole microbes or fragments of the microbe or the toxins it releases. The small amounts of these introduced into the body parenterally or via the oral or nasal mucosal routes are recognized as foreign by the innate immune system, which in turn stimulates the cells of the adaptive immune system, the T and B lymphocytes, to produce antibodies. This generates an immunological memory, which allows the immune system to quickly recognize the microbe in the future and mount a more rapid and effective immune response, preventing the disease or reducing its severity. Depending on the vaccine type, repeated doses over a period of time may be required to generate an effective immune response. Vaccines containing killed microbes or fragments of a microbe commonly require multiple successive doses to be effective, while a single dose of a live attenuated vaccine may be sufficient on its own (New Zealand Ministry of Health, 2017).

Very young children are at particularly high risk of developing severe disease as their immune system is immature. Newborn babies rely in part on maternal antibodies received from their mothers for active protection against a wide range of illnesses and to attenuate infections so infants can generate an active immunity without severe illness. Where the mother has antibodies to a disease,

Box 3

Paracetamol (acetaminophen) is arguably the most widely used medicine for children. In some countries (previously), paracetamol has been given prophylactically before and after vaccinations to reduce fever. However, paracetamol has also been shown to reduce immune response to vaccination and therefore the authors do not recommend its use for this indication.

these are transferred from the mother to the baby via the placenta from approximately 28 weeks of gestation. Babies born before this age will have little or no maternal antibodies, while babies born beyond 28 weeks gestation, but still prematurely, will have received lower levels of maternal antibodies than a full-term baby and will hence have a reduced duration of protection from illness. Maternal antibodies are also actively transported into breast milk, and the presence of these antibodies in the breast milk is one of the reasons breast milk is preferred over formula, especially in preterm and newborn infants (New Zealand Ministry of Health, 2017).

As passive immunity wanes and the immune system develops, vaccines are introduced to generate protection from diseases that can have significant consequences. Each country will have their own schedule of vaccinations depending on the resources available and the diseases of most risk in that country. These vaccination schedules typically start at six weeks of age and cover diseases such as polio, measles, diphtheria, pertussis, and rubella. Vaccination programs vary in effectiveness, due mainly to the extent of uptake of the vaccine. Smallpox has been eradicated, and extensive vaccination programs in the past few decades have led to polio being close to eradicated worldwide. Other vaccine-preventable diseases such as measles and mumps continue to cause periodic epidemics in a number of countries.

Pharmacists have a role to play in providing evidence-based information on immunization and encouraging parents to have their children immunized appropriately. In recent years there has been a significant increase in jurisdictions allowing pharmacists to perform immunizations, though in many places this is restricted to vaccinating older children and adults (e.g., with the annual influenza immunization) and pharmacist vaccination programs often do not yet include all childhood schedule vaccinations (Box 3).

Emerging and Future Roles of the Pharmacist

Historically, the role of the pharmacist has primarily been concerned with compounding and dispensing medications and providing primary health care. However, in more recent times, pharmacists have progressively become more involved in clinical roles. In the past decade there has been widening agreement that the scope of practice for pharmacists is expanding to increasingly provide more patient-focused care. Pharmacists have broader roles and responsibilities for providing independent clinical services and working as part of collaborative health teams and an expansion in both the number and type of pharmacist-provided services is taking place in all practice settings (International Pharmaceutical Federation (FIP), 2017). Correspondingly, there is an increase in both the role of the pharmacy technician and a rise in automation of the dispensing process, as more routine aspects of the role are delegated to enable pharmacist time to be used on clinical care.

The role and responsibilities available to clinical pharmacists vary considerably by geographical location. In some countries, advanced roles are rapidly becoming reality. For example, the Scotland National Health Service published a vision document in 2013 that described the aim to have all pharmacists accredited as independent prescribers by 2023, in order to provide clinical care to patients in the community (The Scottish Government, 2013). The intention of this scheme is to optimize the complementary skills of doctors and pharmacists, with diagnosis continuing to be completed by doctors and postdiagnosis management being assigned to prescriber pharmacists (The Scottish Government, 2013). In other countries, pharmacists are only just becoming established members of the health care team, and more advanced roles will take some time to develop. Alongside the development of advanced clinical roles, enabling developments are required concurrently in legislative and regulatory arenas, the infrastructure of the health system and pharmacy education and training to support these roles (International Pharmaceutical Federation (FIP), 2017). In some cases there is resistance to the development of new roles by other health professionals who fear the loss of part of their own scope (and possibly funding) due to the emerging pharmacist role. A significant barrier to implementation is often provision of funding to support the advanced roles, particularly in the community setting. In many countries, members of the public are used to accessing advice from a community pharmacist, but historically funding for services have been limited to the payment of dispensing fees, with additional income derived from retail sales. For advanced services to be sustainable, remuneration for pharmacist time must be provided by the patient and/or a funding body (whether government or an insurance scheme).

Advanced Clinical Roles

While clinical pharmacist roles have been established for some time, specialization and integration within health care teams continues to increase. Following the trends in medicine, which initially saw pediatrics develop as a specialty followed by subspecialists in the different areas of pediatric medicine, pharmacists continue to develop subspecialist interests and knowledge in different areas of pediatrics. Where once pediatric pharmacy was a specialist role in itself, a large tertiary pediatric hospital may now include pediatric pharmacists working specifically in different specialties such as renal, infectious diseases and antimicrobial stewardship, cardiology and neonatal or pediatric intensive care. In many cases, their role within these teams continues to grow,

with pharmacists increasingly developing niche roles in both in-patient and out-patient settings in much the same way they do in adult settings. For example, having a pharmacist working in a pediatric complex care clinic has been shown to be beneficial in identifying, preventing, and resolving medicines-related issues at The Hospital for Sick Children (SickKids) in Toronto, Canada (Tjon et al., 2017).

Recent years have also seen a growing trend of embedding clinical pharmacists in primary care settings such as general practice. While this has mainly focused on adult patients to date, as these roles increase in number and scope it is likely that these pharmacists will become involved in pediatric patient care as well. With the ongoing development of electronic health resources it is likely that specialist pediatric pharmacists will over time have an increased ability to provide advice and input on patient care from a distance, allowing patients in more rural or remote communities to benefit from specialist knowledge. There is also a growing trend in the introduction of advanced practice credentialing, which sees pharmacists recognized as having specialist knowledge and skills in a particular area, including pediatrics (International Pharmaceutical Federation (FIP), 2017).

Pharmacist Prescribers

Many developed countries are establishing pathways to independent prescribing for pharmacists in specialized areas of practice. Pediatrics is no different in this regard, and pharmacist prescribers are well established in pediatric settings in some countries, such as the UK where over half the neonatal intensive care unit (NICU) pharmacists who responded to a recent survey were qualified independent prescribers (Mulholland, 2018). Conversely, in New Zealand where pharmacist prescribing is in its infancy, as at June 2017 there were only 14 pharmacist prescribers out of a total of 3718 registered pharmacists (Pharmacy Council, 2017), and only one of these was practicing in pediatrics.

Educators

For many years, the route to training as a pediatric pharmacist has been an informal one, consisting mainly of on-the-job learning and teaching and mentoring by a more experienced pharmacist. Pediatric pharmacists have always thus had a role in teaching more junior colleagues the fundamentals of pediatric practice, as well as being responsible for their own learning within their specialty or subspecialty.

With the expansion of pediatric pharmacist roles there is a need for specialist training for pediatric pharmacists, and experienced pediatric pharmacists have an emerging role in the development of training material for newly established postgraduate programs. For example, in 2016, Liverpool John Moores University started a Masters Certificate of Professional Development in Medicines Use in Pediatrics and Neonates course as a distance learning program for pharmacists and other health care professionals who wish to develop their role or expand their knowledge and expertise in pharmaceutical care for children and neonates (Aragon-Cuevas, 2017).

Similar expansions in roles and specializations are also occurring in other health professions, and experienced pediatric pharmacists are also finding their expertise is needed in teaching other health professions, particularly with the increase in nonmedical prescribers, who generally require postgraduate education in pharmacology as part of their training as a prescriber.

Vaccinators

Currently, many countries allow pharmacists to administer vaccinations to predefined population groups—mainly adults, and in some cases older children and pregnant women. Pharmacist vaccination does not generally include routine childhood immunization schedule vaccinations, but as the pharmacist vaccinator workforce grows and the role becomes more established and widely accepted it is likely that this will emerge as a role for pharmacists to increase their involvement with pediatric patients.

Public Health Promotion and Care

In some countries, pharmacists are involved in the provision of health care and education as part of public health campaigns. New Zealand has high rates of rheumatic fever and much effort has been expended in decreasing the impact of this disease. "Sore throat clinics" have been set up in schools, general practices, pharmacies, after-hours medical centers, and pathology laboratories to swab the throats of children presenting with a sore throat and prescribe antibiotics for those at risk of Group A Streptococcus (GAS) infection leading to rheumatic fever. Children and young people aged 4–19 years who identify as Māori and Pacific and/or live in the areas of highest social deprivation are assessed and treated at these clinics at no cost to the family. In a formative review of these services, pharmacy clinics were popular with patients due to perceived accessibility, affordability, and acceptability, and were particularly noted for their short wait times, seeing patients on a drop-in basis and generally completing swabbing within 10 minutes of arrival, compared to general practices where patients reported often being unable to get an appointment for 2–3 days or having to wait for prolonged periods at after-hours clinics (Litmus Limited, 2016). Pharmacists working within these services are able to supply antibiotics to patients using this service who meet the criteria, either at the time of swabbing or on confirmation of GAS infection on the swab, depending on the set-up of the service. In the aforementioned review, pharmacy-provided services were also noted to be particularly vigilant at explaining the importance of taking the full course of antibiotics even after the sore throat symptoms disappeared, refuting any concerns regarding inappropriate antibiotic usage (Litmus Limited, 2016).

There is considerable scope for the development of future roles based on a similar model, with pharmacists being involved in health promotion activities or providing health care on an assess-and-treat basis for various conditions, either as independent prescribers or under delegated authority in accordance with the regulatory requirements in individual jurisdictions. There is also the potential for pharmacists to become involved in health promotion activities such as collaborating with other providers in the provision of healthy lifestyle programs.

Summary

Children form a distinct and important group with specific considerations that must be taken into account when prescribing and administering medications. Physiologic changes during childhood result in changes to pharmacokinetic parameters, which may result in different doses and formulations being required at different ages.

Dosage forms are particularly important in the pediatric population and need to be able to cater to vastly different sized patients, as well as being suitable for administration to developmentally diverse patients. A lack of licensed products continues to hinder the safe and effective use of medicines in children, and manipulation of products designed for adults is often required to enable the treatment of children. Consideration must be given to the dose, route of administration, volume, and excipients of a formulation.

The role of the pharmacist in the pediatric setting is similar to that of those working with adults, but the team involved in the care of the child often includes those who provide care and education to the child, including parents, teachers, and play specialists, and information provided by the pharmacist must be carefully tailored to the recipient. With the ongoing increase in professional roles available to pharmacist, pediatric-centered roles are emerging in vaccination, health promotion, primary health care, and education, as well as more advanced clinical roles, including prescribing.

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Clinical Pharmacy Considerations in Special Population: Pregnancy and Lactation

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Learning Objectives

Upon completion of this chapter, the reader will be able to:

- Describe physiological changes during pregnancy and factors that affect pharmacokinetics of drugs during pregnancy.
- List drugs that are contraindicated and safe to use during pregnancy and lactation.
- Describe the epidemiology, pathophysiology, clinical presentation, and complications of various medical disorders that occur during pregnancy such as hypertension, diabetes, coagulation abnormalities, gastrointestinal and psychiatric disorders.
- Discuss the management of the various medical disorders of pregnancy.
- Describe the epidemiology, pathophysiology, clinical presentation, and management of abnormalities that occur during induction of labor and delivery such as preterm labor.
- Describe the role of the pharmacist in patient management of disorders that occur during pregnancy and lactation.

Take Home Messages

1. Several factors affect the pharmacokinetics of drugs during pregnancy and lactation.
2. Drugs are classified into five categories based on evidence of known risk to fetus. Similarly, drugs are classified into five categories based on pharmacokinetics of secretion into breastmilk.
3. Hypertension and its complications occur in about 10% of all pregnancies. Hypertension can be treated using labetalol, methyldopa, and sometimes delivery of the placenta is essential to treat preeclampsia (PE) with acute complications. Aspirin may be useful in the prevention of hypertensive disorders of pregnancy.
4. Gestational diabetes mellitus is a common cause of hyperglycemia during pregnancy. Lifestyle modifications and self-monitoring of glucose are recommended for management. Insulin is the first-line treatment, while metformin can be considered as well.
5. Hematological disorders that occur during pregnancy include both coagulation as well as bleeding disorders. Management involves normalization of clotting factor or platelet levels and anticoagulation. Vaginal delivery is preferred.
6. Gastrointestinal tract disorders in the form of nausea and vomiting of pregnancy is one of the most common disorders that occur during pregnancy and affects up to 90% of pregnancies. Nonpharmacologic approaches such as ginger and pharmacologic management with a combination of thiamine and pyridoxine are effective.
7. Mental health disorders occur during or in the immediate postpartum period. Depression is the most common mental health disorder. Psychotherapy is the initial treatment of choice for mild to moderate depression, while antidepressants are reserved for severe major depression.
8. Preterm labor is a concern among pregnant women. Prevention is more important as it is difficult to predict. Vaginal progesterone therapy or cervical cerclage has been tried without much success. Therefore, screening for risk factors is important.
9. Clinical pharmacists have an important role to play in the management of disorders during pregnancy and lactation. Pharmacists have the skills and competence to:
    a. obtain patient medication history and assess current medication management
    b. obtain evidence on safety and efficacy of current and potential medications
    c. develop medication management plan and monitor response to therapy
    d. perform therapeutic drug monitoring

Introduction

Pregnancy is a common physiological state that most women experience during their reproductive years. However, some pregnant women experience pathological disorders that warrant medical attention during pregnancy or in the immediate postpartum period. On the other hand, women with preexisting diseases often become pregnant. This chapter focuses on clinical pharmacy considerations in pregnancy and the key aspects of the clinical management of common disorders of pregnancy.

Clinical Pharmacy Considerations in Pregnancy

Physiological Changes in Pregnancy

Pregnancy is characterized by a number of physiological changes in several organ systems (Soma-Pillay et al., 2016). There is a gradual increase in plasma volume throughout normal pregnancy. As early as 8 weeks, there is an increase in cardiac output by 20%. Peripheral vasodilation leads to decrease in systemic vascular resistance that allows an increase in cardiac output. Due to renal vasodilation, an increase in renal blood flow occurs by 50%. Pregnancy is a hypercoagulable state accompanied by an increase in the levels of certain clotting factors, such as VIII, IX, and X, are increased. Fibrinogen levels rise also significantly and fibrinolytic activity

Table 1 Pregnancy risk categorization of drugs

Pregnancy risk category	*Definition*
Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

is decreased. This could be attributed to the changes in levels of hormones. Because of the physiologic changes inherent in pregnancy, this can lead to substantial underdosing, or, in some cases, excessive dosing of drugs.

Factors Affecting Pharmacokinetics of Drugs During Pregnancy

Several factors affect the absorption, distribution, metabolism, and excretion of drugs during pregnancy (Koren and Pariente, 2018; Pariente et al., 2016). Some of the key factors include:

- Increase in total body weight and fat
- Delayed gastric emptying and increased transit time
- Increased cardiac output and renal blood flow
- Decreased albumin concentration with reduced protein binding
- Altered hepatic cytochrome P450 enzyme activity

Risk Categorization of Drugs for Use in Pregnancy

Drugs are generally classified into various categories based on the level of evidence and the risk to the fetus. The risk categorization of drugs in pregnancy is detailed in **Table 1** (Food and Drug Administration, 1980). It is important to note that since 2015, the US FDA is transitioning from the letter category of pregnancy risk to a new format that is simpler and easy to interpret. Per the Pregnancy and Lactation Labeling Rule (PLLR), the pregnancy and lactation part of the product label will be categorized in three categories. The first category is "Pregnancy", the second "Lactation" and the third "Females and Males of Reproductive Potential". The third category is newly created and has information related to on pregnancy testing , recommendations on contraception and the effect of the drug on fertility. https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm427798.pdf; https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm

The tables list some commonly used drugs that are contraindicated (**Table 2**) (Cooper et al., 2004; Viguera et al., 2007) and safe (**Table 3**) (Lalonde, 2011) to use during pregnancy. This is not an exhaustive list of drugs, and health-care practitioners should refer to other resources to determine whether the medications they intend to prescribe are safe.

Clinical Pharmacy Considerations in Lactation

Use of Drugs in Breastfeeding and Lactation

Breastfeeding is the gold standard for infant nutrition. It provides all essential elements for nutritional, emotional, cognitive, and immunological needs. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of infant's life, after which, complementary foods are introduced, and breastfeeding continues up to 2 years of age or beyond (WHO, 2018). Around 80%–90% of mothers initiate breastfeeding, while 40% of them exclusively breastfeed their 0–6 months infant (WHO, 2018). During this period, mothers with chronic medical conditions or acute illnesses might need to be on medications, which necessitate the understanding of medication use, transfer to milk, as well as safety of use to milk production and to breastfed infants.

Table 2 Commonly used drugs contraindicated in pregnancy

Drugs	*Adverse effects*
Antibiotics	
Chloramphenicol	Grey baby syndrome
Ciprofloxacin	Cartilage abnormalities
Sulfonamides	Brain damage due to hyperbilirubinemia
Tetracyclines	Bone development affected, yellowing of teeth
Anticoagulants	
Warfarin	Fetal warfarin syndrome (nasal hypoplasia)
Antidepressants	
Lithium	Ebstein's anomaly
Antiepileptics	
Sodium valproate	Cleft lip and cleft palate
Anti-neoplastic drugs	Multiple birth defects
Hormonal preparations	
Progestins	Cryptorchidism
Or Estrogen	Hypospadias
	Clitoral hypertrophy
Diethylstilbestrol	Cancer of female genital tract
Thalidomine	Phocomelia, amelia

Table 3 Commonly used drugs considered safe in pregnancy

Antibiotics
Amoxycillin
Ampicillin
Cephalosporins
Erythromycin
Analgesics
Acetaminophen
Endocrine
Levothyroxine
Insulin
Vitamins
Folic acid
Vitamin B6
Antihypertensives
Hydralazine
Methyldopa
Anticoagulants
Heparin

Factors Affecting Pharmacokinetics of Drugs During Breastfeeding

Certain drugs have the potential to cause adverse effects on infants receiving breastfeeding. In such circumstances, withholding breastfeeding may be warranted. Considering the large number of medications available in the market, generally, most of the medications are not of a concern for breastfeeding (Hotham and Elizabeth, 2015). Several factors play a role in determining the transfer of drugs into breast milk. These include breast milk, drugs, and maternal- and infant-related factors.

Breast Milk

Breast milk characteristics affect drug transfer (Chaves and Lamounier, 2004). Lipid and protein compositions in the milk vary between initial stages of lactation (e.g., colostrum compared to mature milk), and even vary between stages of breastfeeding (e.g., foremilk versus hindmilk). These variations affect the amount of drug transferred from mother's plasma into the milk.

Pharmacological Properties of Drugs

Pharmacological properties of drugs play a major role in determining the transfer of drugs into the breast milk. Drugs with low molecular weight (e.g., less than 200 Da) are secreted more easily into milk than drugs with a higher molecular weight. As milk is acidic (pH 6.5), drugs that are weak bases tend to concentrate in the milk. Fat-soluble drugs and drugs that have low plasma protein binding characteristics reach the milk compartment more easily than highly protein bound drugs. Furthermore, drugs with long half-life remain in the bloodstream for longer duration, and consequently, in the milk. Drugs with poor oral bioavailability are preferred during breastfeeding, as their absorption is poor by the infant. Heparin has a large molecular weight and poor oral bioavailability, so it would not be expected to be appreciably excreted into breastmilk or absorbed by the infant. On the other hand, lithium has low molecular weight with no protein binding, making it readily excreted into the milk. Drugs with known toxicity in infants such as antineoplastic or radioactive drugs should be avoided regardless of their pharmacological properties (Burkey and Holmes, 2013; Chaves and Lamounier, 2004; Hotham and Elizabeth, 2015; Sachs and Committee On, 2013).

Maternal-Related Factors

Factors affecting drug metabolism or excretion in the mother might impact on drug concentration in the milk. Patients with liver or renal diseases may have higher levels of drug in the milk due to increased circulation of drug in the mother's bloodstream. Furthermore, the route of administration of medication affects its concentration in the plasma, and subsequently in the breast milk. Several topical and inhaled medications reach the bloodstream in minimal amounts. The dose as well as the duration of treatment also impact on the safety of drug use during lactation (Burkey and Holmes, 2013; Chaves and Lamounier, 2004; Hotham and Elizabeth, 2015; Sachs and Committee On, 2013).

Infant-Related Factors

Infant-related factors include age, renal and hepatic handling, and volume of milk intake. Hepatic and renal functions are more efficient in older infants compared to newborn, where the effect of drugs is more pronounced. The effect of ingested drugs is even stronger in preterm infants as organ functions are more immature. On the other hand, younger infants consume less volume of milk compared to older infants, which also has an impact on the amount of exposure to the drug (Chaves and Lamounier, 2004; Hotham and Elizabeth, 2015).

Measurement of Infant Exposure to Drugs During Lactation

The amount of infant exposure to drugs is measured using milk-to-plasma ratio, and absolute and relative infant doses methods, which are enumerated below (Burkey and Holmes, 2013; Chaves and Lamounier, 2004; Hotham and Elizabeth, 2015; Sachs and Committee On, 2013). Milk-to-plasma ratio estimates the relative amount of drug in the milk; the lower the ratio, the lower the concentration of drug in the milk.

$$\text{Milk} - \text{to} - \text{plasma ratio} = \frac{\text{drug concentration in milk}}{\text{drug concentration in plasma}}$$

The absolute infant dose is equal to drug concentration in milk multiplied by the volume of milk ingested. However, accurate measure is difficult to obtain. An estimation of the relative infant dose is used according to this equation:

$$\text{Relative infant dose } (\%) = \frac{\text{Absolute dose } (\mu g/kg/day) \times 100}{\text{Maternal dose } (\mu g/kg/day)}$$

A relative dose of 10% or more is of concern. Lithium is an example, where breastfeeding is generally of a concern. Careful monitoring for blood levels for mother and infant is required, while some authors recommend avoiding breastfeeding.

Minimizing Infant Exposure to Drugs While Lactating

- Use the lowest effective dose when a drug is needed.
- Select a drug with a large molecular weight, short half-life, low lipid solubility, poor absorption, high protein binding, large volume of distribution, and low serum concentrations, when possible.
- Temporarily hold breastfeeding if toxic drug is used (along with breastmilk expression).
- Time period to resume breastfeeding is determined based on half-life of the drug.
- Continuation of breastfeeding might not be possible if lengthy period of treatment is needed.

Metoclopramide and domperidone increase prolactin production indirectly. They interfere with dopamine action of decreasing prolactin secretion by the pituitary gland. These medications are used to increase milk supply, however, such use is off-label.

Table 4 Drugs that are a concern while breastfeeding

Hazard to infant	*Hazard to milk production*
Amiodarone	Amantadine
Chemotherapeutic/antineoplastic agents	Pseudoephedrine
Radioactive substances	Phenylephrine
Certain psychotropic medications	Bromocriptine
Chloramphenicol	Cabergoline
Retinoids	Tamoxifen
	Raloxifene

Commonly Used Drugs Contraindicated During Breastfeeding

Only few medications are contraindicated in breastfeeding. Medications with a potential or actual hazard for the breastfed infant or to breast milk production are best avoided while breastfeeding. Table 4 provides examples for these medications.

Categorization of Drugs for Use During Breastfeeding

Medications are categorized for their safety in breastfeeding according to Hale's categories as follows: L1, safest; L2, safe; L3, moderately safe; L4, possibly hazardous; and L5, contraindicated (Hale, 2012). This categorization is based on the pharmacokinetic aspects for breastfeeding mothers and their infants and based on recently published scientific articles.

Clinical Pharmacy Considerations in Commonly Encountered Disorders of Pregnancy

Hypertensive Disorders of Pregnancy

Hypertensive disorders are some of the major health issues complicating up to 10% of pregnancies worldwide and are the leading cause for maternal, fetal, and infant morbidity and mortality (Duley, 2009; Hutcheon et al., 2011; Umesawa & Kobashi, 2017). A number of guidelines classify hypertensive disorders of pregnancy (HDP) into four categories based on the timing of diagnosis and associated signs and symptoms: (1) chronic or preexisting hypertension; (2) gestational hypertension (GH); (3) preeclampsia-eclampsia; and (4) chronic hypertension with superimposed PE (Butalia et al., 2018; Magee et al., 2014; Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). A 2017 systematic review of several epidemiological studies, conducted in different regions globally, reported a prevalence of GH and PE that ranged from 1.8%–4.4% and 0.2%–9.2%, respectively (Umesawa and Kobashi, 2017).

Etiology and Pathophysiology of Hypertensive Disorders of Pregnancy

The etiology of HDP is still unknown; however, the pathophysiologic mechanisms of such conditions have been discussed in multiple scientific studies and reviews (Gude et al., 2004; Hutcheon et al., 2011; Mammaro et al., 2009). During healthy pregnancy, the invasion of uterine tissues by the embryonic trophoblasts and the remodeling of maternal spiral arteries into larger vessels, to accommodate adequate placental perfusion, ensure normal placental development and adequate exchange of blood and nutrients to the fetus (Gude et al., 2004; Mammaro et al., 2009). On the other hand, abnormal trophoblast invasion and vascular remodeling induce placental ischemia and oxidative stress, causing the placenta to release inflammatory mediators into the mother's circulation. Such mediators damage the endothelial cells of the vascular circulation, consequently, reducing the ability of the blood vessels to relax and inducing cellular protein leakage resulting in one or more of the HDPs (Granger et al., 2002; Gude et al., 2004; Mammaro et al., 2009). Several risk factors have been associated with the development, or worsening, of hypertensive disorders during pregnancy. Some examples of modifiable and nonmodifiable risk factors are obesity, alcohol intake, preexisting hypertension or diabetes, multiple pregnancies, and previous history of GH or other complications encountered during pregnancy (Hutcheon et al., 2011; Mustafa et al., 2012; Umesawa and Kobashi, 2017; Uzan et al., 2011; Vest and Cho, 2014). Although the only cure for these conditions is placental delivery, several protocols have been developed to guide the management of women with HDP.

Clinical Presentations and Complications of Hypertensive Disorders of Pregnancy

PE is a multisystem disease where proteinuria is often a marker of kidney damage but could also indicate damage in other organs such as the brain, liver, and retina (Karumanchi and Granger, 2016; Umesawa and Kobashi, 2017). Thus, the clinical presentation of preeclamptic mothers can vary widely, ranging from no or mild signs and symptoms, such as generalized edema or infrequent urination, to severe and life-threatening manifestations such as visual disturbances, unusual headache, epigastric pain, seizures, or even death (MacKay et al., 2001; Muti et al., 2015; Riaz et al., 2011). In addition, HDP carry significant risk of fetal and maternal short-term and long-term complications. In the short term, HDP can result in premature delivery, fetal growth restriction, and neonatal developmental delays. In the long term, it can result in recurrent PE and remote maternal chronic diseases (renal disease,

chronic hypertension, diabetes mellitus, cardiovascular diseases). Furthermore, it can lead to complications such as ischemic heart diseases or stroke in offsprings in their adulthood (Brown et al., 2013; Hutcheon et al., 2011; Kajantie et al., 2009; Mannisto et al., 2013).

Management of Hypertensive Disorders of Pregnancy

The treatment of HDP depends on the different BP categories defined by international guidelines (Butalia et al., 2018; Magee et al., 2014; Mammaro et al., 2009). For example, according to Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy, antihypertensive therapy is recommended for both "severe" (≥160/110 mmHg) and "nonsevere" (≥140/90 mmHg) hypertension (Butalia et al., 2018). On the other hand, the American College of Obstetricians and Gynecologists guideline recommends the initiation of antihypertensive agents for the treatment of "severe BP elevation" (≥160/110 mmHg), while only close monitoring is recommended for "mild hypertension" (140-159/90–109 mmHg) (American College of, Gynecologists, & Task Force on Hypertension in, 2013).

The most common first-line BP lowering agents for the treatment of HDP are labetalol, methyldopa, and nifedipine (Butalia et al., 2018; Kattah and Garovic, 2013; Magee et al., 2014). Moreover, another means of treating severe PE, or related complications, is the early termination of pregnancy. However, in stable mothers beyond 34-weeks' gestation, the administration of a 48-h course of corticosteroids before delivery is recommended to help preserve the fetal lung maturity (Butalia et al., 2018; Magee et al., 2014). In addition, during an eclamptic seizure, the administration of magnesium sulfate is superior to other conventional anticonvulsants, such as phenytoin or diazepam, and is considered a first-line therapy (Kattah and Garovic, 2013). Furthermore, in women at high risk of PE, including those with a history of recurrent PE, preventative measures such as the administration of low-dose aspirin (80 mg/day) can be undertaken, as means of counteracting inflammation, and calcium supplementation (Butalia et al., 2018; Kattah and Garovic, 2013; Magee et al., 2014).

Diabetes During Pregnancy

Diabetes mellitus (DM) is a chronic metabolic disorder, which is considered to be a rapidly growing global burden that predisposes individuals to a wide array of economic, health, and social consequences (American Diabetes Association, 2012b). According to the International Diabetes Federation (IDF), the prevalence of DM has reached 425 million adults in 2017, 204 million of whom were women (Cho, 2017). In addition, hyperglycemia (abnormally elevated blood glucose), the hallmark characteristic of DM, is the most common complication encountered during pregnancy, and was evident in 21.3 million live births worldwide in the year 2017 (Cho, 2017).

Furthermore, hyperglycemia first detected during pregnancy (HFDP) is classified into two categories based on the severity of blood glucose elevation: (1) diabetes mellitus in pregnancy (DIP) and (2) gestational diabetes mellitus (GDM) (Hod et al., 2015). DIP, the more severe form, is defined as either a preexisting disease (type1 or type 2 pregestational DM), or a previously undiagnosed DM first detected during pregnancy (overt DM). On the other hand, GDM, the milder form of hyperglycemia, is the most common type of HFDP, underlying up to 86.4% of the hyperglycemic cases encountered during pregnancy worldwide in 2017.

Etiology and Pathophysiology of Diabetes During Pregnancy

The etiology of GDM is explained by the pathophysiologic events that occur during pregnancy. In normal pregnancy, the physiologic state of glucose metabolism and insulin response is altered (Barbour et al., 2007; Catalano et al., 1999; Hodson et al., 2013; Law and Zhang, 2017; Sonagra et al., 2014). Healthy gestation is characterized by up to 50% decrease in insulin-mediated glucose disposal, in addition to an estimated 200%–250% increase in insulin secretion as a compensatory mechanism for the increased insulin resistance observed with advanced gestation. The mechanism for such metabolic changes in pregnancy is attributed to the secretion of placental-derived hormones and proinflammatory mediators that hinder the insulin signaling pathways (Barbour et al., 2007; Catalano et al., 1999; Christian and Porter, 2014; Hodson et al., 2013). Women at risk of prolonged insulin resistance states (obesity, family history of DM/GDM, genetic predisposition for glucose intolerance, polycystic ovarian syndrome, and pancreatic beta-cell dysfunction) are those prone to developing GDM and other implications responsible for maternal and fetal-related morbidity (Catalano, 2010; Catalano et al., 1999; Law and Zhang, 2017).

Clinical Presentation and Complications of Diabetes During Pregnancy

According to the American Diabetes Association (ADA), GDM is often diagnosed during the second or third trimester, although it can, less commonly, be detected during early pregnancy. In addition, other than reporting the classic symptoms of diabetes (polydipsia, polyuria, polyphagia), women with GDM are usually asymptomatic (American Diabetes Association, 2012a; NICE Guideline [NG3], 2015). Therefore, clinical guidelines recommend screening for GDM at 24–28 weeks' gestation via the 75 g-oral glucose tolerance test (OGTT) and fasting blood glucose (FBG), or at the first prenatal visit for those with known risk of developing overt diabetes (American Diabetes Association, 2012a; NICE Guideline [NG3], 2015; Whalen and Taylor, 2017).

Screening for hyperglycemia is crucial since DM increases the risk of developing short- and long-term maternal and fetal/neonatal complications, such as cesarean delivery, the need for labor induction, secondary chronic DM/hypertension, eclampsia, macrosomia, birth trauma, secondary DM in the offspring, and perinatal mortality (Hartling et al., 2013). Since the risk of developing such

complications increases with progressive hyperglycemia, the treatment of hyperglycemia is recommended by means of achieving optimal glycemic control, HbA1c <6%–6.5% and FBG <5.3 mmol/L.

Management of Diabetes During Pregnancy

Several management modalities have been recommended to counteract insulin resistance and reduce the risk of hyperglycemia-related complications (Buchanan et al., 2012; Hartling et al., 2013; Landon et al., 2009; Poston et al., 2017). Essentially, lifestyle modification (diet, physical activity, and weight management) and glucose-self monitoring are recommended for all pregnant women with hyperglycemia (Viana et al., 2014; Wang et al., 2017). Pharmacologic interventions are added for those who do not achieve glycemic targets with lifestyle management or those who present with higher initial degrees of hyperglycemia. Moreover, insulin is the first-line pharmacologic agent recommended for the treatment of GDM, owing to its adequate efficacy and safety profiles (American Diabetes Association, 2012a; NICE Guideline [NG3], 2015). In addition, the observed efficacy and short-term safety of metformin and glyburide support their use for the treatment of hyperglycemia as adjunctive or alternative therapy (Gui et al., 2013; Langer et al., 2000). However, unlike insulin, both metformin and glyburide cross the placenta; although long-term safety data are lacking for both agents, metformin is preferred since glyburide was associated with higher risk of macrosomia and neonatal hypoglycemia (Nachum et al., 2017).

Hematological Disorders of Pregnancy

Pregnancy is associated with the promptness of several changes to multiple organ systems in order to accommodate for the "growing fetoplacental unit" (Bauer, 2018). One of the most common dramatic physiologic changes that occur during pregnancy is an alteration to the process of hemostasis (Bauer, 2018; Katz and Beilin, 2015; Townsley, 2013). Although such physiologic changes aim to ameliorate the risk of ante/postpartum bleeding, pathologic states can further complicate pregnancy through the exacerbation of underlying/inherited hematologic disorders or the development of acquired disorders of coagulation (Katz and Beilin, 2015; Lefkou and Hunt, 2012). Coagulopathy in pregnancy can be classified as (1) inherited coagulopathies, such as von Willebrand disease (vWD) and hemophilia A and B; (2) acquired coagulopathies, such as amniotic fluid embolus and liver disease, causing disseminated intravascular coagulation (DIC) secondary to uncontrolled activation of the coagulation cascade; and (3) qualitative and quantitative platelet abnormalities, such as gestational thrombocytopenia (GTP), immunological thrombocytopenic purpura (ITP), and disorders of platelet aggregation (Katz and Beilin, 2015; Lefkou and Hunt, 2012).

von Willebrand disease (vWD), the deficiency of von Willebrand factor (vWF), the carrier protein of factor VIII), is the most common (~1%) hereditary blood-clotting disorder in the general population and was observed to be among the most frequent (up to 11.9%) blood disorders of pregnancy associated with history of menorrhagia (Dilley et al., 2001; James et al., 2004; Kujovich, 2005; Lillicrap, 2013; Nichols et al., 2008; Philipp et al., 2003; Saxena et al., 2003). On the other hand, while hemophilia A and B (severe deficiency of factor VIII and IX, respectively) are rare in females, the carrier status happens to be more prevalent, with 35% of carriers having factor concentrations below the normal range (Chi et al., 2008; Katz and Beilin, 2015). In addition, despite the overall low prevalence of DIC in pregnancy (up to 0.35% in population-based studies), it is relatively high in those with pregnancy-specific complications that tend to exacerbate the condition, for which the prevalence of DIC reached up to 83% of pregnancies complicated by amniotic fluid embolism and 21% of those complicated by hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (Callaghan et al., 2012; Erez et al., 2014; Gilbert and Danielsen, 1999; Rattray et al., 2012; Shamshirsaz and Clark, 2016; Sibai et al., 1993). Furthermore, platelet defects are the most common hematological disorders encountered during pregnancy (Katz and Beilin, 2015; Lefkou and Hunt, 2012; Philipp et al., 2003, 2005). A platelet count below the normal threshold ($150–400 \times 10^9$/L) is often found in 5%–8% of all pregnancies, whereby GTP is the most common cause (75%) of this physiological, mild platelet count reduction (S. A. Hale et al., 2012; Lefkou and Hunt, 2012; Philipp et al., 2005).

Etiology and Pathophysiology of Hematological Disorders of Pregnancy

Normal gestation is characterized by a hypercoagulable state, which serves as a physiologically adaptive mechanism to maintain the placental function and to protect the mother against excessive hemorrhage during, or after, delivery (1). This phenomenon is obtained through a shift in the balance between the hemostatic system and the fibrinolytic system that favors clot formation (S. A. Hale et al., 2012). On one hand, a significant increase in coagulation factors (II, VII, VIII, IX, X, XII, XIII, and von Willebrand factor), prothrombin, and plasma fibrinogen, accompanied by a decrease in Protein S levels, is observed during pregnancy (Hellgren, 2003; Paidas et al., 2005). On the other hand, the fibrinolytic activity decreases, due to the gradual increase of plasminogen activator inhibitors (PAI)-1 and PAI-2 derived from the placental tissues, which then returns to normal levels upon placental delivery. Consequently, compared with nonpregnant women, an otherwise healthy pregnant woman is at an increased risk of thrombosis (Bauer, 2018; Katz and Beilin, 2015; Townsley, 2013). However, it can be difficult to quantify the range of spectrum between the hemorrhagic risk and the thromboembolic risk in those with pregnancies complicated by coagulation disorders. Although some congenital bleeding disorders may improve secondary to the pregnancy-induced prothrombic state, acquired and functional bleeding problems are at risk of worsening throughout gestation and during or following delivery. Thus, pregnant women with history of coagulopathy (personal or family history), history of bleeding abnormalities (e.g., menorrhagia and epistaxis), evidence of antepartum trauma (e.g., placental abruption), or known consumption of causative agents (e.g., aspirin, alcohol) must be thoroughly evaluated by a multidisciplinary team. Accordingly, factor levels must be checked at conception, at 28 and 34 weeks' gestation, and before delivery or other invasive procedures (Dunkley et al., 2009; Lee et al., 2006).

Clinical Presentations and Complications of Hematological Disorders of Pregnancy

The clinical presentation of coagulation disorders in pregnancy is often related to the clinical classification of the disease (type and severity) and the particular coagulation factors/proteins involved. For example, pregnant women with classical vWD-type 1 (mild factor deficiency) are often asymptomatic or present with easy bruising, since normal factor levels are attained throughout gestation. However, pregnancy can exacerbate the bleeding tendency in those with vWD-type 3 (complete factor absence), leading to an increase in the risk of bleeding episodes (Laffan et al., 2014; Lefkou and Hunt, 2012). Another instance is while women with ITP rarely bleed and carry the risk of passing down neonatal thrombocytopenia (up to 14%), those with GTP are asymptomatic and carry no transplacental risks to the fetus. Furthermore, apart from the high prevalence of maternal morbidity and mortality associated with the HELLP syndrome, other maternal and fetal complications associated with blood disorders in pregnancy can include: prolonged/excessive bleeding with miscarriages or spontaneous abortions, prolonged/excessive bleeding postpartum (as factors' levels fall to prepregnancy levels), treatment-related complications (thrombosis, infections, etc.), bleeding/infections secondary to invasive monitoring methods, transplacental transfer of antifactor/antiplatelet antibodies, and neonatal intracranial hemorrhage upon delivery (Dunkley et al., 2009; Gernsheimer, 2016; Lee et al., 2006; Lefkou and Hunt, 2012).

Management of Hematological Disorders of Pregnancy

The management of bleeding disorders in pregnancy depends on the type, subtype, and severity of the disorder ((Dunkley et al., 2009; Lee et al., 2006). Generally, patients should be provided with a "birth plan," indicating their preferences, disease information, and treatment plan (Dunkley et al., 2009; Lee et al., 2006). In addition, normalization of factor/platelet levels, especially in those with severe disorders, should be attained as close as possible to labor and delivery, while aiming to maintain those levels for up to 7 days after delivery. The treatment/prophylaxis modalities available for patients, or carriers, of bleeding disorders in pregnancy are 1-desamino-9-d-arginine vasopressin, tranexamic acid, recombinant proteins (preferred), and blood components (plasma and cryoprecipitate). Such methods aim to achieve clot stabilization, increase factor concentration, and directly activate the coagulation cascade (Katz and Beilin, 2015). However, given the increased risk of venous thromboembolism encountered during labor and delivery, prophylactic anticoagulation is considered for parturient women for whom hemostasis is achieved (Dunkley et al., 2009; Katz and Beilin, 2015; Lee et al., 2006). Moreover, owing to the lack of safety data on the appropriate mode of delivery in such patients, vaginal delivery and neuraxial anesthesia are recommended, unless a clinical judgment presumes otherwise.

Gastrointestinal Tract Disorders During Pregnancy

Gastrointestinal tract (GIT) symptoms such as nausea, vomiting, heartburn, diarrhea, and constipation are common in pregnancy. Pregnancy may also complicate GIT diseases such as inflammatory bowel disease (IBD) and gastroesophageal reflux disorder (GERD). Therefore, other pathologic conditions and causes should be considered during the evaluation of a pregnant patient who presents with these GIT symptoms. The common GIT symptoms and disorders of pregnancy may be associated with adverse health outcomes and decreased quality of life in the mother and the fetus (Ayyavoo et al., 2014; Bustos et al., 2017; Gomes et al., 2018; Wood et al., 2013). Nausea and vomiting of pregnancy is a common occurrence, affecting 50%–90% of pregnant women (Body and Christie, 2016; Ebrahimi et al., 2010). However, the incidence of hyperemesis gravidarum, a more severe form of vomiting in pregnancy, is much lower, occurring in about 0.3%–3% of pregnant women (London et al., 2017). This has significant effect on the patient's quality of life, daily activities, and work capacity (Ayyavoo et al., 2014; Wood et al., 2013). GERD is another common GIT symptom of pregnancy, and its incidence is reported to be from 17% to 45% (Vazquez, 2010, 2015). It usually begins at the end of the first trimester and can significantly impair the patient's quality of life. However, complications of GERD such as esophagitis, bleeding, and strictures are not commonly reported (Body and Christie, 2016). Furthermore, constipation is also a common symptom experienced during pregnancy with a prevalence rate ranging from 11% to 44% (Bradley et al., 2007; Prather, 2004; Rungsiprakarn et al., 2015; Shi et al., 2015).

Etiology and Pathophysiology of Common Gastrointestinal Tract Disorders of Pregnancy

Several body systems including the GIT undergo important physiological and structural alterations and adaptations during pregnancy to allow fetal development and the mother's well-being (Body and Christie, 2016; Gomes et al., 2018; Tan and Tan, 2013). For instance, increased levels of hormones, such as progesterone, contribute to delayed gastric emptying (Gomes et al., 2018; Tan and Tan, 2013). In addition, there is increased gastric acidity due to increased production of gastrin by the placenta (Tan and Tan, 2013). On the other hand, the growth of the fetus in the uterus may also result in anatomical alteration of abdominal organs and can result in the common GIT symptoms of pregnancy such as nausea, vomiting, diarrhea, heartburn, and constipation.

Although, the exact mechanism of nausea and vomiting is not completely understood, it is believed that elevated level of progesterone has an inhibitory effect on the smooth muscle of the pylorus and small bowel, decreasing gastrointestinal motility, and delaying gastric emptying (Body and Christie, 2016). GERD is also believed to be associated with a similar mechanism. Multiple pregnancies have been associated with more prevalent and severe symptoms due to the higher levels of human chorionic gonadotropin (Matthews et al., 2015). Furthermore, psychological factors such as anxiety, depression, unwanted pregnancies, and negative relationships with family may also play an important role in the pathogenesis of nausea and vomiting of pregnancy and have been linked to a higher prevalence (Body and Christie, 2016; Gomes et al., 2018). Furthermore, pregnancy-induced diarrhea may be due to elevated levels of prostaglandins.

Clinical Presentations and Complications of Common Gastrointestinal Tract Disorders of Pregnancy

Nausea and vomiting symptoms begin early (between the 4th and 6th week of gestation), reach their peak between the 8th and 12th week, and typically cease around the 20th week of gestation (Body and Christie, 2016). Although the term "morning sickness" is popularly used to refer to nausea and vomiting of pregnancy, these symptoms persist throughout the day in the majority of affected women (Lee & Saha, 2011). Other differential diagnosis for pregnancy-induced nausea and vomiting include GERD and peptic ulcer disease. Most women with nausea and vomiting of pregnancy have normal vital signs and other physical examination findings (Lee and Saha, 2011). Hyperemesis gravidarum is associated with severe nausea and excessive vomiting that usually start before the end of the 22nd week of gestation (Bustos et al., 2017). It is characterized by prolonged vomiting leading to dehydration and electrolytic imbalance, nutritional deficiency, ketonuria, and a weight loss of more than 5% of prepregnant weight, often leading to hospitalization and other fatal outcomes (American College of Obstetricians and Gynecologists, 2015; London et al., 2017; Verberg et al., 2005). Patients also commonly present with excessive salivation (ptyalism) and heartburn. These have been the most commonly used criteria for the diagnosis of hyperemesis gravidarum (American College of Obstetricians and Gynecologists, 2015). Electrolytes and acid–base abnormalities may include hyponatremia, hypokalemia, and hypochloremia (London et al., 2017). Mild elevation in enzymes such as lipase, amylase, and liver transaminases are also often found in patients with hyperemesis gravidarum (Lee and Saha, 2011). Patients may also present with signs and symptoms of severe dehydration such as tachycardia, orthostatic hypotension, dry skin, and lethargy (Lee and Saha, 2011; London et al., 2017).

Heartburn is presented as a burning sensation in the upper part of the GIT including the throat (Richter, 2005). Complications such as erosive oesophagitis, bleeding, and strictures are rare in heartburn during pregnancy (Body and Christie, 2016; Richter, 2005; Vazquez, 2015); therefore, diagnostic investigations such as endoscopy, oesophageal manometry, and pH studies are not routinely conducted (Richter, 2005; Vazquez, 2015). The diagnosis of pregnancy-induced heartburn is mainly based on clinical history and physical examination.

Management of Nausea and Vomiting of Pregnancy

A number of nonpharmacologic and pharmacologic approaches are used for the treatment of nausea and vomiting of pregnancy including hyperemesis gravidarum. These include lifestyle and dietary changes, pharmacotherapy, intravenous fluid replacement, and nutrition therapy. Most women will not require pharmacotherapy and can be managed with dietary modifications and other nonpharmacologic options. Dietary guidelines and recommendations have been proposed to tackle the intensified sense of smell and metallic taste that appears to aggravate nausea and vomiting (Ebrahimi et al., 2010). The dietary recommendations include (1) small frequent meals and avoidance of fatty foods and fresh vegetables that can delay gastric emptying; (2) maintaining adequate hydration and electrolytes through daily consumption of 1.5–2 L of water or drinks containing glucose, salt, and potassium; (3) avoiding strong tasting and odorous foods (e.g., spicy and food with metallic taste); (4) eating simple dry carbohydrates (e.g., crackers and biscuits) before getting out of bed in the morning; and (5) snacking on high protein diets and nuts between meals (American College of Obstetricians and Gynecologists, 2015; Body and Christie, 2016; Bustos et al., 2017; Ebrahimi et al., 2010).

Ginger (*Zingiber officinale*) has traditionally been used and is considered a nonpharmacologic option for the treatment of pregnancy-induced nausea and vomiting (Giacosa et al., 2015). Multiple preparations of ginger are available including dietary supplement forms, or extracts in teas and capsules (Ebrahimi et al., 2010). A Cochrane review has evaluated nine randomized controlled trials (RCTs) involving ginger (Matthews et al., 2015). Another recent meta-analysis of RCTs suggests that ginger improved nausea symptoms in pregnancy compared to placebo, but did not significantly decrease vomiting episodes (Viljoen et al., 2014). The reviewers conclude that ginger could be considered as a harmless and potentially effective alternative for the treatment of pregnancy-induced nausea and vomiting.

Both thiamine (vitamin B1) and pyridoxine (vitamin B6) have been studied for their antiemetic properties, have proven effective, and are indicated as routine supplements in patients with nausea and vomiting (Body and Christie, 2016). Pyridoxine dose of 10–40 mg/day has been used to reduce the severity of nausea and vomiting symptoms, but could be used in higher doses up to 200 mg/day (American College of Obstetricians and Gynecologists, 2015; Vutyavanich et al., 1995). Histamine receptor blockers (anti-H1), such as diphenhydramine, dimenhydrinate, cyclizine, cinnarizine, and doxylamine, are considered first-line treatment, because no adverse fetal effects have been found (Body and Christie, 2016; Magee et al., 2002). Doxylamine has the advantage of being safe when symptoms begin. The American College of Obstetricians and Gynecologists recommends doxylamine either alone or in combination with pyridoxine as first-line treatment for pregnancy-induced nausea and vomiting (American College of Obstetricians and Gynecologists, 2015). Diclectin (also marketed as Diclegis in USA) is a delayed-release formulation containing a combination of doxylamine succinate 10 mg and pyridoxine HCl 10 mg, recommended in a standard dose of four tablets daily (one in the morning, one in the afternoon, and two at bedtime).

Phenothiazines such as chlorpromazine, perphenazine, prochlorperazine, promethazine, and trifluoperzaine are also considered first-line treatment options (Body and Christie, 2016; Magee et al., 2002). Finally, metoclopramide, a dopamine antagonist with upper GIT motility stimulant effect, has been used for the treatment pregnancy-induced nausea and vomiting. Given the limited safety data and its potential extrapyramidal side effects on both the fetus and the mother, metoclopramide is considered a second-line option (Body and Christie, 2016). Serotonin receptor antagonists such as granisetron and ondansetron are used for the treatment of severe nausea and vomiting and hyperemesis gravidarum (Lee and Saha, 2011), although their safety in pregnancy is controversial (Bustos et al., 2017; Siminerio et al., 2016).

Management of Heartburn During Pregnancy

The first-line treatment for heartburn in pregnancy is dietary and lifestyle modification, including reduction of fatty foods intake as well as reducing the size and frequency of regular meals (Body and Christie, 2016; Vazquez, 2010). Other commonly recommended lifestyle measures for heartburn in pregnancy include raising the head of the bed and caffeine intake reduction. Vazquez et al., in their clinical review found that antacids (with or without alginates) provide effective relief of heartburn of pregnancy. The review, however, conclude that there is no definitive evidence of effectiveness for H_2-receptor antagonists, proton pump inhibitors, and dietary and lifestyle modifications (Vazquez, 2015).

Psychiatric Disorders During Pregnancy

Mental disorders are common during and after pregnancy (Howard et al., 2014; Kent, 2011). In fact, prenatal and postnatal period represents the highest prevalence of mental disorders in women (Howard et al., 2014; Kent, 2011; Pereira et al., 2012). Despite delivering a baby is a happy moment, many women develop depressive disorders during the postnatal period (Howard et al., 2014). The manifestation of postpartum depression ranges from mild symptoms that are typically self-limiting to minor or severe depression. This can lead to adverse outcomes for the mother and the baby, if left untreated (Grigoriadis et al., 2013; Howard et al., 2014; Stein et al., 2014).

Depression is the most frequent mental disorder of pregnancy affecting nearly 20% of women (i.e., one in every five) (Bennett et al., 2004; Pereira et al., 2012). This has adverse consequences not only on the mother's health and well-being but may also affects the infant's development (Grigoriadis et al., 2013; Norhayati et al., 2015; O'Hara and McCabe, 2013; O'Hara and Wisner, 2014; Pereira et al., 2012). In general, the prevalence of postpartum depression is estimated to be between 10% and 15% (Bennett et al., 2004; Couto et al., 2015; Pereira et al., 2012). Onset of postpartum depression occurs before, during, or after pregnancy. However, among women whose postpartum depression begins postdelivery, onset is most common within the first few months of parturition, with the first month postpartum representing the peak prevalence of depressive symptoms (Iwata et al., 2016).

Etiology and Pathophysiology of Postpartum Depression

The pathophysiology of postpartum depression is not fully understood, and it is unknown whether it represents a distinct subtype of depression or not (Iwata et al., 2016; O'Hara and Wisner, 2014; Yonkers et al., 2011). However, key factors implicated in postpartum depression include hormonal changes and dysregulation (Meltzer-Brody, 2011; O'Hara and McCabe, 2013), genetic susceptibility and epigenetics (Couto et al., 2015; Meltzer-Brody, 2011), psychological factors, and social and economic factors (Ghaedrahmati et al., 2017; O'Hara and McCabe, 2013). Postpartum depression is associated with fluctuations in hormonal levels of estrogen, progesterone, cortisol, oxytocin, and thyroid hormone (Meltzer-Brody, 2011; Norhayati et al., 2015; O'Hara and McCabe, 2013; O'Hara and Wisner, 2014; Yonkers et al., 2011). It has been suggested that women with postpartum depression may be particularly sensitive to sudden decline in gonadal steroids (Meltzer-Brody, 2011; O'Hara and Wisner, 2014). Furthermore, elevated levels of neurotransmitter monoamine oxidase-A in the cortex are associated with postpartum depression. This could lead to the metabolism and depletion of neurotransmitters such as norepinephrine, dopamine, and serotonin, leading to depression (Sacher et al., 2015).

Several possible risk factors associated with postpartum depression have been identified. The risk factors could be classified into psychological, biological, obstetrical, socioeconomic, and lifestyle (Ghaedrahmati et al., 2017). Identified risk factors include, but are not limited to, previous history of depression, antenatal depression, family history of psychiatric illness or postpartum depression, high levels of postnatal stress, stressful life events during or after pregnancy, poor social support (e.g., economic and emotional support) in the puerperium, young age (e.g., 13–19 years), multiparity, unintended pregnancy, fear of childbirth, season of delivery, adverse pregnancy and neonatal outcomes, and childcare stress (Ghaedrahmati et al., 2017).

Clinical Presentation and Symptoms of Postpartum Depression

Symptoms of postpartum depression and other nonperinatal types of depression appear to be similar. The Diagnostic and Statistical Manual, Fifth Edition (DSM-5) outlines the diagnostic criteria for a major depressive episode. The criteria include depressed mood most of the day (e.g., feels sad, empty, hopeless, appears tearful), markedly diminished interest or pleasure in all, or almost all, activities most of the day, significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day, diminished ability to think or concentrate, or indecisiveness, nearly every day, and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. In addition, the above symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and that that the episode is not attributable to the direct physiological effects of a substance or to another medical condition.

The episodes of postpartum depression vary in their severity, which guides selection of treatment regimen. Postpartum depression may resolve spontaneously or with treatment, or develop into a chronic depressive disorder (Fitelson et al., 2011; Howard et al., 2014). The adverse consequences of postpartum depression include impairment of maternal functioning, poor infant nutrition and health, interference with breastfeeding, abnormal development and cognitive impairment of the infant, and impairment of maternalinfant bonding, care of the infant, and relationship with partner (Grigoriadis et al., 2013; Pereira et al., 2012; Stewart, 2011).

The following symptoms should prompt a clinician to suspect postnatal depression: sadness for at least 2 weeks, concerns about her ability to care for the infant, anxiety about the health of the infant, negative perception of infant temperament and behavior, lack of interest in the infant's activities, lack of response to support, nonadherence to postnatal care, frequent nonroutine visits to the obstetrician or pediatrician, and use of tobacco, alcohol, or illicit drugs (Pearlstein et al., 2009; Yonkers et al., 2011). The US Preventive Services Task Force practice guidelines recommend that clinicians (including obstetricians, gynecologists, and pediatricians) should screen all postpartum women for depression and ensure follow-up for potential diagnosis and treatment (Siu et al., 2016). This is also in line with the recommendations of the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence (NICE) guidelines. Screening for postnatal depression is emphasized because it is associated with negative sequela, it is highly prevalent, underdiagnosed, and amenable to treatment (Milgrom and Gemmill, 2014). Currently, standardized and validated screening tools are available and the most commonly used is the Edinburgh Postnatal Depression Scale (EPDS), a 10-item tool that can be completed in 5 min (Milgrom and Gemmill, 2014).

Management of Postpartum Depression

Psychotherapy is the initial treatment of choice for mild to moderate postpartum major depression (Fitelson et al., 2011; Meltzer-Brody, 2011; O'Hara & McCabe, 2013; Stewart, 2011). Psychotherapy alone is appropriate if the depressive disorder does not include suicidal ideation or obvious impairment of function. Furthermore, psychotherapy alone is a reasonable alternative to antidepressants in patients with severe postpartum depression and a previous history of poor response to antidepressants or if they decline pharmacotherapy (National Institute for Health and Care Excellence, 2014). Psychotherapy approaches for the treatment of postpartum major depression include cognitive behavioral therapy, behavioral activation, nondirective counseling, and psychodynamic psychotherapy. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and bupropion are indicated if psychotherapy is not successful, or it is declined by the patient, or if the patient has responded to an antidepressant previously (Fitelson et al., 2011; Kim et al., 2014; Meltzer-Brody, 2011; O'Hara and McCabe, 2013; Stewart, 2011). Furthermore, combination of psychotherapy and pharmacotherapy is beneficial for some patients. The benefits of using antidepressants outweigh the potential risks to the infant in patients who are breastfeeding.

In general, the choice of an antidepressant depends primarily on history of prior treatment. In addition, the selection of the antidepressant in breastfeeding mothers also depends on prior treatment history and potential risk for the mother and the infant. However, there is no compeling evidence regarding safety differences among commonly used antidepressants. SSRIs such as sertraline, paroxetine, and citalopram are recommended for patients with severe major depression who are breastfeeding and are antidepressant-naïve because of their demonstrated efficacy and tolerability for postpartum depression (Kim et al., 2014; Meltzer-Brody, 2011; O'Hara and McCabe, 2013; Weisskopf et al., 2015). Fluoxetine, fluvoxamine, and escitalopram are used less frequently for the initial treatment of postpartum depression in breastfeeding mothers (Weisskopf et al., 2015). It is worthwhile to mention that SNRIs, atypical antidepressants such as bupropion and mirtazapine, and tricyclics antidepressants, such as nortriptyline, are reasonable alternatives to SSRIs (O'Hara and McCabe, 2013; Sie et al., 2012).

Preterm Labor

Preterm labor is defined as "regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy" ("American College of Obstetricians and Gynecologists frequently asked questions"). It occurs in approximately 12% of all pregnancies, leading to the delivery of a premature baby (American Pregnancy Association). Therefore, preterm labor is a major cause of perinatal morbidity (e.g., neonatal disability such as blindness) and mortality. Due to the high cost of caring for a premature baby, it is important to identify women at risk of premature labor so that they can be monitored closely for the signs and symptoms.

Etiology and Pathophysiology of Preterm Labor

The underlying causes of preterm labor include inflammation and infection, vaginal bleeding during the first trimester, pathological uterine distension and the activation of the maternal or fetal hypothalamic–pituitary–adrenal (HPA) axis, and chronic stress (Lockwood and Berghella, 2018b). There are several risk factors for preterm labor such as history of preterm births, multiple pregnancy, uterine over distention, uterine anomalies, cervical incompetence, bacterial vaginosis, bleeding in early pregnancy, poor socioeconomic status, elderly or adolescent age, tobacco use, and poor nutrition. However, the most important risk factor is previous history of preterm labor (Schleussner, 2013). A history of one preterm labor increases the risk of recurrence in future pregnancies by 14.3%.

Clinical Presentation of Preterm Labor

The signs and symptoms of preterm labor that a pregnant woman will experience include pain in the lower back, light vaginal bleed, mucus discharge from the vagina, cramping similar to the one experienced in menstruation, and frequent contractions (every 10 min or less) (Lockwood and Berghella, 2018b; MedlinePlus). Upon presentation to a physician with the signs and symptoms suggestive of preterm labor, a comprehensive diagnostic evaluation is performed after obtaining history and preforming standard physical examination. Other investigations and evaluation performed include speculum examination (to estimate cervical dilation, examine for uterine bleeding, check if fetal membrane is intact or ruptured), cervical examination, transvaginal ultrasound (to determine length of the cervix), and ultrasound imaging (to determine any abnormalities to the fetus, or placenta) ("American College of

Obstetricians and Gynecologists frequently asked questions," Lockwood and Berghella, 2018b). Furthermore, laboratory tests are done to check for infection (e.g., group B streptococcus in the vagina, bacteria in the urine or sexually transmitted infections such as gonorrhea, chlamydia, and bacterial vaginosis) and fetal fibronectin protein level in vaginal discharge. The presence of fetal fibronectin (a protein that supports the amniotic sac to stay connected to the interior of the uterus) in the vaginal discharge is a predictor of spontaneous preterm birth. Based on the findings from the history and physical examination, imaging, and lab tests, an accurate diagnosis of preterm labor is made on the basis of the frequency of regular contractions (i.e., ≥6 contractions/h), dilation of the cervix (>3 cm) between 24 and 37 weeks of gestation, vaginal bleeding, ruptured membranes, and the presence of fetal fibronectin in the vaginal secretions (Rundell and Panchal, 2017).

Management of Preterm Labor

Due to the difficulty of predicting preterm labor even in women at high risk, prevention is therefore very important. Primary prevention of preterm labor with the goal of reducing the number of preterm labor cases focuses on risk factor avoidance before and during pregnancy. These risk factors targeted for primary prevention include avoiding smoking or smoking cessation, maintaining healthy bodyweight, adopting proper nutrition prior to pregnancy and during pregnancy, and effectively managing stress (Schleussner, 2013). For women with a history of spontaneous preterm delivery, progesterone therapy (injection or vaginal) starting around 16–24 weeks of gestation and continuing until 34 weeks of gestation is effective in preventing spontaneous preterm delivery (Fonseca et al., 2007). However, vaginal progesterone from 22–24 to 34 weeks of pregnancy was not efficacious in reducing preterm birth in women at high risk of preterm birth (Norman et al., 2016). A surgical procedure (cervical cerclage) that involves placing a suture around the cervix has been performed in women with shortened cervix or structural defects of the cervix to reduce the risk of preterm delivery, but its efficacy has not been proven *via* prospective randomized trials (Simcox and Shennan, 2007). However, meta-analyses have revealed perinatal morbidity and mortality reduction of the cervical cerclage surgical procedure in high-risk pregnant women with a single fetus, who have previous history of spontaneous preterm birth, and shortened cervix (Berghella et al., 2011).

The main goal of treatment of pregnant women (less than 34 weeks' gestation) with preterm labor is to provide an intervention that will give the newborn the best chance of survival with minimal complications. Treatment measures include a course of corticosteroids (e.g., betamethasone), tocolytic drugs for up to 48 h (e.g., nifedipine), antibiotics that target group B streptococcus, and magnesium sulfate (Lockwood & Berghella, 2018b). The role of the tocolytic agent for up to 48 h is to reduce uterine contractions (i.e., painful, palpable contractions that last longer than 30 s each and occur more than three times in 30 min), thereby delaying delivery so that the corticosteroid can maximally improve fetal lung maturity. During this period, the pregnant woman can be transferred to an institution that provides advanced care for preterm infants. Classes of tocolytic drugs include calcium channel blockers (e.g., nifedipine), oxytocin-receptor antagonists (e.g., atosiban), prostaglandin-synthase inhibitors (e.g., indomethacin), β_2-agonists (e.g., terbutaline, salbutamol), nitric oxide donors (e.g., nitroglycerin), and magnesium sulfate (Hubinont and Debieve, 2011). Nifedipine and atosiban are the most widely used tocolytics in practice (Walker and Thornton, 2016). In the randomized controlled APOSTEL III trial that compared the effectiveness and safety of 48 h of treatment with nifedipine and atosiban in women threatened with preterm birth, both medications had similar perinatal outcomes (i.e., composite of adverse perinatal outcomes, which included perinatal mortality, bronchopulmonary dysplasia, sepsis, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis) (van Vliet et al., 2016).

The purpose of administering corticosteroids is to reduce the neonatal morbidity and mortality by speeding up the maturation of the lungs, brain, and digestive system of the developing fetus ("American College of Obstetricians and Gynecologists frequently asked questions"). It is most effective when given between 24 and 34 weeks of pregnancy (Rundell and Panchal, 2017; Schleussner, 2013). A Cochrane review found that a single course of antenatal corticosteroid (betamethasone, dexamethasone, or hydrocortisone) is associated with a significant reduction in perinatal death, neonatal death, significant reduction in moderate/severe respiratory distress syndrome, and reduction in the need for mechanical ventilation (Roberts et al., 2017).

Magnesium sulfate is usually administered to pregnant women prior to week 32 of pregnancy (24–32 weeks) when they are at risk of delivering within the next 24 h to provide neuroprotection against cerebral palsy [American College of Obstetricians and Gynecologists frequently asked questions," Lockwood and Berghella (2018a,b); UpTODate 2018 Preterm labor]. Antibiotics are administered because of the association of vaginal bacterial infections with preterm labor and preterm rupture of membranes; hence, it makes sense to administer prophylaxis against bacterial infections ("American College of Obstetricians and Gynecologists frequently asked questions," Lockwood and Berghella, 2018b). Intrapartum antibiotic prophylaxis targeting group B streptococcus is therefore given to all pregnant women in premature labor who are likely to deliver (Hughes et al., 2017).

Induction of Labor

Full-term delivery occurs when a baby is delivered anytime from the gestational age of 37–42 weeks (Spong, 2013). In general, pregnant women will go through spontaneous labor by 42 weeks of gestation and deliver the baby. There are three stages of spontaneous labor. During the first stage, there is uterine contraction and complete cervical dilation. This is followed by the second stage where the baby is delivered. The third stage is the delivery of the placenta, and it carries the risk of postpartum hemorrhage (Dresang and Yonke, 2015). Beyond 42 weeks of pregnancy, there are some risks associated with the pregnancy, hence the need to induce labor.

Etiology and Pathophysiology of Labor Induction

When labor is induced with medication or *via* other methods to stimulate the contraction of the uterus to allow vaginal delivery, it is referred to as labor induction ("American College of Obstetricians and Gynecologists frequently asked questions"). During the 38th week of pregnancy visit, there should be discussion about induction of labor between the 41st and 42nd weeks of pregnancy if needed (National Collaborating Centre for Women's and Children's Health Clinical Guideline). In addition to prolonged pregnancy, another reason for labor induction is the rupture of membranes after 34 weeks of pregnancy. Other reasons to induce labor are hypertensive disorders, maternal medical complications, death of the fetus, restriction of fetal growth, chorioamnionitis, multiple pregnancy, and vaginal bleeding (WHO). Elective induction, which usually occurs after 39 weeks of pregnancy, refers to labor induction for nonmedical reasons such as living far away from the delivery center.

Management of Induction of Labor

Medications used in labor induction include vaginal prostaglandin E2, misoprostol, and mifepristone (National Collaborating Centre for Women's and Children's Health Clinical Guideline). Examples of contraindications for labor induction include placenta previa, vasa previa, active genital herpes umbilical cord prolapse, and transverse fetal lie (Lockwood and Berghella, 2018a).

Early Pregnancy Loss

Early pregnancy loss usually occurs in the first trimester of pregnancy. It is the loss of intrauterine pregnancy. The risk factors include previous early pregnancy loss, maternal smoking, advanced maternal age, exposure to teratogens, and fetal chromosomal abnormalities ("American College of Obstetricians and Gynecologists frequently asked questions," Lockwood and Berghella, 2018a, 2018b). Some of the preventive measures of early pregnancy loss include pharmacologic (e.g., estrogen, aspirin) and nonpharmacological therapies (counseling). Other modifiable risk factors (e.g., maternal diabetes, maternal weight, exposure to teratogens) could be managed/prevented to minimize the chances of early pregnancy loss. After definitive diagnosis of early pregnancy loss, treatment options include expectant management (i.e., complete expulsion of the fetus within 8 weeks), medical treatment (oral mifepristone plus vaginal misoprostol or misoprostol alone if mifepristone is unavailable), or surgery to evacuate the uterus.

The Role of Pharmacist in Pregnancy and Lactation

Challenges of Medication Management in Pregnancy and Lactation

Medication management during pregnancy and lactation is complex and represents a challenge to health-care professionals including the pharmacists. One prime concern is safety of fetal or infant exposure to drugs in the uterus or through breastfeeding. This is further compounded by conflicting evidence on safety/efficacy and lack of evidence regarding risks and benefits of medications in pregnancy and lactation (Grzeskowiak, 2015). Considering the physiological, pharmacokinetic, and pharmacodynamics changes that occur during pregnancy and lactation, the transfer of medication to the fetus and breastfed infant, and the efficacy and safety of medications are extremely essential in managing these patients (Burkey and Holmes, 2013). Furthermore, as pregnant and lactating women are not involved in clinical trials, this restricts the availability of evidence for managing medical conditions in this population (Burkey and Holmes, 2013). The limited role of risk categorization of medications in the decision making for safety of medications is another problem faced by health-care providers, where risk–benefit ratio assessment is difficult (Pernia, 2016).

The presence of these challenges while managing pregnant and lactating women highlights the important role of clinical pharmacists in optimizing medication use. As medication experts, clinical pharmacists contribute toward therapeutic decision making, influence prescribing and therapeutic recommendations, and improve overall health outcomes.

The Role of Clinical Pharmacists in Pregnancy and Lactation

The concepts of clinical pharmacy practice while providing care to pregnant and lactating women are the same as in other populations, but with more emphasis on the needs of these specialized populations. The general roles of clinical pharmacist include:

- Obtaining evidence regarding the safety and efficacy of medications, critical appraisal of obtained information, and providing drug information to health-care providers and patients.
- Obtaining accurate medication history and assessing current medication management.
- Developing medications management plan, monitoring therapeutic outcomes, and recommending changes if needed to achieve desired therapeutic goals.
- Performing therapeutic drug monitoring and accurately interpreting results and implementing changes in patients' drug therapy.
- Assessing allergy, side effects, and adverse drug reactions.
- Developing and implementing evidence-based guidelines and formulary in the setting of practice.
- Conducting medication use audits and improving the quality use of medications.

Other Specialized Roles of Clinical Pharmacists in Pregnancy and Lactation

In addition to the general practice concepts of clinical pharmacy, clinical pharmacists dealing with pregnant and lactating women provide specialized education to patients and health-care providers and contribute to research activities related to obstetrics and gynecology or women health in general (Burkey and Holmes, 2013; Grzeskowiak, 2015; Samuel and Einarson, 2011).

Patient education is a key area where a clinical pharmacist plays an essential role. Women receiving chronic medications for their medical conditions require education regarding medication management before, during, and after pregnancy. Clinical pharmacist provides education for lactating women about the safety or risk of infant exposure while the mother uses medications, the need for infant monitoring, and the timing between medications intake and breastfeeding, if needed. Medication adherence can be enhanced with the proper counseling about the safety and importance of taking medications as prescribed. Furthermore, clinical pharmacy contributes to family planning clinics through assessing eligibility for contraceptive and educating women about its proper use.

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Further Reading

Key Resources for Medication Use during Pregnancy and Lactation

- Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk by Briggs, Freeman and Yaffe
- Medications and Mother's Milk by Thomas W. Hale
- Australian Medicines Handbook
  https://amh.net.au/
- Women's Pregnancy and Breastfeeding Medicines Guide, Royal Women's Hospital, Victoria
  https://thewomenspbmg.org.au/
- Prescribing Medicines in Pregnancy Database
  https://www.tga.gov.au/prescribing-medicines-pregnancy-database
- Teratogen Information System (TERIS)
  http://depts.washington.edu/terisdb/
- Lexi-Drugs
  https://online.lexi.com/
- Micromedex
  https://www.micromedexsolutions.com/
- Motherisk
  http://www.motherisk.org/

Clinical Pharmacy Considerations in ICU

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Introduction

Critical illness is a complex syndrome that usually involves dysfunction of multiple organ systems and caring for a critically ill patient in the intensive care unit (ICU) is not a straightforward process (Bersten et al., 2014). Patients cared in the ICU have a higher mortality and receive twice as many regular drugs as compared to the patients in the general ward (Kane-Gill et al., 2017). The ICU is

a complex environment, which usually involves usage of multiple combinations of drugs with rapidly changing dosing in line with patients' clinical response and organ function. This extremely busy environment creates a situation with an increased likelihood of drug errors, and consequently, a higher rate of adverse events (Benkirane et al., 2009; Cullen et al., 1997; Garrouste-Orgeas et al., 2010; Merino et al., 2012; Rothschild et al., 2005; Valentin et al., 2006). In a 1-year prospective observational study involving two ICUs in the United States (US), Rothschild and colleagues reported an adverse event rate of 80.5 events per 1000 patient-days (Rothschild et al., 2005). In this study, 223 serious errors were reported (149.7 serious errors per 1000 patient-days) with drugs being responsible in 78% of the errors. Of all the reported adverse events, approximately 50% of the cases were deemed to be preventable. Importantly, reports such as these are not isolated and have been increasingly documented and observed in numerous ICUs across different countries (Aljadhey et al., 2013; Ewig et al., 2017; Gokhul et al., 2016; Jennane et al., 2011). In the context of the financial burden incurred, countries such as the United States currently spend more than US 100 billion dollars annually on the care of critically ill patients, representing more than 8% of the country's total health-care expenditure (Coopersmith et al., 2012).

With specialized knowledge and skills in niche areas such as disease pathophysiology, pharmacology, pharmacotherapeutics, and pharmacoeconomics, the role of a clinical pharmacist is crucial for optimizing patient care in the ICU through the promotion of safe, effective, as well as economical, usage of medicines (Preslaski et al., 2013). The importance of the clinical pharmacist in the ICU is further epitomized by the findings of a prospective, observational, multicenter study (PROTECTED-UK), which was conducted over a 2-week period in 21 ICUs across the United Kingdom (UK) (Rudall et al., 2017; Shulman et al., 2015). In this study, the contributions made by clinical pharmacists to the care of critically ill patients were substantial; interventions were made in approximately 1 in 6 of all prescribed drugs and importantly, two-thirds of these interventions were deemed to be of moderate to high clinical impact (Shulman et al., 2015). Additionally, drug errors were also inversely correlated with the presence of a consultant clinical pharmacist, suggesting that the availability of an experienced clinical pharmacist may lead to more effective prescribing in the ICU.

Clinical pharmacists have demonstrated value in improving the quality, safety, and efficiency of patient care, and these have been achieved in the setting of increasingly complex ICU population. As intensive care practice continues to advance with respect to patient and technological complexity, clinical pharmacists are well placed to promote and further expand their services in the ICU.

Clinical Pharmacist Contributions to the Multidisciplinary Critical Care Team

The role of hospital pharmacists has gradually evolved over the past 30 years from traditional dispensing responsibilities to becoming an integral part of the multidisciplinary team in specialist areas such as the ICU (Jurado and Steelman, 2013; Preslaski et al., 2013). This role shift has allowed clinical pharmacists to be physically present in the ICU providing direct patient care and serving as the pharmacotherapy and medicines management experts. Clinical pharmacists' specialized knowledge on pathophysiology, pharmacology, pharmacotherapeutics, and pharmacoeconomics positions them to assist clinicians and other critical care members with pharmacotherapy-decision making that increases the likelihood of therapeutic success and improves drug management systems. Increasing evidence supports improvement in patient therapeutic outcomes through interventions made by clinical pharmacists working in the ICU as a member of a multidisciplinary critical care team consisting of intensivists, critical care nurses, respiratory care practitioners, rehabilitation therapists, and other allied health practitioners (e.g., dieticians, physiotherapists) as well as nonclinicians such as spiritual care providers and social workers (Donovan et al., 2018). The unique contribution and specific expertise of members of the critical care team is pivotal in the provision of optimal care in the ICU and addresses the diverse needs of critically ill patients and their family members. The following sections below briefly review the unique roles of selected healthcare providers and members of the multidisciplinary critical care team in the ICU.

Intensivist

An intensivist is a physician who has completed a fellowship in critical care medicine and specializes in the care of critically ill patients in the ICU. The intensivists are highly trained in the management of various conditions commonly encountered in the ICU and they are proficient with the technical procedures and devices used in the critical care setting. Intensive care delivery and patient outcomes can be optimized by an intensivist-led, high-intensity, multidisciplinary critical care team in the ICU. They are often the leaders of the critical care team and are primarily responsible to coordinate and facilitate patient care. Increasing data have suggested that patient survival, ICU length of stay, and drug safety can be improved in units with high-intensity intensivist staffing (Banerjee et al., 2011; Cavallazzi et al., 2010; Nishisaki et al., 2012; West et al., 2014).

Critical Care Nurses

Critical care nurses are pivotal to the hour-to-hour running and operation of the ICU as they perform the majority of patient assessment, evaluation, and care in the unit. All nurses working in an ICU should be trained and certified in critical care nursing. Optimal numbers of nurses in the ICU have been associated with improved patient survival, adverse drug events reduction, and shortened length of hospital stay (Burns and Earven, 2002; Danckers et al., 2013; Neuraz et al., 2015; West et al., 2014).

Respiratory Care Practitioners

Respiratory care practitioners play an important role in caring for both intubated and nonintubated patients in the ICU. They are directly involved in all aspects of respiratory care of critically ill patients and perform their tasks according to physician's orders and approved protocols. Multidisciplinary ICU care involving respiratory care practitioners has been associated with early patient

mobility and optimal weaning from mechanical ventilation (Balas et al., 2013; Ely et al., 1996; Girard et al., 2008). Respiratory care practitioners are also vital in arterial blood gases monitoring and airway management (Bishop et al., 2001; McConnell et al., 2016). In some countries, this role is shared by critical care nurses and physiotherapists.

Dieticians

As malnutrition is common in the ICU, the specialized expertise of a dietician is needed to optimize nutrition delivery in critically ill patients thereby preventing negative clinical outcomes in these patients such as infection, poor wound healing and prolonged ventilator support. Critically ill patients achieve nutritional goals faster with nutritional recommendations from dietician and additionally, they are capable of performing tasks such as placement of feeding tubes and the initiation of enteral and parenteral nutrition in the ICU (Brantley et al., 2014; Braunschweig et al., 1988; Cresci and Martindale, 2003; Peterson et al., 2010; Taylor et al., 2014).

Rehabilitation Therapists

Rehabilitation therapists, which may include a physical therapist, occupational therapist, and speech pathologist, are needed in the ICU to promote early rehabilitation in critically ill patients that is essential for the improvement of functional and cognitive outcomes. ICU patients on mechanical ventilator who receive early physical therapy demonstrated longer ventilator-free days, shorter duration of ICU and hospital stay, shorter duration of delirium, as well as better motor and cognitive outcomes at hospital discharge (Alvarez et al., 2017; Morris et al., 2008; Schweickert et al., 2009). Speech pathologists are mainly responsible to facilitate communication and to assess and manage dysphagia in critically ill patients in the ICU (Baumgartner et al., 2008; de Mestral et al., 2011; Rumbach et al., 2016). Interprofessional collaboration with other team members is vital as early rehabilitation programs can and are often delayed due to deep sedation practices, which may impact functional and cognitive outcomes of critically ill patients.

Knowledge and Skill Requirements of Clinical Pharmacist in the ICU

A critical care pharmacist in the ICU is a practitioner who has an expert level of competency in critical care pharmacy practice (Jurado and Steelman, 2013; Preslaski et al., 2013; The Royal Pharmaceutical Society, 2016). The pharmacist provides patient care in the ICU, in a consistent and efficient manner, according to the philosophy of pharmaceutical care. To be able to deliver high-quality clinical pharmacy services in the ICU, a critical care pharmacist should be qualified and well-trained in the niche area of critical care pharmacotherapy. However, the training to become a clinical/critical care pharmacist in the ICU varies throughout the world. In the United States, for example, following didactic and experiential learning, a licensed pharmacist may seek Board of Pharmacy Specialties (BPS) certification to achieve privileges for independent and collaborative practice, which include specialties such as ambulatory care and critical care pharmacy. BPS-certified pharmacists must initially pass a rigorous examination and certification can be renewed or maintained by continuing education or additional testing every 7 years. Some countries, such as Australia and Malaysia, recommend that critical care pharmacist to obtain postgraduate qualifications in clinical pharmacy, which usually include lectures and clinical clerkships/attachments. In the United Kingdom, however, at least 3 years of foundation training (e.g., fundamental clinical training, pharmaceutical manufacturing, medicine information services, pharmacy law and governance, and patient services) are initially required before a pharmacist can begin to specialize in specific aspects of practice. Those interested in the area of critical care will start their specialization and will be working in the ICU under the supervision and guidance of a pharmacist consultant (experienced critical care pharmacist). The competency framework and training pathways, which have been published by the Royal Pharmaceutical Society Faculty, will also guide aspiring critical care pharmacists in the United Kingdom to finally become consultant-level practitioners in the ICU (The Royal Pharmaceutical Society, 2016).

A clinical pharmacist in the ICU should be able to (1) design, implement, monitor, evaluate, and modify treatment regimens to ensure safe and effective as well as economical patient care; (2) retrieve, analyze, evaluate, and interpret scientific evidence to provide medicine information to health-care professionals and patients; (3) participate in the generation of new knowledge on appropriate use of medicines; (4) educate health-care professionals and the public regarding rational use of medicines; and (5) engage in continuing education exercises and programs for self-development. Direct contribution from clinical pharmacists has improved specific therapeutic areas, including the management of infections and thromboembolic events in the ICU as well as optimizing sedation and analgesia in critically ill patients receiving mechanical ventilation. Some examples of these benefits are presented and discussed below and although are not exclusive to interventions in critical care units, highlight the impact of pharmacist clinical activities.

Management of Infections

Li and colleagues investigated the impact of a clinical pharmacist-directed antimicrobial stewardship program versus a nonpharmacist stewardship program in eight ICUs across Zhejiang province in China (Li et al., 2017). During the study period, the clinical pharmacist recommended changes in 38.2% of the antimicrobial orders, and these interventions were made primarily in the context of antimicrobial deescalation and discontinuation. The pharmacist-directed antimicrobial stewardship program demonstrated lower hospital mortality rate (19.3% vs. 29.0%, $p = 0.007$), shorter duration of empirical antimicrobial use (2.7 days vs. 3.0 days, $p = 0.002$), and total antimicrobial use (4.0 days vs. 5.0 days, $p = 0.030$), as well as a lower rate of resistance emergence (23.8% vs.

31.7%, $p = 0.037$) when compared to the nonpharmacist directed program. In this study, the odds of hospital mortality were 43% lower in the clinical pharmacist-directed program (OR 0.57; 95% CI 0.36–0.91, $p = 0.017$).

Gentry and colleagues evaluated the impact of a clinical pharmacist-directed antimicrobial control program in one of the teaching hospitals in Oklahoma (Gentry et al., 2000). Over a 2-year period, the clinical pharmacist reviewed >1000 orders for antibiotics and recommended changes in >50% of these orders primarily on the basis of spectrum of activity and/or dosing appropriateness. These interventions were associated with a 2.4-day decrease in length of hospital stay and a reduction in mortality from 8.28% to 6.61% for patients with infection. The acquisition cost of intravenous antimicrobials was also reduced by 30.8% annually with a total cost saving of US 291,885 dollars.

Okada and colleagues assessed the outcome of a therapeutic drug monitoring (TDM) program in a Japanese hematology ward (Okada et al., 2016). In this retrospective cohort analysis, 145 hematology patients receiving antimicrobials (arbekacin, teicoplanin, and vancomycin) for methicillin-resistant *Staphylococcus aureus* (MRSA) infection were included. The pharmacist-led TDM program had higher rates of target concentration achievement than the traditional program (74.0% vs. 55.0%, $p = 0.05$), which did not involve pharmacists in treatment decision making. Additionally, optimal antimicrobial concentrations (HR 0.46; 95% CI 0.18–0.89, $p = 0.026$) and pharmacist-led TDM interventions (HR 0.43; 95% CI 0.20–0.92, $p = 0.029$) were independent factors associated with reduced hospital stay in patients with lymphoma.

Anticoagulation Therapy

In a recent randomized controlled trial, Lakshmi and colleagues compared the impact of a pharmacist-managed anticoagulation service with usual medical care in 80 stroke patients treated in a tertiary care hospital in India (Lakshmi et al., 2013). In this study, patients who received pharmacist counseling demonstrated better and significant improvement in knowledge scores on oral anticoagulation compared to those who received standard medical care (Δ 8.2 vs. Δ 0.3, $p = 0.001$). During the 6-month study period, 77.4% of patients in the pharmacist-managed group achieved the target international normalized ratio (INR) range as opposed to 46.5% in the standard care group ($p < 0.001$). The patients in the standard care group were more likely to demonstrate supratherapeutic INR levels when compared to those in the pharmacist-managed group (23.6% vs. 8.31%, $p < 0.001$).

To and colleagues evaluated the impact of a clinical pharmacist-directed anticoagulation service in 193 patients with heparin-induced thrombocytopenia receiving direct thrombin inhibitors (To et al., 2011). Compared to patients receiving standard anticoagulation care, in-patient pharmacist-directed anticoagulation service significantly improved the time to achieve therapeutic aPTT by 34% (18.9 h vs. 6.4 h, $p < 0.001$) and the percentage of time within the therapeutic aPTT range by 32% (64.4% vs. 84.7%, $p < 0.001$). The rate of thrombolysis in myocardial infarction (TIMI) major bleeding was also significantly lower in the pharmacist-directed anticoagulation group (0.0% vs. 7.4%, $p = 0.006$).

Saokaew and colleagues compared the anticoagulation control and clinical outcomes between warfarin therapy provided by a clinical pharmacist-managed warfarin clinic and standard medical care in 433 patients in a tertiary care hospital in Thailand (Saokaew et al., 2012). In this study, 284 interventions were performed by clinical pharmacists, and the majority of them (80.3%) were accepted by physicians. The most common intervention was related to warfarin dosing adjustment (88.0%). At the end of the study period (9 months), the pharmacist-managed group had a higher percentage of time within the therapeutic INR range than those receiving standard care (47.7% vs. 39.5%, $p = 0.003$). Rates of major bleeding were 4.4 versus 4.5 events per 100 person-years for the pharmacist-managed and standard care group, respectively.

Sedation and Analgesia

Louzon and colleagues evaluated the benefits of a pharmacist-managed sedation program as compared to a standard, physician-managed program in 70 critically ill patients receiving mechanical ventilation at a large teaching hospital in Orlando (Louzon et al., 2017). When compared to the standard care group, patients who received care via the pharmacist-directed sedation program had less exposure to continuous sedation (150.3 h vs. 252.2 h, $p = 0.003$) and a lower usage of sedative infusions (12.6 infusion drips vs. 27.6 infusion drips, $p < 0.001$), particularly for the benzodiapines (2.7 infusion drips vs. 7.3 infusion drips, $p = 0.003$). The pharmacist-led group also had a reduction in ventilator days (7.4 days vs 8.6 days, $p = 0.07$) and ICU length of stay (11.5 days vs. 16.5 days, $p = 0.011$) when compared to standard care. These clinical benefits have resulted in estimated savings of $1.2 million in direct hospital costs and $183,216 in drug costs.

MacLaren and colleagues investigated the impact of a pharmacist-driven sedation and analgesia protocols compared to empiric-based therapy in 158 critically ill patients in a Canadian ICU (MacLaren et al., 2008). When compared to patients in the empiric-based group, the protocol-based group patients demonstrated significantly lower incidence of agitation (22.4% vs. 11.0%, $p < 0.001$) and pain (9.6% vs. 5.9%, $p < 0.05$). The protocol-based group patients were also more likely to achieve the goal level of sedation (17.2% vs. 29.6%, $p < 0.01$).

Marshall and colleagues evaluated the clinical impact of a sedation protocol both with and without active pharmacist intervention in 156 critically ill patients in two medical ICUs in Boston (Marshall et al., 2008). The majority of interventions made by pharmacists were related either to the initiation of alternative sedative agents (32%) or to discontinuation of continuous sedation (20%). In this before–after study, patients who were managed with pharmacist interventions were observed to have a reduction in the duration of mechanical ventilation (14.0 days vs. 7.4 days, $p < 0.001$), ICU length of stay (380 h vs. 238 h, $p = 0.001$), and hospital length of stay (537 h vs. 369 h, $p = 0.001$) than those managed by the sedation protocol alone.

Reducing Adverse Drug Events in the ICU

One of the earliest and probably best example highlighting pharmacists' vital contribution in the ICU was described by a landmark trial conducted by Leape and colleagues. Leape and colleagues prospectively evaluated the impact of clinical pharmacist participation during medical ICU rounds in the context of reducing the rate of preventable adverse drug events (Leape et al., 1999). During the 8-month study period, pharmacist participation during the medical ICU rounds was shown to significantly reduce the rate of adverse drug events by 66% from 10.4 to 3.5 events per 1000 patient-days.

Bosma and colleagues assessed the clinical and financial impact of interventions made by ICU pharmacists during patient rounds in two ICUs in the Netherlands (Bosma et al., 2018). In this study, 334 critically ill patients were included and 548 interventions were recommended by pharmacists, of which 64.8% of the recommendations were accepted by physicians. The most frequent intervention made was related to the discontinuation of unnecessary drugs for patients (21.7%) and the most commonly involved drugs are gastrointestinal (e.g., proton-pump inhibitors) and antimicrobial agents. On average, between 18 and 23 adverse events were prevented by pharmacist interventions during this study, and this observation corresponds to 0.5 to 0.6 adverse events prevented per patient round. The estimated cost benefit in this study was €128 per accepted intervention.

Tripathi and colleagues performed a retrospective review of medical records, from 2003 to 2013, to evaluate the role of clinical pharmacists in a pediatric ICU (PICU) in Minnesota (Tripathi et al., 2015). During the 11-year period, pharmacists made 27,773 clinical interventions and 79.8% of these were accepted and changed medical treatment. The two most common interventions were changes in drug dosing regimen (52.3%) and drug selection (21.4%). The number of pharmacist interventions significantly increased from 1643 interventions in 2003 to 3566 in 2013 ($p < 0.001$). Each additional hour of pharmacist presence in the PICU led to an additional 191.5 interventions and this presence was thought to prevent 1056 adverse events during the 11-year period. Patients who required pharmacist interventions the most were younger at admission (7.3 years vs. 8.1 years, $p < 0.001$), had prolonged ICU (4.3 days vs. 1.1 days, $p < 0.001$) and hospital stay (11.5 days vs. 3.6 days, $p < 0.001$), as well as a prolonged duration of mechanical ventilation (4.8 days vs. 0.8 days, $p < 0.001$).

A General Approach to Clinical Pharmacy in Critically Ill Patients

Previously, there was no standardized and structured approach to guide clinical pharmacist to provide optimal pharmaceutical care in the ICU. The FASTHUG mnemonic was introduced in 2005 to guide ICU physicians in the management of critically ill patients, ensuring that all essential aspects of patient care are adequately met and delivered (Vincent, 2005). Mabasa and colleagues then modified this approach and developed a new mnemonic for clinical pharmacist (i.e., FASTHUG MAIDENS) to standardize the approach to identify drug-related problems and optimize pharmacotherapy in the ICU (Mabasa et al., 2011). The FASTHUG MAIDENS approach to clinical pharmacy in the ICU is advantageous in several ways including: (1) a standardized and structured approach ensures that the pharmaceutical needs of critically ill patients are met consistently; (2) provide confidence and reduce anxiety among new pharmacist who are not familiar with the ICU environment by providing a stepwise approach to perform their functions; and (3) a good teaching tool for pharmacy students and residents with limited ICU experience (Mabasa et al., 2011; Masson et al., 2013). However, it is still important for pharmacist to have a sound clinical knowledge in the area of critical care pharmacotherapy while using the mnemonic (**Table 1**)

Table 1 FASTHUGS MAINDENS approach to clinical pharmacy in the ICU

Mnemonic	*Explanation*
FASTHUGS	
F	Feeding
A	Analgesia
S	Sedation
T	Thromboprophylaxis
H	Head elevation (30–45 degree)
U	Ulcer prophylaxis
G	Glucose control
S	Stool therapy
MAIDENS	
M	Medication reconciliation
A	Antibiotics
I	Indications for medications
D	Drug dosing
E	Electrolyte, hematology, and other laboratory results
N	No drug–drug interactions
S	Stop dates

Absorption Issues in Critically Ill Patients

The pathophysiological changes associated with critical illness on the gastrointestinal (GI) system have a significant effect on the absorption of drugs (Roberts and Hall, 2013). Clinical pharmacists in the ICU must consider this potential impact on drug dosing, administration, and monitoring. This section will describe potential pathophysiological changes of the GI tract due to critical illness that could affect drug pharmacokinetics (i.e., absorption), and consequently, dosing requirements in critically ill patients.

Pathophysiology Changes During Critical Illness that can Affect Gastrointestinal Function

Altered GI function in critically ill patients is common and has been reported up to 80% of patients receiving mechanical ventilation. Impaired GI function in critically ill patients can be caused by impaired enteric nerve and smooth muscle function, systemic inflammation (e.g., sepsis and/or septic shock), surgery, drugs, electrolyte disturbances, increased intracranial pressure, and underlying concomitant diseases (Heyland et al., 1996; McArthur et al., 1995; Nguyen et al., 2007, 2008). In critically ill patients with sepsis and/or septic shock, the release of endotoxins coupled with stress response may lead to impaired GI motility (Joukhadar et al., 2001, 2002). Preexisting diseases such as diabetes mellitus, GI pathologies and gut surgeries, malnutrition disorders, and other metabolic disorders may also predispose critically ill patients to GI dysfunction. Patients with head injury and increased intracranial pressure are also more likely to have significant delays in gastric emptying (Nguyen et al., 2007). The use of several drugs such as opioids, catecholamines, proton-pump inhibitors, and calcium channel blockers, which are all commonly prescribed drugs in the ICU, may also contribute to the slowing of gastric emptying (Adike and Quigley, 2014; Roberts and Hall, 2013; Stupak et al., 2012). These drugs can alter GI functions through various pharmacological effects including GI hypomotility, pyloric hyperactivity, and prolonging the duration of GI contraction.

Malabsorption leading to malnutrition is one of the major complications of impaired GI function in critically ill patients (Ritz et al., 2000). Reduced GI motility leads to impaired absorption of drugs and more importantly, the essential nutrients that are required by these patients to meet their high metabolic demand.

Common Absorption Issues in ICU Setting

Absorption of drugs in critically ill patients can be impaired when GI motility is reduced as described in the previous section. In the ICU, drugs are most often administered via the intravenous (IV) route to circumvent the erratic and unpredictable absorption associated with impaired GI blood flow and motility in this patient population. During the acute phase of critical illness, peripheral and splanchnic vasoconstriction is likely to impair oral drug absorption, and this phenomenon can be further exacerbated by the use of vasopressors and preexisting diseases (Roberts and Hall, 2013). Importantly, drug administered via IV route provides immediate onset of action through rapid drug delivery into systemic circulation, which is sometimes required in critically ill patients. Although the majority of drugs are administered through IV route, some of the drugs (e.g., beta-blockers and proton-pump inhibitors) in the ICU are also given via the oral route, and therefore the absorption of these oral formulations can be altered in such a situation. In the presence of tube feeding, relevant issues such as drug-feed (e.g., voriconazole, ciprofloxacin) and drug–drug interactions need to be considered (Mimoz et al., 1998; Williams, 2012). Another important issue is when patients receive parenteral nutrition, as there may be incompatibilities with certain commonly prescribed IV drugs in ICU setting (e.g., acyclovir, dopamine, midazolam) (Trissel et al., 1999).

The Use of Nasogastric or Nasojejunal Tube Feeding

The use of nasogastric (NG) or nasojejunal (NJ) feeds are common in the ICU and are indicated for critically ill patients who require short- or medium-term nutritional support. Approximately 25% of critically ill patients on NG feeding are receiving suboptimal nutrients due to GI dysfunction and intolerance (Adam and Batson, 1997). Progressive intolerance to tube feeding may likely lead to GI stasis, diarrhea, and infections in these patients (Power et al., 1998; Shimizu et al., 2011). This leads to inadequate nutrients and suboptimal drug delivery in these patients. Dosing adjustment or alternative treatment may be required when a significant interaction is expected to occur in patients receiving tube feeding. IV drug administration is preferable when oral drug administration is impossible.

The Use of Parenteral Nutrition

In critically ill patients who do not tolerate enteral feedings (oral or tube feeding), the administration of parenteral nutrition is common in this setting as an alternative or supplement to enteral nutrition (Bersten et al., 2014). Parenteral nutrition consists of administration of amino acids, glucose, and fat emulsion with appropriate additives (e.g., vitamins and trace elements) in one mixed solution. Various issues, particularly in relation to interaction due to incompatibility, need to be considered in patients receiving parenteral nutrition and IV drugs. Incompatibilities need to be evaluated from various aspects including IV lines, solutions, and between drug and parenteral nutrition components (Trissel et al., 1999).

Managing Absorption Issues in Critically Ill Patients

Enhancement of nutrient delivery to the GI tract in critically ill patients with impaired GI function can be achieved through direct delivery of nutrients via feeding tubes (Chapman et al., 2013; Ritz et al., 2000; Stupak et al., 2012). Drugs can also be given through

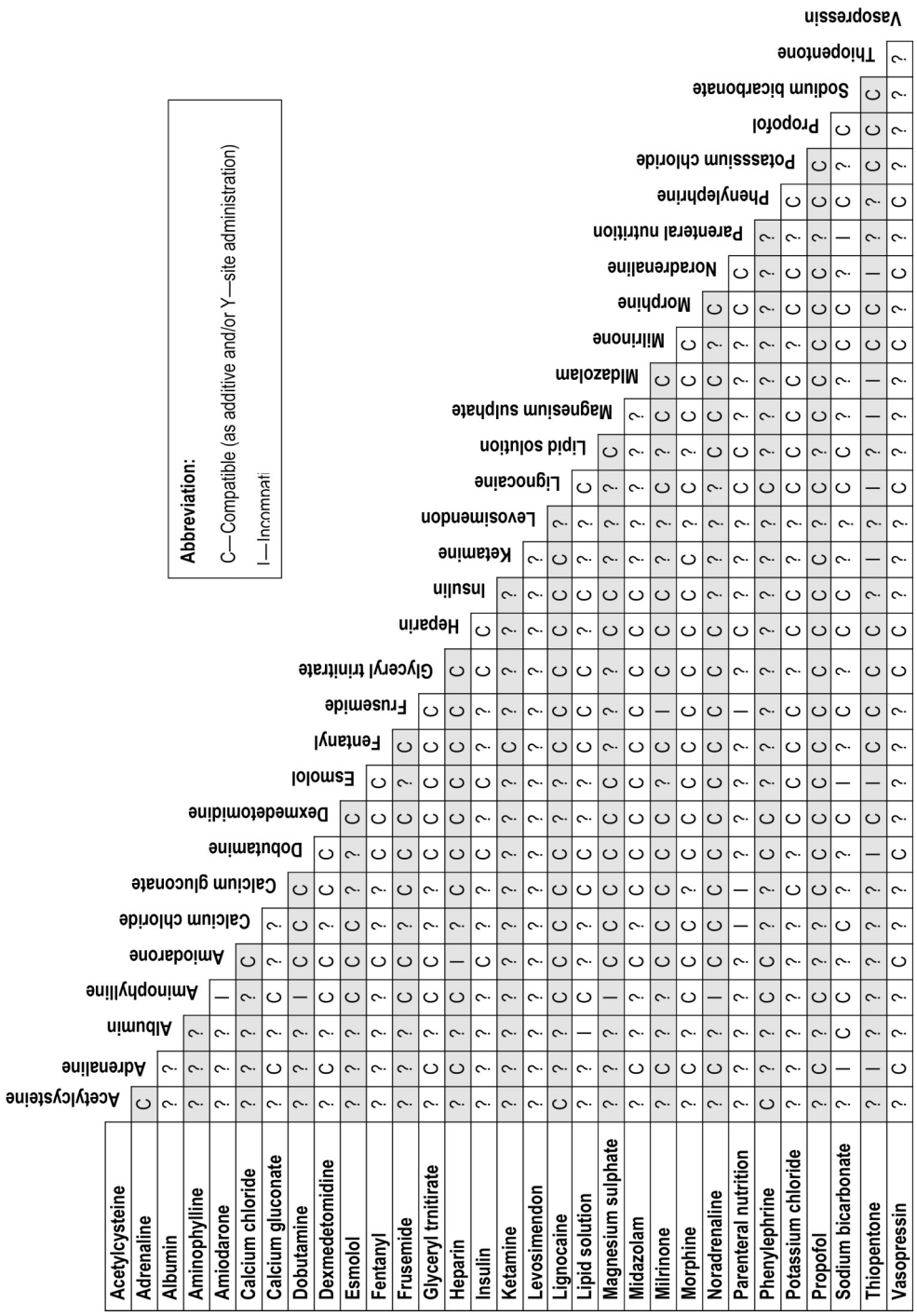


Figure 1 The Y-site compatibility for commonly used drugs in ICU setting

the inserted feeding tubes. Drugs can be crushed, dispersed, or given as the liquid form if available and administered via the feeding tubes in those patients who are unable to swallow oral drugs (Williams, 2008). Liquid formulations can be used but are commonly unsuitable for critically adult patients due to the use of indigestible sugars as sweeteners. Some oral drug formulations cannot be crushed due to more complex formulation (e.g., controlled-release and enteric-coated formulations). Therefore, it is important to identify oral drugs that can be crushed and administered through the feeding tubes. In such a situation where it is contraindicated to crush the oral drug, the IV route of administration should be preferred. Alternatively, choosing an alternative agent (either oral or IV) within the same pharmacological class can be considered. When IV drugs are used, the IV solution compatibility needs to be evaluated particularly when multiple IV drugs are prescribed through limited IV lines (Fig. 1 and Table 2).

Table 2 List of common oral drugs used in ICU setting

Medication(s)	*Oral solution availability*	*Crush tablet for tube feeding*	*Caution*
Acetylsalicylic acid	✓		Do not crush the ER tablet
Gabapentin		✓	Do not crush the ER tablet
Itraconazole	✓		
Metformin		✓	Do not crush the ER tablet
Metoclopramide	✓	✓	
Olanzapine	✓		
Risperdal	✓		
Oxycodone	✓		Do not crush the ER tablet
Phenytoin	✓		
Paracetamol	✓		Do not crush the ER tablet
Ranitidine	✓		
Prednisolone	✓		
Sodium valproate	✓		Do not crush the ER tablet
Theophylline	✓		Do not crush the ER tablet
Tranexamic acid	✓		
Warfarin		✓	
Bisacodyl			Do not crush
Captopril		✓	Unstable in aqueous solution
Carbamazepine	✓		
Esomeprazole		✓	Use oral granules for NG tube administration
Frusemide		✓	
Pantoprazole	✓		Use oral granules for NG tube administration
Propranolol			Do not crush the ER tablet
Metoprolol		✓	Do not crush the ER tablet

ER, extended release; NG, nasogastric.

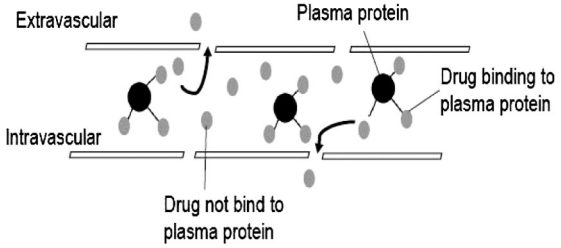
Impaired GI motility in critically ill patients can also be managed through pharmacological interventions (Ritz et al., 2000; Stupak et al., 2012). Dopamine receptor antagonists (e.g., metoclopramide, domperidone) are one of the commonly used drugs that can help improve GI motility, increasing the lower esophageal sphincter tone, and sensitizing the GI system (Doherty and Winter, 2003; Zaloga and Marik, 2000). The macrolide antibiotic erythromycin is another agent that is commonly used in the ICU to promote upper GI motility by stimulating motilin receptors (Janssens et al., 1990). The high potential for drug–drug interactions with this drug and potential for QT-prolongation should be carefully monitored when prescribed. As opioids are commonly used in the ICU for analgesia and sedation, critically ill patients who are prescribed these drugs are predisposed to baseline upper GI dysmotility. Thus, there are several pharmacological agents that are recommended to overcome upper GI dysmotility, including opioid antagonists (e.g., naloxone and methylnaltrexone) and cholecystokinin receptor antagonist (Meissner et al., 2003; Quigley, 2005; Yuan et al., 2000, 2002).

Distribution Issues in Critically Ill Patients

The pathophysiological changes associated with critical illness can result in changes in drug distribution throughout the body. Some concomitant conditions, principally obesity and severe burns, can also affect drug distribution and others, such as infections in specific sites require specific consideration of distribution (Alobaid et al., 2016; Udy et al., 2018). For ensuring optimal drug outcomes for patients, clinical pharmacists need to consider these changes. This section will describe the pathophysiological changes that could change a drug's distribution and the subpopulation of critically ill patients that are most vulnerable to these changes leading to suboptimal exposure of the drugs used.

Pathophysiological Changes during Critical Illness that can Affect Drug Distribution

Molecular weight, degree of ionization, lipid solubility, and protein binding are intrinsic properties that determine drug distribution (Pea, 2018; Varghese et al., 2011). Lipophilic agents, such as ciprofloxacin and fentanyl, have a larger volume of distribution (Vd) and greater tissue distribution (e.g., adipose and muscle tissues). In contrast, hydrophilic agents (such as the beta-lactams and digoxin) are principally restricted to the extracellular space, resulting in a relatively small Vd. By using critically ill patients with septic shock as an exemplar, the pathogenesis of systemic inflammatory response syndrome can lead to capillary leakage causing significant fluid shifts from the intravascular space into the interstitial space. This phenomenon can alter the Vd of hydrophilic drugs. Furthermore, in certain clinical conditions, such as in patients with major burns, this phenomenon can be significantly



Highly protein bound drugs that are commonly used in the ICU

Drugs	Protein binding estimation (%)
Frusemide	>90
Phenytoin	80-95
Acetylsalicylic acid	>90
Warfarin	>95
Valproic acid	80-90
Flucloxacillin	>90
Ertapenem	85-95
Ceftriaxone	85-95
Piperacillin + tazobactam	30-35

Figure 2 The effect of plasma protein changes on drugs that are highly bound to plasma protein.

increased, as a result of the widespread capillary leak and massive interstitial edema. This is further compounded by the aggressive initial ICU management undertaken, which usually includes administration of large volume of IV fluids and the combined use of multiple vasopressors and inotropes to restore normal hemodynamic status (Fig. 2).

Common Drug Distribution Issues in Critically Ill Patients

Some clinical conditions can alter distribution of drugs in critically ill patients potentially leading to treatment failure. Generally, the presence of fluid shifts due to severity of critical illness can alter the distribution of hydrophilic drugs. Drug physicochemical properties (e.g., lipophilicity, molecular size, and ionization properties) need to be considered in certain clinical situations particularly in obese critically ill patients and patients with respiratory and central nervous system (CNS) infection, where special considerations on the dosing or drug administration are required for the drug to reach the target site.

Drug Distribution into the Cerebrospinal Fluid

Central nervous system (CNS) infection is not uncommon in the ICU, particularly in ICUs managing a large number of patients with neurotrauma. CNS infections are associated with substantial morbidity and mortality, permanent disability, as well as prolonged ICU length of stay. Managing nosocomial infections in this subpopulation of critically ill patients is complicated because antibiotic delivery to the site of infection (i.e., cerebrospinal fluid) can be impaired due to inability of the antibiotic to cross the blood–brain barrier (Kumta et al., 2018; Lonsdale et al., 2013). Although antibiotic penetration may be sufficient in the initial stages of CNS infection, difficulty in achieving adequate antibiotic concentration in cerebrospinal fluid in the latter stages of infection has been frequently demonstrated in several clinical studies (Luque et al., 2014). Several factors need to be considered while managing CNS infection, including reduced meningeal permeability that could impair antibiotic distribution into the CSF, and most importantly the physicochemical properties that determines its ability to cross the blood brain barrier. In addition, some antibiotics have different abilities to penetrate into the CSF; some are only able to penetrate the CSF minimally and therefore, an alternative method of administration such as the intraventricular route may be necessary to achieve optimal drug exposure in the cerebrospinal fluid.

Ventriculitis, the inflammation of the ventricles in the brain, and meningitis, an acute inflammation of the meninges, are commonly caused by an infection. Surgically inserted intraventricular devices such as external ventricular drains are common approaches for intracranial pressure monitoring in patients with brain injury; however, these devices predispose patients to an increased risk of developing ventriculitis. Compared to meningitis, low meningeal inflammation may be present in patients with ventriculitis resulting in reduced penetration of certain antibiotics across the blood–cerebrospinal fluid barrier. Conversely, in meningitis, junctions between endothelial cells are opened, and the blood–brain barrier may become more permeable, and CSF outflow may be increased. Thus, passage of hydrophilic antibiotics in ventriculitis such as the beta-lactams and glycopeptides are likely to be reduced (Kumta et al., 2018). The degree of meningeal inflammation influences the penetration of antibiotics into the CSF. While certain drugs such as glycopeptides demonstrate low penetration irrespective of meningeal inflammation, lipophilic agents may have good CSF penetration independent to the degree of meningeal inflammation (Kumta et al., 2018) (**Fig. 3**).

Drug Distribution into the Lungs

Similar to the distribution issue of drugs into the CNS, impaired drug distribution is also significant in critically ill patients with respiratory infections, particularly in those who are intubated and receiving mechanical ventilation (Udy et al., 2013a). Commonly affected drugs include antibiotics and other respiratory agents such as bronchodilators. Changes in the physiology of the respiratory tract due to critical illness, coupled with the impaired ability of the drug to reach the site of the infection or action (i.e., epithelial lining fluid or alveolar macrophage) may complicate dosing for some drugs in these patients. Dosing adjustment and/or alternative route of administration such as nebulization may be required in this clinical scenario (Rello et al., 2017a, 2017b; Sole-Lleonart et al., 2017). Tissue permeability is an important factor that influences drug concentrations in the lung compartments. Hydrophilic antibiotics such as the beta-lactams, carbapenems, and glycopeptides demonstrate poor to moderate lung penetration ranging

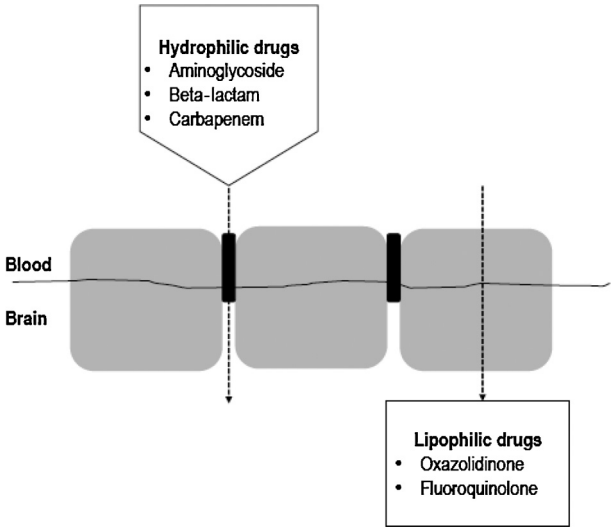


Figure 3 Drug penetration into across the blood–brain barrier.

between 20% and 50% (Jamal et al., 2013). Standard dosing of these drugs rarely achieves optimal exposure in lung compartments and tissues (Abdul-Aziz et al., 2017; Sulaiman et al., 2017). However, lipophilic antibiotics penetrate relatively well into the lung tissues.

Drug Distribution in Critically Ill Obese Patients

Alteration of Vd is also significant for some drugs in critically ill obese patients (Alobaid et al., 2016; Hanrahan et al., 2016). Obesity results in an increase in adipose tissue and lean mass. There can be a significant change in the Vd of both hydrophilic and lipophilic antimicrobials due to increases in both adipose and lean muscle mass. Additionally, regional blood flow to the adipose tissue is significantly lower than the lean mass, thus this will result in lower drug concentrations at the lower part of the subcutaneous adipose tissue. Changes in plasma protein concentration can also affect Vd in obese patients. The use of body size estimators is necessary to ensure more accurate (weight-based) dosing in this population. Patient weight is an important covariate, which predicts larger Vd for drugs such as the aminoglycoside and glycopeptide antibiotics, as well as thiopentone in critically ill obese patients (Velissaris et al., 2014). Higher doses may be required for drugs such as these, at least in the first 24–48 h of therapy, particularly in morbidly obese patients.

Drug Distribution in Burns Patients

Burns patients represent another complex subpopulation of critically ill patients that require particular attention. Burn injuries may result in hemodynamic alterations, including sustained increases in capillary permeability, peripheral and splanchnic vasoconstriction, and myocardial depression. These changes may cause movement of plasma protein into the interstitial space, leading to hypovolemia, systemic hypotension, and hypoperfusion. As the burn injury progresses, the physiological changes may be further complicated by the development of multiorgan dysfunctions. Initiation of immediate and aggressive therapies is warranted such as aggressive fluid resuscitation, the use of inotropes and vasopressors and commencement of organ support, which importantly can affect drug distribution. Generally, it is expected that hydrophilic drugs exhibit larger Vd in patients with burn injury (Jamal et al., 2012). This phenomenon may lead to lower plasma concentration and standard dosing may be suboptimal for hydrophilic drugs (Blanchet et al., 2008; Udy et al., 2018).

Larger Vd has been observed for hydrophilic antibiotics such as the beta-lactams and carbapenems in critically ill burn patients, subsequently leading to lower plasma concentrations. This is important due to risk of significant morbidity and mortality associated with infection in this patient population. In major burns, hypoalbuminemia is pronounced and this is related to the loss of protein-rich fluid via burn wounds, decrease in protein synthesis, and increase in catabolism. This will significantly affect the highly protein-bound drugs causing lower plasma drug concentrations. Therefore, hydrophilic and highly protein-bound drugs may require aggressive dosing adjustment in critically ill burn patients.

Managing Drug Distribution Issues in Critically Ill Patients

In the presence of potential factors that can cause altered drug distribution, dosing adjustment or alternative dosing strategies may be necessary (Roberts et al., 2014). Achieving optimal exposure at the target site can be predicted through the physicochemical characteristics of drugs (i.e., molecular size, lipophilicity, and ionic charge at physiological pH). Various modified approaches to dosing are required, including using higher than standard dosing regimen, measurement of drug concentration at the target site

whenever possible, or alternative dosing strategies (e.g., nebulization) that could enhance drug delivery to its target site (Rello et al., 2017a, 2017b; Sole-Lleonart et al., 2017). When conventional administration fails to achieve the desired therapeutic effect, alternative route of administration into CSF through intraventricular route may be considered for some drugs (Kumta et al., 2018).

Similar to drug penetration into the CSF, many factors need to be considered to ensure optimal medicine distribution into the lung compartments. Identifying drugs that are able to reach the epithelial lining fluid of the airway and alveolar macrophages is important to ensure therapeutic efficacy (Jamal et al., 2013). When the traditional route of administration fails to achieve the desired therapeutic effect, alternative routes of administration such as nebulization may be considered (Rello et al., 2017a, 2017b; Sole-Lleonart et al., 2017).

In critically obese patients, dosing estimation using a body size estimator is important to ensure appropriate drug exposure at the desired target site. Additionally, appropriate dosing estimation may prevent unwanted excessive drug exposure in this population (Alobaid et al., 2016; Hanrahan et al., 2016).

Drug Clearance Issues in Critically Ill Patients

In critical illness, the patient's ability to clear drugs from the body can be either augmented or compromised. Some technologies used in the ICU may contribute to these phenomena. Clinical pharmacists need to understand both the pathophysiological changes and how certain intensive care interventions influence drug clearance (CL) to achieve safe yet effective medicine use. This section will describe the possible pathophysiological changes during critical illness that can affect drugs CL. This chapter will also discuss common issues in the ICU that can cause alteration in drugs CL, which requires dosing adjustment or the use of alternative dosing approaches.

Pathophysiological Changes in Critically Ill Patients that can Affect Drug Clearance

In hyperdynamic state of sepsis where increases in cardiac output are expected, the CL of drugs that are primarily eliminated by the kidneys may be higher due to enhanced renal blood flow (Udy et al., 2011). Administration of inotropes and vasopressors as part of management to restore hemodynamic status of critically ill patients will lead to an increase in cardiac output and subsequently drugs CL, particularly in younger trauma patients without significant organ dysfunction (Udy et al., 2011). As critical illness progresses, this can lead to the development of multiorgan dysfunction, which includes renal and/or liver dysfunction, due to reductionin organ perfusion. Thus, decreased CL and/or metabolism is expected to cause accumulation of drug or its metabolites that could predispose patients to the risk of toxicity. In this clinical situation, dosing adjustment may be necessary. Additionally, the upregulation of CL, in which alternative pathways of CL may occur in the presence of isolated organ dysfunction, may require additional consideration. Drug CL should be carefully estimated to prevent excessive or suboptimal dosing.

Common Drug Clearance Issues in Critically Ill Patients

Changes in drug CL are variable in critically ill patients. Enhancement of drug CL is expected when there is an increase in unbound drug concentration in the systemic circulation, particularly for those that are highly bound to plasma protein. CL can also be augmented when there is an increase in cardiac output due to several factors including systemic physiological changes due to sepsis and/or aggressive ICU management to maintain hemodynamic stability through the use of inotropes and vasopressors. In addition, commencement of extracorporeal treatments for organ support in critically ill patients can also lead to additional drug CL (Jamal et al., 2012, 2015; Shekar et al., 2012b).

However, drug CL can also be reduced in this population, particularly due to organ failure. Thus, one of the most important roles of clinical pharmacists in the ICU is to continuously individualize drug therapy (e.g., drug selection, dose, frequency, administration, and monitoring) for each patient throughout their critical illness and recovery to ensure optimal outcomes.

Augmented Renal Clearance

Augmented renal clearance (ARC) is a phenomenon that is characterized by enhanced elimination of circulating solutes (certain drugs and waste products) by the kidneys and is defined as a creatinine clearance >130 mL/min/1.73 m^2 (Udy et al., 2011). This phenomenon is caused by the inflammatory response during severe sepsis or septic shock leading to increases in cardiac output and blood flow to the major organs (Claus et al., 2013; Udy et al., 2013b, 2014). Additionally, the presence of residual native renal function in these patients, as a response to catabolism and inflammation, may further exaggerate the enhancement of renal elimination. There are several identified risk factors predisposing ARC in critically ill patients including patient-related factors such as younger age and pregnancy and disease-related factors such as traumatic brain injury and burns. The main implication of ARC primarily relates to suboptimal drug exposures, particularly those drugs that are predominantly renally eliminated (e.g., beta-lactam antibiotics and glycopeptides) (Udy et al., 2012). The use of alternative dosing strategies, such as increased doses and frequency, as well as prolonged antibiotic infusion and utilization of TDM is necessary.

Hypoalbuminemia

Hypoalbuminemia in ICU patients can be caused by many factors, which includes underlying diseases that affect liver function, aggressive fluid resuscitation, poor nutritional status, or inadequate protein supplementation during ICU stay. Exaggerated protein loss during critical illness can worsen this condition. Significant exposure changes can occur for drugs that are highly protein bound and primarily renally eliminated (e.g., ertapenem and flucloxacillin) (Ulldemolins et al., 2010, 2011). The higher unbound or free fraction could lead to higher renal CL leading to low plasma drug concentration. The incidence of hypoalbuminemia is common in ICU patients, which has been reported as high as 50% (Finfer et al., 2006). The measurement of unbound drug concentrations is essential and dosing adjustment is required in this clinical condition.

Renal Replacement Therapy

The commencement of renal replacement therapy (RRT) complicates drug use (John and Eckardt, 2007; O'Reilly and Tolwani, 2005). Alteration in drugs CL is expected. Variable RRT modalities and settings lead to varying dosing requirements (Bogard et al., 2011; Jamal et al., 2015; Pea et al., 2007). Intermittent hemodialysis (IHD) is a conventional dialysis approach, not commonly utilized in ICU patients, particularly because it can worsen the unstable hemodynamic status of critically ill patients. This type of RRT mostly applies the principle of diffusion method, a passive transport of solute removal that includes drugs. An alternative technique to IHD, the sustained low efficiency dialysis (SLED) or extended daily dialysis (EDD), has similar principle of solute removal. Thus, CL of similar drugs can be the same. Continuous renal replacement therapy (CRRT) offers different type of solute removal; it can be through passive transport (diffusion) or active transport (convection) or a combination of both. The efficiency of solute removal is higher as compared to the traditional dialysis method. Thus, excessive drug CL can occur during this type of dialysis. However, although CRRT is expected to be continuous, interruption or sudden termination of CRRT can occur due to many reasons, such as during transporting or mobilizing the patient, clot to the hemofilter, or certain ICU procedures (Fealy et al., 2002; Kellum and Ronco, 2010). Thus, efficiency of CRRT and drug CL itself can be erratic and sometimes unpredictable. Patients might be predisposed to toxic accumulation, particularly in those without residual native renal function. The role of clinical pharmacists in proactively planning and actively monitoring and adjusting dosing of drugs is extremely important. Close drug concentration monitoring or dose adjustment may be required where available.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is increasingly being used in adult patients with cardiac and/or respiratory failure. During ECMO, circulating blood from a patient is exteriorized onto the artificial surfaces of circuit tubing and an "artificial lung" (i.e., the oxygenator) membrane in order to provide circulatory and/or respiratory support. Like other critically ill patients, patients on ECMO receive multiple drugs that include sedatives and analgesics, antibiotics, anticoagulants, and vasoactive agents. Data from circuit experiments reveal significant sequestration of certain drugs in the ECMO circuit and the extent of loss depends on their physicochemical properties, type and age of the circuit, and the pumps used (Shekar et al., 2012a, 2012b; Sinnah et al., 2017). Drugs that are unstable at physiological temperature such as meropenem and lipophilic agents such as fentanyl and midazolam are more significantly affected. Alterations in drug exposure are more pronounced for lipophilic drugs and may result in therapeutic failure. Sequestration of drugs in the circuit may have implications on both the choice and dosing of a particular drug prescribed during ECMO. Various alternative approaches to dosing have been recommended in critically ill patients receiving ECMO such as using alternative drugs, higher and aggressive dosing regimens, and close drug level and therapeutic monitoring to ensure for optimal dosing (Cheng et al., 2018).

Indwelling Surgical Drains

Intra-abdominal disease involves pathologic changes such as abscesses, perforation, and ischemia of the bowel. Local increases in fluid volumes within the peritoneal cavity can occur secondary to fluid shifts from the intravascular space to the interstitial space as a result of capillary leak, fluid therapy for restoration of intravascular volume, and inflammatory fluid collections. Ileus can develop due to increased intra-luminal pressure that can impair fluid movement into and out of the gut. This eventually develops a "third space" effect where fluid expansion can occur in the gut lumen. This can increase hydrophilic drug distribution. In patients with indwelling surgical drains, enhanced drug CL, particularly hydrophilic agents, is expected (Adnan et al., 2012). Standard dosing can be suboptimal in this condition due to loss of drug into the "third space" and enhanced CL through the indwelling surgical drain.

Managing Drug Clearance Issues in the Critically Ill Patients

Identifying patients at risk of developing ARC is important. Drug dose adjustment may be required in certain clinical condition to ensure optimal therapy (**Fig. 4**).

Drugs that are highly protein bound may require dose adjustment, particularly in the presence of hypoalbuminemia. The measurement of free drug concentrations may be required, particularly for drugs where the action cannot be observed in a timely manner, such as antimicrobials and antiepileptics, to ensure optimal drug exposure at the site of infection and action.

In patients receiving extracorporeal treatments (e.g., RRT and ECMO), enhanced drugs CL through the extracorporeal treatment can lead to suboptimal dosing and exposure. Dose adjustment is necessary in these patients (Cheng et al., 2018; Kielstein and Burkhardt, 2009, 2011). Frequent drug concentration monitoring may offer additional benefit in ensuring optimal exposure at the

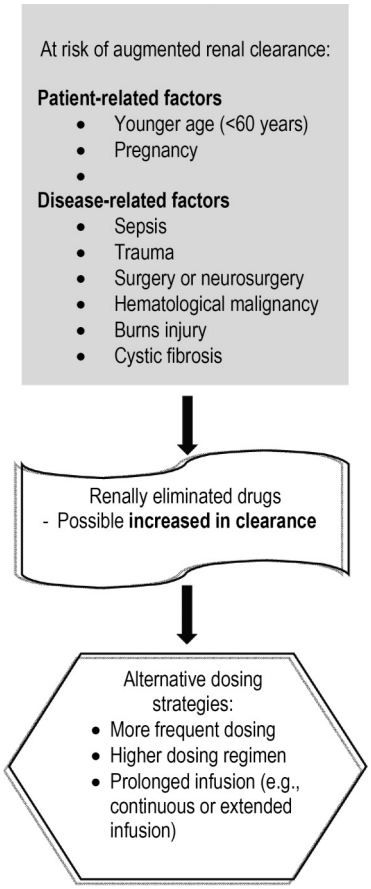


Figure 4 Drug dosing strategies in patients at-risk of ARC

target site. A similar dosing approach is also applied in those patients receiving indwelling surgical drains, in which additional loss of drug with inflammatory fluid through the drains is expected.

Promotion of Best Pharmacy Practice in ICU

ICU patients have complex pathophysiology and therapeutic needs. The ICU is an acute, high stakes, high risk, and high technology environment where change occurs frequently and rapidly. The multidisciplinary ICU team, including clinical pharmacists, works cooperatively to achieve the best outcomes for the hospital's sickest patients. Clinical pharmacy practice in the ICU is integral to the safe and effective use of drugs in critically ill patients. Internationally, reductions in ICU patient mortality, adverse events, and cost have been demonstrated with direct pharmacist involvement in the ICU. Clinical pharmacists can contribute in several ways to optimize pharmacotherapy in the ICU.

Standardized Practice Guidelines and Protocols

Variability in critical care practice has been observed at local, regional, national, and international levels and contributes to increased risk of adverse drug events, staff training, and costs. Standardization of drug practices in critical care settings can facilitate reductions in unwarranted variation and decrease these risks and costs. The development of user-friendly evidence-based guidelines and protocols to support drug selection, dosing, administration, and monitoring is a simple intervention that can be led by a clinical pharmacist and involve the multidisciplinary team (Leguelinel-Blache et al., 2018). At a more sophisticated level, the success observed in the United Kingdom in formulating and adopting a national standard for preparation of drug infusions is a relevant example that is being replicated elsewhere. In order to capitalize on the increased use of technological solutions such as electronic medical records with clinical decision support and "smart" infusion pumps, there is likely to be increased interest in more evidence-based standardized care.

Altered Drug Dosing Approaches

Beyond standard drug dosing and delivery for ICU patients for certain clinical condition, approach such as utilizing the TDM services to guide for optimal therapy could be beneficial to optimize outcome of pharmacotherapy (Abdul-Aziz et al., 2018; de la Pena et al., 2000; Roberts et al., 2008, 2010). Development of dosing nomograms for individual patients can be done based on data from various drug PK studies (Minichmayr et al., 2018). Mathematical models can be used to describe drug behavior relative to measures of organ functions (Vinks, 2002). Dosing simulations can be performed to describe the best dosing regimen required to overcome changes in drug exposures in critically ill patients that can lead to suboptimal patient outcomes. Using dosing–software that is equipped with data derived from a PK model can help to more accurately predict dosing requirement of an individual patient, which saves costs and time while managing critically ill patients (Jelliffe et al., 1993; Roberts et al., 2011).

TDM ensures that all patients achieved the desired therapeutic drug exposure by measuring drug concentration and adapt the dose accordingly (Roberts et al., 2010). For example, for antibiotics, TDM has been expanded beyond the traditional practice, where now TDM of drugs such as the beta-lactams, quinolones, oxazolidinone, daptomycin, and colistin has been widely practiced to ensure great therapeutic achievement. Using dosing software, a recommendation based on patient data derived from TDM can facilitate an immediate decision of accurate initial drug dosing even for drugs with variable PK (Abdul-Aziz et al., 2018; Roberts et al., 2017).

The development of a closed-loop system helps to fill gaps in strategies to optimize drug dose optimization (Rawson et al., 2018). It is minimally invasive and utilizing a microneedle electrochemical sensor technology, where drug concentrations at the dermal interstitial fluid (ISF) can be monitored and estimated without invasive plasma sampling. The system then will allow for the optimization of drug therapy either as continuous or bolus administration to achieve predefined therapeutic goal. This approach can offer precision of drug therapy in various clinical settings.

Continuing Education Exercises

As is the case in all specialty practice areas, clinical pharmacists can contribute to practice beyond bedside care by contributing to education of students, novice, and even expert pharmacist and multidisciplinary colleagues. In the ICU environment, where drug use is continuous and often essential to facilitate care, clinical pharmacists can provide nursing and medical staff with education at both a general and specific patient level to optimize medicines management and patient outcomes. Team-based learning such as simulation and crew resource management is increasingly being used in ICU to support all multidisciplinary team members to contribute effectively, and pharmacists are encouraged to participate in these learning opportunities.

Generation of New Knowledge through Research Undertaking

Due to the relative youth of ICU as a specialty and the rapid progress in technology, clinical and practice research is increasing exponentially. Clinical pharmacists at all levels can be involved in this research. More junior staff may be involved in data collection for ongoing or established research projects or may undertake their own quality assurance or improvement project to address an observed shortcoming in current local practice for example following implementation of a new guideline or protocol. Established practitioners should be contributing to or developing local research to explore questions from clinical practice, which are not adequately answered in the existing evidence and to test new innovations. While more advanced practitioners should be contributing to broader multidisciplinary research on a larger scale. Seeking mentors and advocates within the local multidisciplinary team or broader networks is important in the skills development for research and education.

Continuing education and research in ICU setting are necessary to enhance knowledge and improve practice in this area. Through collaboration or worldwide networking, research data of various ICU population background can help to fill gaps in practice that ultimately can facilitate the standardization of ICU care.

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Irritable Bowel Syndrome (IBS)

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Learning Objectives

- Know the symptoms of IBS
- Understand the way in which IBS is diagnosed
- Have knowledge of the factors believed to contribute to IBS symptoms
- Be aware of alarm symptoms
- Understand the level of evidence for different treatments
- Appreciate the patients' perspective of their condition
- Be aware of the substantial placebo effect of treatments
- Be able to discuss the role of complementary medicines
- Have the ability to explain the condition to patients in plain English

Take Home Messages

- Functional gastrointestinal disorders such as IBS are disorders of gut–brain interaction resulting in any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.
- There is no definitive diagnostic test for IBS and no obvious abnormality can be shown. Patients and/or doctors may therefore perceive uncertainty around the diagnosis. This may result in more testing and specialist referrals.
- Multiple comorbidities may occur in up to two-thirds of patients with IBS consisting of somatic symptoms, pain syndromes, other gastrointestinal disorders, and psychiatric disorders. Multiple medication intolerances or adverse effects may also occur.
- Psychological distress (anxiety or depression) may be secondary to the gut disturbance, where concurrent dysbiosis and moderate inflammation may induce a circulating cytokine reaction.
- IBS subtypes probably result from several contributory factors, which include infection, genetic factors, intestinal immune dysfunction, psychosocial factors, food sensitivities or intolerances, dysbiosis, and abnormalities in bile acids and serotonin activity.
- Where IBS is present, a prolonged search for an alternative explanation or diagnosis is futile, financially inappropriate and time-consuming. It has led to the use of nonevidence-based medicines and consultation with alternative health practitioners.
- Differential diagnoses in IBS are extensive. When diagnostic criteria are satisfied, alarm signs are absent, the history and physical examination suggest IBS and recommended blood tests are normal, the risk of missing organic disease is rare.
- Often people may only want to know why they have symptoms and whether they should be concerned.
- Patients may have misconceptions about IBS, such as it could turn into cancer and increase the risk of inflammatory bowel disease.
- Doctors may have limited awareness of the effect of IBS on patients' lives or patient beliefs about the causes of IBS
- Patients may care more about triggering factors than etiology; they may be more interested in how to manage the symptoms and minimize their effect on daily life.
- The placebo response rate in IBS treatment trials has been found to be 30%–40%.

- Psychological therapies improve many symptoms, do not cause adverse drug effects, and address the significant psychological aspects of FGIDs. While patient resistance may occur, so too may a lack of positive endorsement by health-care professionals.
- General recommendations include regular exercise, stress management, and dietary considerations. This encompasses the concept of putting one's health first rather than second to life events and looking after oneself to best cope with a condition that causes intestinal and extraintestinal problems.
- Referral to a dietician for consideration of exclusion diets, assessment of fiber intake, and use of a FODMAP diet feature in treatment recommendations.
- Currently, there appears to be no clinically useful way of identifying specific disturbances in the gut microbiota of people with IBS. In the future, it may be possible to develop designer probiotics containing organisms that are known to have an impact on symptoms, rather than the current trial and error approach.
- Some herbal medicines improve global symptoms. However, the methodological quality of clinical trials has generally been poor. In addition, purity and consistency concerns have been raised, as well as lack of a clear understanding of the active ingredients
- Evidence for the effectiveness of antispasmodics, motility agents, and antidepressants appear to be much weaker than that for antidiarrheals, laxatives, and prosecretory agents.
- The possible management of gastrointestinal conditions by fecal microbiota transplant needs a significant amount of research. There are questions to be answered over the safety of donor material, the dose, and the best route of administration of the material to the recipient.

Introduction

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder (FGID) characterized by the presence of altered bowel habits, abdominal pain, distention, and bloating. Gastrointestinal conditions may be broadly classified into two: organic and functional disease, with functional disorders accounting for most patients with chronic gastrointestinal symptoms (Keely et al., 2015). The term "functional" has been used to describe a disorder that affects function or performance, causing signs or symptoms of an organic disease, but with no obvious evidence of structural or physiologic abnormalities. Treatment strategies are therefore limited and focus on symptoms rather than cure. However, emerging evidence suggests that distinct pathophysiological disturbances may account for the symptoms of IBS (Ford et al., 2017). Other conditions described as FGIDs include functional dyspepsia, functional constipation, and functional diarrhea. The disturbed gut function and intrusive symptoms caused by IBS impair quality of life and in many people coexist with other FGIDs—commonly functional dyspepsia (Linedale and Andrews, 2017).

Functional disorders can be classified according to the Rome criteria, whose development began in 1988 when a team of experts worked to develop consensus criteria for the diagnosis of IBS. The Rome Foundation classification of FGIDs is based primarily on symptoms rather than physiological criteria. This is because of limited evidence that physiological disturbance (e.g., motility) fully explained patient symptoms and that symptoms are what patients describe to health-care providers. While IBS was not the only FGID, at that time there existed no overarching operational definition or classification for them. The first set of criteria ("Rome I") for 21 functional GI disorders were compiled into a book in 1994. Studies began being published using these criteria, which progressed their acceptance and further use and development through Rome II (1999–2000), III (2006), and IV (2016). Rome III differed from Rome I and Rome II with the use of more evidence-based rather than consensus-based data. This was because a greater number of research studies published using the Rome criteria allowed for more precise patient selection and presented data more representative of these disorders (Drossman, 2016).

To advance the field of FGIDs, Rome IV addressed limitations and made changes, which have included an improved definition of FGIDs that was positive (rather than by the exclusion of other disease); representative of current scientific knowledge and nonstigmatizing to better reflect current understanding; limiting the use of the term "functional," which while entrenched in the literature was considered imprecise and to some degree stigmatizing; adding new information such as the contribution of the microbiome to improve understanding of the luminal aspects of GI function; removing the term "discomfort" because not all languages had a word for "discomfort," because it had different meanings in different languages and because of its ambiguous meaning to patients; and changing (increasing) the frequency with which patients report abdominal pain (Lacy et al., 2016). The Rome IV criteria represent the current standard for diagnosing IBS (Ford et al., 2017).

Rome IV defines functional gastrointestinal disorders as disorders of gut–brain interaction resulting in GI symptoms causing any combination of the following: motility disturbance (change in movement of food and waste through the gastrointestinal (GI) tract), visceral hypersensitivity (heightened experience of pain in internal organs), altered mucosal and immune function, altered gut microbiota (the community of microorganisms) and altered central nervous system processing—how the brain sends and receives messages from the GI tract. The contribution of these factors may be variable. For example, an individual who develops IBS after infective gastroenteritis may have more influence from mucosal immune dysfunction with altered microflora, compared to another individual with IBS who has a lifelong history of chronic symptoms and psychiatric comorbidities relating to altered CNS regulation of GI function (Drossman, 2016).

Because there is no definitive diagnostic test for IBS and no clear abnormality can be shown, the patient and/or doctor may perceive uncertainty around the diagnosis. Uncertainty appears likely to make people feel uncomfortable, which may then result in more testing and specialist referrals. That is why making a criteria-based diagnosis (i.e., based on the patient's

history), selecting only those investigations that are relevant and communicating the diagnosis confidently and effectively to the patient is important in the treatment of IBS (Linedale and Andrews, 2017). IBS is not a diagnosis of exclusion, but a characteristic symptom complex that can usually be identified by asking a few simple questions (Talley and Holtmann, 2016).

IBS can be classified into four subtypes: IBS with diarrhea-predominant symptoms (IBS-D), IBS with constipation-predominant symptoms (IBS-C), IBS with mixed symptoms of constipation and diarrhea (IBS-M), and unsubtyped IBS (i.e., it does not meet the criteria for the other subtypes). This is based on patient's reports of the proportion of time they have had hard or lumpy stools versus loose or watery stools (Ford et al., 2017). Women are more likely than men to seek medical attention and to report IBS-C (Halland and Saito, 2015).

When food enters our intestine, the undigested components are utilized by the intestinal microbes, collectively called the microbiota. The microbiota is dominated by bacteria belonging to the phyla Firmicutes, Bacteroidetes, and Actinobacteria. These microbes inhabit the various regions in the GI tract, of which the colon is most densely populated. The microbiota has a major impact, not only on processes that occur in the GI tract but also on systemic functions and may have an important role in IBS (Barbara et al., 2016). Their activities include the maturation and continued education of the host immune response; protection against pathogen overgrowth; regulation of intestinal endocrine functions and neurologic signaling; biosynthesis of vitamins, neurotransmitters, and multiple other compounds with as-yet unknown targets and metabolism of bile salts (Lynch and Pedersen, 2016).

Evidence supports that the microbiome is significantly altered in patients with IBS when compared with normal patients. Microbial diversity is decreased in IBS, with diminished amounts of Lactobacilli and Bifidobacteria, while aerobes and mucosal bacteria are more abundant than in the normal gut. Studies have also shown specific alterations in patients with constipation predominant-IBS, where sulfate producing bacteria are increased and lactate producing bacteria are decreased (Malikowski et al., 2017).

Determining a patient's predominant symptom pattern guides management because the subgroups respond differently to different treatments. However, symptom patterns can change over time (Sultan and Malhotra, 2017a) and this, together with emerging evidence that IBS is unlikely to be one disease (Ford et al., 2017), may make management challenging.

Incidence and Burden of Disease

The prevalence of symptoms of IBS in the community has been found to vary according to geography, with a pooled prevalence from a meta-analysis of population-based studies of 7% in South East Asia, 12% in northern Europe and North America, 21% in South America, and 14% in Australia (Lovell and Ford, 2012). Global estimates of prevalence have varied from 5% to 15% (Halland and Saito, 2015). Depending upon the criteria used and methods of data collection, prevalence according to country has been reported to vary from as low as 1% to as high as 45% (Lovell and Ford, 2012). Prevalence of each of the four subtypes of IBS (IBS-C, IBS-D, IBS-M, and IBS-U) has been found to be similar in magnitude. The odds of IBS were significantly lower in people aged 50 years or more and there was a female preponderance, with a pooled odds ratio of 1.67 in women versus men. In fact, it has been stated that the syndrome mostly affects people aged 20–30 years (Hookway et al., 2015). Women were more likely than men to seek medical attention and to report abdominal pain and constipation (odds ratio 2.38), whereas men more commonly reported diarrhea (Chey et al., 2015; Ford, 2012). There were only a small number of studies reporting the prevalence of IBS according to socioeconomic status. They revealed no significant difference in prevalence of IBS in those of higher socioeconomic status compared with those of medium or lower socioeconomic status (Lovell and Ford, 2012).

Multiple comorbidities may be associated with IBS such as somatic (i.e., physical symptoms for which there is no identifiable physical cause) pain syndromes (e.g., fibromyalgia, temporomandibular joint pain), other gastrointestinal disorders (e.g., dyspepsia), and psychiatric disorders (e.g., anxiety, major depression) (Chey et al., 2015). Comorbidities may be present in up to two-thirds of patients. Multiple medication intolerances or adverse effects are also frequently encountered (Sayuk and Gyawali, 2015). Longer duration of disease, severity of somatic syndromes, and co-morbid anxiety and depression all predict worse outcomes (El-Serag et al., 2004). While psychological distress (anxiety or depression) commonly accompanies IBS, it may be that in some cases these symptoms of distress begin after and are secondary to the gut disturbance, where concurrent dysbiosis and moderate inflammation may induce a circulating cytokine reaction (Talley and Holtmann, 2016).

In most patients, IBS is a chronic relapsing disease. A systematic review showed that during long-term follow-up of clinic-based IBS patients, IBS symptoms persisted in most patients over a period of several years, but a substantial minority became symptom free within 2 years. Approximately two-thirds of patients either retained the original symptom severity or worsened (El-Serag et al., 2004). Patients may also migrate between different IBS subtypes, most commonly from IBS-C or IBS-D to IBS-M. However, these findings are complicated by the effect of treatments introduced by the doctor or patient, so that it is difficult to judge symptom variation from the effect of medical interventions (Chey et al., 2015).

The financial impact of IBS for patients can be substantial. It has been reported that the average cost per patient per annum was $742 (£490, €667) to $7547 in the United States, compared with £90 to £316 in the United Kingdom and €567 to €862 in France. Further, the average number of sick days taken per person per year was 30 in the United States. About 30% of people with IBS seek regular medical care, and in the United States, an estimated 12% of primary care visits and about 30%–50% of gastrointestinal consultations were related to IBS (Halland and Saito, 2015).

Etiology

Although subtyping of IBS currently guides management, each subtype probably results from several contributory factors. IBS likely includes several diseases with their own pathophysiology that present with similar symptoms. This may account for the heterogeneous response to treatment. That is, irrespective of whether symptoms arise from the gut, after infective gastroenteritis or from the brain, they are similar (Chey et al., 2015; Ford et al., 2017).

Factors related to pathogenesis have included (Barbara et al., 2016; Camilleri, 2012a, 2016; Chey et al., 2015; Ford et al., 2017; Halland and Saito, 2015; Keely et al., 2015; Malikowski et al., 2017; Sayuk and Gyawali, 2015; Theoharides et al., 2015):

1. **Infection—**After acute bacterial, protozoal, or viral gastroenteritis, IBS-type symptoms may persist in 10%–20% of patients and may be due to mild persistent inflammation or increased number of intestinal mast cells. Mast cells are immunologic (allergy) cells originating from stem cells, which store and release mediators (chemical messengers) like tumor necrosis factor and interleukin-6 (IL-6), which may cause abdominal cramps and diarrhea. Mucosal permeability may be increased with altered expression of tight junction proteins resulting in increased fluid secretion or activation of sensory mechanisms, resulting in IBS-D.
2. **Genetic factors—**Functional alterations of host mucosal immune response to microbial pathogens may alter bowel barrier function. Genetic susceptibility may confer a predisposition to immune activation in a subset of patients. For example, colonic transit has been found to be associated with inflammation-susceptibility genes that include toll-like receptor 9 (TLR9) and the genes encoding cadherin 1 (CDH1) and IL-6. Genetic factors (e.g., KLB—the gene-encoding klotho-β and mutation of GUCY2C (the gene encoding the guanylate cyclase C receptor) may also confer a predisposition to increased bile acid synthesis or increased enterocyte (intestinal cell) secretion, resulting predominantly in accelerated transit time and diarrhea. These factors result in familial aggregation in IBS. Genetic factors may also be involved in causing visceral hypersensitivity. Apart from effects on ion transport and barrier function, altered mucosal expression of genes may cause immune dysfunction.
3. **Intestinal immune dysfunction—**The intestinal mucosa of some IBS patients shows increased activation of the innate (i.e., the same immune mechanisms that each of us inherit) and adaptive (the immune system adaptations that occur according to individual environmental exposure) immune system. Functional symptoms are mediated by interaction of innate and adaptive responses and share immune pathways with food allergy and inflammatory bowel diseases. Abdominal pain is associated with increased localization of leucocytes, particularly mast cells, at enteric nerves. In addition, secretion of histamine (released from mast cells) drives smooth muscle contraction that contributes to symptoms of pain and constipation in IBS. Histamine release can also drive chloride-led water transport across the epithelium, manifesting as diarrhea and "leaky gut syndrome," increasing exposure to antigen and food allergens and driving dysbiosis (i.e., disturbance of the microbiome). Dysbiosis contributes to the loss of immune homeostasis and increase in T-helper 17 (Th17) cells that can drive eosinophilia in a Th17/GM-CSF (GM-CSF = granulocyte-macrophage colony-stimulating factor) dependent manner, while Th2 cytokines signaling and GM-CSF can also activate eosinophils to release tissue-damaging peroxidases. When tissue damage and inflammation persist, further "gut homing" immune cells are recruited from the circulation, perpetuating the inflammation. For example, it has been found that serum titers of the inflammatory cytokines interleukin 1b (IL-1b), tumor necrosis factor alpha (TNF-α), and IL-6 correlate positively with both IBS symptoms and the inflammation that also occurs in inflammatory bowel disease.
4. **Psychosocial factors—**Although it is unclear as to whether the etiology of disease lies with the psychological or gastrointestinal symptoms of IBS, there is increasing evidence to suggest that there is a bidirectional association along the gut–brain axis, such that IBS symptoms start in a significant number of patients before psychological distress develops. For example, there is a significant correlation of circulating levels of TNF-α with symptoms of anxiety. Notwithstanding this, psychosocial factors are often present. Women are more likely to have experienced verbal, sexual, or physical abuse, which may contribute to brain–gut dysfunction. In some patients, hypervigilance (abnormally increased arousal, responsiveness to stimuli, and screening of the environment for threats) and catastrophizing may lead to gastrointestinal and nongastrointestinal symptom amplification. Mood disorders (stress, anxiety, depression, and maladaptive coping strategies) or somatization (i.e., reports of symptoms such as back pain, headaches, and chest pains for which there is no apparent organic cause and which probably reflect a disorder of brain or emotional functioning) significantly increase the likelihood of developing functional gastrointestinal disorders.
5. **Food sensitivity/intolerance—**The majority of IBS patients associate ingestion of a wide range of foods with symptoms, particularly abdominal bloating and pain. The contribution of true food allergies is probably small, whereas food intolerances are common. The effect of food could be mediated through direct interactions between dietary components and mucosal receptors that may have been sensitized to these stimuli, or via down-stream events triggered by dietary components such as the release of gut hormones, changes in epithelial morphology, generation of immune responses, or altered signaling between the gut and the brain. Patients frequently report reduced consumption of milk products, wheat products, spicy foods, alcohol, and certain fruits or vegetables that are high in poorly absorbed short-chain carbohydrates and sugar alcohols (e.g., onions) and in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs; e.g., grapes and pears). While malabsorption of sugars such as lactose, fructose, and sorbitol may mimic the features of IBS, maldigestion of complex carbohydrates may be more prevalent, which may then provide substrate for the generation of short-chain fatty acids (SCFAs) by colonic bacteria. This may stimulate colonic transit. FODMAPs can yield methane, hydrogen, and carbon dioxide implicated in bloating. Osmotically active carbohydrate by-products may precipitate fluid secretion and enhance intestinal contraction, leading to diarrhea. Many IBS patients report symptoms in response to wheat-containing products, reminiscent of

the sensitivity to gluten that characterizes celiac disease, despite negative celiac serology and normal small intestinal morphology. Data on the above dietary adjustments in IBS are variable.

6. **Intestinal microbiota—**Lifestyle and diet are crucial determinants of microbiota composition and function. The fermentation of complex carbohydrates by microbiota, such as fibers and resistant starches, produce SCFAs, which act as fuels for intestinal cells and serve as signaling molecules. Carbohydrate fermentation also results in the formation of intestinal gases. This may induce intestinal reflex responses through bowel distention that causes inadequate relaxation of the diaphragm, pushing out the abdomen and causing visible abdominal distention. Intestinal microbiota may also be involved in the pathogenesis of IBS due to findings such as fecal microbiota substantially different in IBS and postinfectious IBS compared with healthy controls, with reduced microbiota diversity; innate and adaptive immune activity directed toward microbiota-derived molecules, such as the expression of toll-like receptors (TLRs) in the mucosa (TLR9 is an inflammation susceptibility gene); abnormal concentrations of fermentation end products in some patients due to different levels of SCFAs; probiotics (which seek to alter the microbiota) that have been shown to improve abdominal pain, bloating, and flatulence; increased levels of firmicutes or ratio of firmicutes to bacteroidetes, modified by antibiotics or probiotics. Currently, research continues into the role of microbiota and major limitations still hamper the definition of the role of the microbiota. There appears no consensus on the nature of the microbial signatures that may be consistently (either positively or negatively) correlated to FGIDs. These inconsistencies may relate to several factors including methodological differences, variations in sample sources, intrinsic variability between subjects, differences in subject selection and definition of study populations, overlap between the various FGIDs, and differences in diet, therapy, or other environmental exposures.
7. **Bile acids—**Bile acids play a central and critical role in the digestion and absorption of fat and fat-soluble vitamins. An efficient enterohepatic circulation ensures appropriate concentrations in the gut. Concentrations increase with a high fat diet, with changes in the microbiome (increase in firmicutes and reduction in bacteroidetes) observed. Bile acids have a variety of physiological effects of relevance to the FGIDs; on motility, intestinal secretion, membrane permeability, and visceral sensation. They act as signaling molecules, with effects beyond the GI tract. Luminal bile acid signaling to enteric nerves may cause increased sigmoid and rectal motility, with malabsorption identified in significant numbers of patients with IBS-D. Altered metabolism of bile acids by colonic bacteria and an elevated rate of synthesis of bile acids have also been identified.
8. **Serotonin—**Serotonin (5-hydroxytryptamine [5-HT]) is an amine primarily contained in the gut (95%) and only minimally in the brain (5%). Serotonin is synthesized from tryptophan mainly in enterochromaffin cells (90%) and autonomic nerves. Synthesis and release of serotonin occurs through bowel wall distension and the influence of factors, which include food, amino acids, hyper-osmotic solutions, and glucose. SCFAs, which may be produced in increased amounts by intestinal microbiota fermentation of carbohydrate substrates, can also promote the release of serotonin. Serotonin stimulates afferent neurons, which synapse in the myenteric plexus with ascending and descending neurons to evoke motility- and secretion-induced reflexes and transmit information to the brain. Serotonin reuptake transporter (SERT) terminates serotonin action. Hypofunction of SERT may increase serotonin concentrations leading to gut hypercontractility, hypersensitivity, diarrhea, and pain. Hyperfunction may result in IBS-C. These findings are reflected by the effect of selective serotonergic agonists (e.g., prucalopride) and antagonists (e.g., alosetron, ondansetron) on different subtypes of IBS. The enteroendocrine and immune systems are widely interconnected, immune cells being proximal to enterochromaffin cells. Immune cells (including B and T lymphocytes, monocytes, macrophages, and dendritic cells) express serotonergic receptors and mast cells, macrophages and T cells synthesize serotonin from tryptophan. Serotonin is chemotactic for dendritic cells, mast cells, and eosinophils and may participate in the recruitment of these immune cells in the intestinal mucosa. Low-grade inflammation, such as has been detected in FGIDs can, in turn, contribute to altered serotonin synthesis and reuptake through changes in SERT expression. T helper-1 (Th1) responses generate IFN-gamma (interferon) and TNF-a, which inhibit SERT.

Diagnosis

Despite the prevalence of IBS, frustration and dissatisfaction in patients and doctors resulting from the diagnostic process, which may include insufficient or excessive investigations and repeat consultations and reinvestigation, has been noted. The diagnostic process should ideally involve

- Making a provisional diagnosis based on application of criteria
- Using targeted investigations to exclude other causes
- Communicating the diagnosis effectively to the patient to ensure acceptance and ownership (Linedale and Andrews, 2017).

While these components are true for any disease, they appear particularly important in IBS, for which there is no definitive diagnostic test or obvious abnormality. This may generate doubt about the diagnosis, creating a desire for more consultations and testing. Where IBS is present, a prolonged search for an alternative explanation or diagnosis is futile, financially inappropriate and time-consuming. It may encourage unrealistic expectations and delay effective management. It may result from the use of unclear or uncertain language used by general practitioners and specialists to patients due to lack of confidence in diagnosing and managing IBS (Linedale and Andrews, 2017). It may also create a desire in the patient to seek alternative and complementary medicines.

An estimated 70%–80% of the world's population use non-Western medicine in the form of herbal preparations for their primary health care. The predominant user group of complementary medicines in Australia comprises younger women (under 35 years old)—the group in which IBS symptoms appear to be most common. In Australians aged 50 years or more, 46% have been reported to use complementary medicines, of whom 87% use them alongside conventional therapy. The 10 most commonly used herbal preparations in Australia include peppermint (Byard et al., 2017), a medicine with antispasmodic properties useful for treating abdominal spasm and cramps in IBS. Other medicines (such as slippery elm [Ulmus rubra]) may expose patients to high cost and false claims.

In the absence of established structural lesions to account for IBS symptoms, there is currently no accurate, noninvasive test. Research has focused on developing novel biomarkers such as genes, proteins, or metabolites to aid in diagnosis. However, studies examining all currently described approaches to diagnosing IBS have found that biomarkers performed no better than symptom-based criteria (Ford et al., 2017).

IBS presents with a characteristic symptom complex. Patients present with long-standing abdominal pain, directly linked to a disturbed bowel habit (diarrhea, constipation, or both). They also often have bloating, sometimes with visible distention. The pain may be relieved or aggravated by defecation. With pain, the stool is often altered in frequency or form (Talley and Holtmann, 2016).

Guidelines (Hookway et al., 2015) recommend that a diagnosis of IBS be considered only if the person has abdominal pain or discomfort that is relieved by defecation or is associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms:

- Altered stool passage (straining, urgency, incomplete evacuation)
- Abdominal bloating (more common in women than in men), distension, tension, or hardness
- Symptoms made worse by eating
- Passage of mucus.

Other features such as lethargy, nausea, backache, chronic fatigue, fibromyalgia, and bladder symptoms are common in people with IBS and may be used to support the diagnosis.

Although physical examination is usually normal in patients with IBS, mild abdominal tenderness may be present. A digital rectal examination has been recommended in patients with IBS-C to exclude dyssynergic defecation, a condition that arises from the inability to coordinate with the abdominal wall, anal sphincter, and pelvic floor muscles in a way that enables normal defecation. This is important to exclude in patients with constipation, with anorectal symptoms such as bleeding and pain and to rule out rectal cancer (Chey et al., 2015; Sultan and Malhotra, 2017a).

Alarm or "red flag" symptoms—all people presenting with possible symptoms of IBS should be asked if they have any of the following "red flag" indicators and referred for further investigations such as

- Unintentional or unexplained weight loss
- Rectal bleeding
- Family history of bowel or ovarian cancer
- A change in bowel habit to looser or more frequent stools (or both) persisting for more than 6 weeks in a person aged over 60 years

All people should also be assessed for the following and referred for further investigations if necessary:

- Anemia
- Abdominal masses
- Rectal masses
- Markers for inflammatory bowel disease

Other clinical alarms to elicit and exclude in the diagnostic process include new onset symptoms in the last 6 months in a person aged greater than 50 years; abdominal pain awakening a patient from sleep; documented unexplained fever; family history of inflammatory bowel disease; family history of celiac disease; enlarged lymph nodes (Ford, 2012; Sultan and Malhotra, 2017a).

Testing—guidelines (Hookway et al., 2015) recommend that in people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- Full blood count
- Erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- Antibody testing for celiac disease (endomysial antibodies or tissue transglutaminase antibodies).

The following tests are not necessary to confirm the diagnosis in people who meet the IBS diagnostic criteria; ultrasound, rigid or flexible sigmoidoscopy, colonoscopy, barium enema, thyroid function test, fecal ova, and parasite test, fecal occult blood, and hydrogen breath test (for lactose intolerance and bacterial overgrowth).

Fecal calprotectin has been stated to be very good at discriminating between functional and organic lower gastrointestinal disease. Increased levels occur due to neutrophil degranulation in the mucosal inflammation of inflammatory bowel disease. In a

young patient with at least 6 months symptom duration and no alarm symptoms, negative test results (levels less than 40 μg/g) provides strong confirmation of functional disease (Linedale and Andrews, 2017).

Other suggestive symptoms include gastrointestinal symptoms that wax and wane for more than 2 years and are exacerbated by psychosocial stress; the presence of other gastrointestinal functional disorders such as nonulcer or functional dyspepsia and the presence of psychiatric comorbidity (Sultan and Malhotra, 2017a).

Differential diagnoses in IBS are extensive. When diagnostic criteria are satisfied, alarm (or red flag) signs are absent, the history and physical examination suggest that IBS and recommended blood tests (above) are normal, and the risk of missing organic disease is rare—it may be as low as 1%–3%. Expert consensus is that doctors should limit evaluation to fulfilment of the Rome criteria if no alarm symptoms are present (Ford, 2012; Sultan and Malhotra, 2017a).

Although identifying patients with IBS-D or IBS-C may be straightforward, patients with IBS-M may require a more detailed history to determine whether a mixed bowel pattern represents the disease state or is a consequence of medical intervention. All medicines (prescribed, over-the-counter or complementary and alternative) that may affect IBS symptoms should be considered. These include medicines commonly associated with constipation (see Table 1 in the chapter on constipation) and those that may produce loose motions (such as magnesium-containing products, metformin, and nonsteroidal anti-inflammatory drugs). IBS-M patients who report periods without a bowel movement or small hard stools followed by multiple stools of varying consistency (interpreted as diarrhea) may have IBS-C, with periods of progressive stool accumulation resulting in bowel purging (Chey et al., 2015).

Studies have shown that more than one in four people with IBS-D have evidence of bile acid diarrhea, found on testing by administering a bile acid radiolabeled with the gamma-emitting isotope selenium-75 (known as ^{75}SeHCAT [^{75}Se-homocholyl-taurine] testing). Whole-body retention is measured by means of a scanning gamma-camera after seven days. However, this test may not be readily available. Biochemical testing of blood (e.g., testing for serum 7α-hydroxy-4-cholesten-3-one [C4, a bile acid precursor]) may also be coming into use. A therapeutic trial of a bile acid sequestrant may represent an easier alternative (Ford et al., 2017).

Treatment

Once the patient understands and accepts the diagnosis of IBS, management needs to cater to those concerns, beliefs and symptoms most troubling to the patient, as it has been stated that IBS of itself does not need or mandate management. Often people may only want to know why they have symptoms and whether they should be concerned (Linedale and Andrews, 2017).

In a qualitative study to understand patients experiences and expectations for management of IBS, it was found that IBS entailed serious reordering of patient's daily lives; a significant percentage of patients believed that the condition turned into cancer and increased the risk of inflammatory bowel disease; etiology was viewed as a personal attribute or caused by the occurrence of some discrete event in the past; it was felt that current medical knowledge could not contribute to effective relief; diagnosis and treatment was a confusing and frustrating process; many patients felt that they should have had more tests; there was dissatisfaction with the often unclear explanation by their general practitioner (GP); and patients cared more about triggering factors than etiology. They were more interested in how to manage the symptoms and minimize their effect on daily life; dissatisfaction with GP's was more about the lack of current knowledge of causes and effective treatments of IBS rather than GPs themselves, who were perceived as trying their best (Casiday et al., 2009b). These findings identified many of the issues discussed above.

A qualitative study was also conducted to understand GPs explanatory models and management strategies. It was found that although most GPs had a realistic understanding of current knowledge about IBS, the many unresolved questions regarding background and management had a negative impact on their attitudes toward patients suffering from IBS. They often viewed IBS resulting from disordered bowel activity in response to people's response to their environment, rather than of the environment itself. They had limited awareness of the effect of IBS on patients' lives or patient beliefs about the causes of IBS (Casiday et al., 2009a).

Placebo use—When considering the money spent on nonevidence based complementary and alternative medicines (CAMs), the placebo response should be considered. The placebo response rate in IBS treatment trials has been found to be 30%–40% (Ford et al., 2017). For example, in a placebo randomized controlled trial using acupuncture, patients were divided into three groups: a "waiting list" that controlled for any effects of assessment and observation (Hawthorne effects), as well as the effects of the natural course of the illness and regression to the mean; "limited interaction," providing placebo treatment with minimal interaction with the practitioner; or "augmented interaction," providing placebo treatment with a defined positive patient–practitioner relationship. The placebo treatment was delivered with a validated sham acupuncture device. An incremental improvement in symptoms was found in a manner resembling a graded dose escalation of component parts. An enhanced relationship with a practitioner, together with the placebo treatment, provided the most robust effect, indicating that such factors as warmth, empathy, duration of interaction and the communication of positive expectation might indeed significantly affect clinical outcome. The percentage of patients reporting adequate relief was comparable with the responder rate in clinical trials of drugs then currently used in the treatment of irritable bowel syndrome (Kaptchuk et al., 2008).

In another study, the clinical efficacy of open-label placebos (i.e., where patients are told that the treatments are placebos) compared with no treatment was investigated in a systematic review and meta-analysis (Charlesworth et al., 2017). Only five trials met inclusion criteria. The clinical conditions were irritable bowel syndrome, depression, allergic rhinitis, back pain, and attention deficit hyperactivity disorder. Notwithstanding the limited number of studies, the moderate risk of bias, and lack of blinding,

open-label placebos were found to have a medium-sized effect in reduction of symptoms (standardized mean difference 0.88 (0.62–1.14), $P < 0.00001$, I2 = 1%) (Charlesworth et al., 2017).

In a study of qualitative responses on perceptions of placebo use by USA patients, it was found that a lack of harm and potential benefit were the most common themes to justify acceptability of placebo use. Responses citing potential benefit were associated with higher education. Of the minority of respondents who judged it never acceptable for doctors to recommend placebo treatments, the most often referenced rationale was obligation of the doctor to do more. Additional themes emerged around the issue of whether a doctor was transparent about placebo use, including honesty, patient's right to know, and power of the mind (Ortiz et al., 2016). Perhaps people selling alternative therapies do a better job of selling them than health-care professionals do when recommending evidence-based approaches.

Treatment; Nonpharmacological

General recommendations—Several general recommendations can be made (eTG complete, 2016; Halland and Saito, 2015; Hookway et al., 2015; Sultan and Malhotra, 2017a) and include

- Patient education, reassurance, and reinforcement—education about the role of psychological stressors; awareness of dietary triggers; assistance with the development of self-management strategies; reassurance that there are no long-term sequelae; explanation that the cause of IBS is multifactorial, so treatment may need to address different aspects simultaneously, e.g., psychological health, gut microbiota; acknowledgement that their symptoms have physiologic causes that are real but poorly understood and that they may be able to control symptom triggers.
- Regular exercise—walking may reduce symptoms, bloating, and gas production. Exercise improves gas transit and defecatory patterns and may reduce stress. Yoga has also been shown to benefit, as it focuses attention on muscle contraction and relaxation.
- Stress management—meditation, support groups, and adequate sleep.
- Eating—have regular meals and take time to eat, drink at least eight cups of fluid (water, herbal teas) a day, restrict tea and coffee to three cups a day, reduce intake of alcohol and fizzy drinks, and limit fresh fruit to three portions a day.

Management should be based on the nature and severity of symptoms. The treatments discussed below assume that choice is determined by the predominant symptom(s).

Psychological therapies—The rates of psychological disorders such as anxiety, depression, and bipolar affective disorder are two- to threefold higher in patients with IBS than in controls without IBS (Ford, 2012). Treatments such as cognitive behavioral therapy (CBT), hypnotherapy, and multicomponent psychological therapy have shown robust results and reproducibility across numerous studies. Their numbers needed to treat have been estimated at 2–4, with the caveat that the efficacy of psychological interventions outside the context of a structured clinical trial was not known (Halland and Saito, 2015). The efficacy of hypnotherapy has been shown to be similar to that of another type of nonpharmacologic treatment; a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet (Ford et al., 2017).

CBT has been shown to improve quality of life and reduce symptom severity, especially with symptoms such as pain perception and comorbid depressive and anxiety disorders, with a number needed to treat superior to most drug therapies. Limited studies suggest that combining pharmacotherapy with behavioral therapies may provide the best symptom relief and quality of life (Sultan and Malhotra, 2017a).

There appeared to be a difference of opinion as to when psychological treatments should be commenced. On the one hand, it has been suggested that they are probably best reserved for patients who fail more conventional treatments (Ford, 2012). One guideline recommendation stated that they should be considered in people who do not respond to drug treatments after 12 months and who develop a "continuing symptom profile (described as refractory IBS)" (Hookway et al., 2015). The benefit of early use in management has been stated to be unclear, especially given the difficulty many patients have finding appropriate providers (Ford et al., 2017).

However, a case has been made for more frequent use of psychological interventions (Linedale and Andrews, 2017). Such treatments offer global rather than targeted symptom control; are as effective as antidepressants; double the number of patients who experience symptomatic improvement compared with patients who receive "usual physician treatment," "supportive therapy," or "symptom monitoring"; have been shown to directly affect visceral hypersensitivity and gastrointestinal motility when gut-directed hypnotherapy has been used; do not cause adverse drug effects and address the significant psychological aspects of FGIDs. While patient resistance may occur, so too may a lack of positive endorsement by doctors. Complaints of affordability should be considered in the context of the money spent on CAMs (Linedale and Andrews, 2017).

Dietary therapies—Many patients strongly associate IBS symptoms with ingestion of certain foods. This may suggest food intolerance, though immunologically mediated food allergy is uncommon in IBS. There is no available investigation that can accurately identify all the foods causing a patient's symptoms (eTG complete, 2016). If food intolerance is clinically suspected, the appropriate investigation is a trial of an exclusion diet—that is, excluding food groups or components of food groups from the diet. Such diets are implemented for the shortest time possible to assess symptom improvement, are supervised by a dietician, and are only used after screening for eating disorders. A food diary may identify common food triggers such as caffeine, alcohol, carbonated drinks, fatty food, fiber, lactose-containing food, and wheat. Evidence supporting elimination diets is limited (Sultan and Malhotra, 2017a). If there is no clear benefit from initial dietary therapy, a low FODMAP diet could be considered, also under

the supervision of a dietician. Sensitivity to food chemicals (such as sulfites in dried fruit and salicylates in fruits and vegetables) is possible but rare (eTG complete, 2016).

Fiber—Adequate fiber intake (e.g., 25 g daily for females and 30 g daily for males) is recommended in treating patients with IBS-C. This can be done by gradually increasing the intake of fruit and vegetables, as fiber-related gas production may exacerbate bloating and flatulence. Soluble fiber is preferred. A less fermentable soluble fiber supplement (e.g., psyllium) or a nonfermentable insoluble fiber supplement (e.g., sterculia) can be recommended, while making sure of adequate fluid intake to maximize their effect (eTG complete, 2016; Sultan and Malhotra, 2017a). Psyllium has been shown to be beneficial in the management of IBS (Ford et al., 2017).

FODMAPs—FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) are fermentable carbohydrates that are poorly absorbed from the gastrointestinal tract and become substrates for bacterial metabolism in the large bowel, which result in bloating, altered intestinal motility, and abdominal discomfort/pain in those susceptible people with visceral hypersensitivity. A diet low in FODMAPs has been shown to significantly reduce global symptom scores in IBS, provide the greatest short-term gains in up to three quarters of patients, and improve the quality of life (Ford et al., 2017). An odds ratio of 1.81 (1.11–2.95) has been reported for efficacy from six randomized controlled trials (Linedale and Andrews, 2017). It can be recommended regardless of subtype and is supervised by a dietician. The impact of long-term restriction of FODMAPs on the gut microbiota is yet to be established. Long-term use of a low FODMAP diet is therefore not recommended and tolerated FODMAP-containing foods need to be reintroduced to normalize the diet (Linedale and Andrews, 2017).

Probiotics—The gut microbiota may be altered by diet (particularly fiber), probiotics, or antibiotics. Currently, there appears to be no clinically useful way of identifying specific disturbances in the gut microbiota of people with IBS (eTG complete, 2016). Species in probiotics shown to be of benefit in trials measuring improvement in global symptom scores have been Bifidobacterium and *Lactobacillus plantarum* (Ford et al., 2017). In a summary of the efficacy of treatments for FGIDs in recent systematic reviews (15 trials, $n = 1838$), probiotics were shown to have an odds ratio of 2.24 (1.81–2.75), a gain of symptom improvement above control of 13.5% and a NNT of 7–8 (Linedale and Andrews, 2017). Probiotics should not be used in people who are immunocompromised as they may result in infection.

In addition to bacteria, the gut microbiota contains a variety of other organisms such as viruses, particularly in the form of phages, fungi, and yeasts. However, there is little information on their role in IBS (Pearson and Whorwell, 2017)

It seems reasonable to conclude that probiotics have a positive effect in patients with IBS, but different preparations may not be as effective as others. In addition, the benefits may take time to accumulate, and they are probably best suited to the milder forms of the condition. In the future, it may be possible to develop designer probiotics, containing organisms that are known to have an impact on symptoms rather than the current trial and error approach (Pearson and Whorwell, 2017).

Treatment; Pharmacological

Overview—Most of the currently available treatment options for IBS focus on relieving individual symptoms. Patients with constipation-predominant IBS (IBS-C) may be administered osmotic laxatives, guanylate cyclase-C agonists such as linaclotide and plecanatide or a chloride channel activator such as lubiprostone (see below). Patients with diarrhea-predominant IBS (IBS-D) are treated with opioids; loperamide is the standard over the-counter medication. Eluxadoline recently received approval from the US Food and Drug Administration (FDA), and alosetron, a 5-HT3 antagonist, is an older drug that was approved for IBS-D. Both eluxadoline and alosetron are associated with warnings from the FDA regarding risks of pancreatitis, especially in patients with prior cholecystectomy or ischemic colitis, respectively. Medications used to treat pain associated with IBS-D (i.e., antidepressants and pain modulators) work in the central nervous system to try to reduce the pain arising in the gut. Symptoms revolving around bloating and distention may be treated with diets, including the FODMAP diet, as well as antibiotics and probiotics. However, the evidence supporting the use of these approaches is relatively limited given the small clinical trials in which they have been tested (Camilleri, 2017).

Laxatives—In addition to the information provided on laxatives in the chapter on constipation, the following recommendations have been made;

- Discourage people with IBS-C from taking lactulose (Hookway et al., 2015). It is broken down by colonic flora and produces excessive gas (Sultan and Malhotra, 2017a).
- Advise people with IBS how to adjust their doses of laxative according to the clinical response. Titrate the dose according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol stool form scale type 4) (Hookway et al., 2015).
- Manage constipation in IBS as for functional constipation (eTG complete, 2016).
- Stimulant laxatives may cause considerable cramping and pain in patients with IBS (eTG complete, 2016).

Herbal medicines—The use of herbal medicines for the treatment of irritable bowel syndrome is common, particularly if patients are dissatisfied with traditional treatments. Some clinical trials have shown a benefit for symptomatic treatment of this condition. A Cochrane systematic review identified and included 75 randomized clinical trials evaluating the effects of various herbal preparations (including single herbs or mixtures of different herbs) for treating people with irritable bowel syndrome (Liu et al., 2006). Compared with placebo, a standard Chinese herbal formula, individualized Chinese herbal medicine, STW 5

(Iberogast—see below) and STW 5-II, the Tibetan herbal medicine Padma Lax, the traditional Chinese formula Tongxie Yaofang and Ayurvedic preparation showed significantly improvement of global symptoms. Compared with conventional therapy in 65 trials testing 51 different herbal medicines, 22 herbal medicines demonstrated a statistically significant benefit for symptom improvement, and 29 herbal medicines were not significantly different than conventional therapy. In nine trials that evaluated herbal medicine combined with conventional therapy, six tested herbal preparations showed additional benefit from the combination therapy compared with conventional monotherapy. No serious adverse events from the herbal medicines were reported (Liu et al., 2006).

The review showed that some herbal medicines improve global symptoms such as abdominal pain, diarrhea, and/or constipation. However, the methodological quality of most of the clinical trials evaluating these herbs was generally poor. In addition, purity and consistency concerns have been raised (Sayuk and Gyawali, 2015), as well as lack of a clear understanding of the active ingredients (Chey et al., 2015).

STW 5 (Iberogast) is a liquid multiherbal supplement containing bitter candytuft, angelica root, chamomile flowers, caraway fruit, St Marys thistle, lemon balm leaves peppermint leaves, celandine, and liquorice root. In vitro it has been shown to affect gastrointestinal transit, reduce gastric tone, and small intestinal secretion. In animal models, components have been shown to bind both muscarinic (M3) and serotonergic (5-HT_3 and 5-HT_4) receptors. These findings appear to provide plausible mechanisms to explain the clinical benefits (Halland and Saito, 2015). Iberogast has been reported to have a relative risk of symptom improvement with intervention compared to control of 1.9 (1.15–3.14) and a gain (i.e., gain of symptom improvement above control) of 15–25% in FGIDs (Linedale and Andrews, 2017).

Antispasmodic drugs—(peppermint oil, hyoscine butylbromide, mebeverine); some patients have abnormal gastrointestinal motility and contractility of smooth muscle (Ford et al., 2017). Antispasmodics may help to control abdominal pain and occasionally diarrhea (eTG complete, 2016). They are used on as as-needed basis. They all reduce pain by reducing smooth muscle contraction and may reduce visceral hypersensitivity (Sultan and Malhotra, 2017a). While a clinically meaningful improvement from randomized and nonrandomized controlled trials has been demonstrated (Linedale and Andrews, 2017; Sultan and Malhotra, 2017a), it has also been stated that benefit of anticholinergic agents in IBS is questionable—they may be useful in patients with abdominal pain but are likely to cause adverse effects (Australian Medicines Handbook, 2018). These anticholinergic adverse effects may affect people with IBS-C and the elderly, who are more sensitive to adverse effects such as dry mouth, blurred vision, constipation, and confusion. The American Gastroenterological Society suggested using antispasmodics over no drug treatment in patients with IBS. However, this represented a conditional (weak) recommendation based on low-quality evidence (Weinberg et al., 2014).

Motility agents—Many motility agents have been withdrawn or reintroduced with caution due to safety issues. Examples include cisapride (which has serotonergic prokinetic effects) because of cardiac side-effects: alosetron (a 5-HT_3 receptor antagonist) due to a small number of cases of ischemic colitis and tegaserod (a partial 5-HT_4 receptor agonist with predominantly motor effects in the gut), due to cases of severe central and peripheral ischemia (Enck et al., 2010).

Domperidone is a dopamine antagonist for which only a few studies of efficacy in IBS have been published in the past with a very low number of patients included. Its NNT has been found to be 9–10 [OR: 1.65 (0.74–3.68)] indicative of moderate efficacy. However, none of the studies met quality criteria (Enck et al., 2010). Its use is problematic in patients with prolonged QT intervals or in combination with drugs that inhibit liver cytochrome 3A4.

Prucalopride is a 5-HT_4 receptor agonist that increases gastrointestinal motility. It has been shown to be effective (i.e., greater than three spontaneous complete bowel motions per week) in chronic idiopathic constipation for only 20%–30% of patients compared with 10%–13% for placebo. Further study is needed to establish efficacy compared to (and in combination with) other laxative regimens and with long-term use (Australian Medicines Handbook, 2018). There has been no evidence to support the use of prucalopride in patients with IBS-C (Tse et al., 2017).

Alosetron has been shown to reduce abdominal pain, IBS-related global symptoms, and diarrhea in patients with IBS-D by increasing colonic compliance and reducing intestinal transit (Sultan and Malhotra, 2017b). The American Gastroenterological Society (AGA) (Weinberg et al., 2014) stated that the overall quality of the evidence was moderate (due to downgrading for inconsistency). When limited to consideration of abdominal pain improvement as the primary outcome, the quality of the evidence was greater (high). Several important caveats should be noted; alosetron was only FDA approved for use in women, and because of concerns about idiopathic, non-dose-dependent ischemic colitis (approximately 1 case/1000 patient-years), the drug was voluntarily withdrawn from the market and subsequently reintroduced only under a specific physician-based risk management program. The AGA suggested using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms. This was a conditional (weak) recommendation based on moderate evidence (Weinberg et al., 2014).

Prosecretory agents—lubiprostone is a prostaglandin derivative and linaclotide and plecanatide are 14- and 16-amino acid peptides, respectively, that act on the guanylate cyclase C receptor (Camilleri, 2012b). Lubiprostone and linaclotide act on intestinal enterocytes to increase fluid (through chloride and bicarbonate) secretion into the gastrointestinal tract, accelerating transit. Their effects appear to be modest, with nausea (lubiprostone) and diarrhea (linaclotide) the main adverse effects (Ford et al., 2017). Both have been shown to improve global, abdominal, and constipation symptoms in IBS-C (Chey et al., 2015). Additionally, linaclotide reduces abdominal pain through an effect on pain fiber activity, but this may take up to 12 weeks to reach its maximal effect (Halland and Saito, 2015; Sultan and Malhotra, 2017a).

An algorithm for the management of chronic constipation in IBS-C patients has been developed (Tse et al., 2017). It suggested that after lifestyle modifications (e.g., dietary fiber, fluid, and exercise), those IBS patients with constipation predominant

symptoms and/or predominant functional abdominal pain should be commenced on a prosecretory agent. Additional options for constipation predominant symptoms included laxatives (stimulant or osmotic). Additional agents suggested for patients with predominant functional abdominal pain consisted of pharmacological (e.g., antidepressants, antispasmodics) and nonpharmacological (e.g., meditation, relaxation, and hypnosis) treatments (Tse et al., 2017).

The American Gastroenterological Association (AGA) has recommended using linaclotide over no drug treatment in patients with IBS-C. This represented a strong recommendation based on high-quality evidence. They added that patients' who place a high value on avoiding diarrhea and avoiding higher out-of-pocket expenses associated with linaclotide may prefer alternate treatments (Weinberg et al., 2014). For lubiprostone, the ACA has recommended its use (over no drug treatment) in patients with IBS-C. This represented a conditional (weak) recommendation based on moderate-quality evidence. The same comment was made regarding higher out-of-pocket expenses associated with lubiprostone; alternate treatments may be preferred (Weinberg et al., 2014).

Antidepressants—Australian guidelines state that there is "some evidence" that tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) reduce visceral hypersensitivity, which improves abdominal pain and appears to provide global symptom relief (eTG Complete, 2016). Their mechanism of action was unclear (Sultan and Malhotra, 2017a). The benefit was not restricted to patients with anxiety or depression. Despite doses being lower than those used to treat depression or anxiety, anticholinergic and other adverse effects may occur, with SSRIs recommended as an alternative (eTG complete, 2016). It has been suggested that different antidepressants can be leveraged to address different IBS subtypes—TCAs (because they may cause constipation) in IBS-D and SSRIs (because they may have prokinetic effects) for IBS-C (Chey et al., 2015).

National Institute of Health and Care Excellence (NICE) guidelines (Hookway et al., 2015) state that TCAs should be considered as second-line treatment if laxatives, loperamide, or antispasmodics have not helped. SSRIs should be considered only if TCAs are ineffective. These recommendations were based on very low-quality randomized controlled trials and no trials which met United States Federal Drug Authority (FDA) approved end points (Ford et al., 2017).

The AGA suggested using TCAs (over no drug treatment) in patients with IBS (Weinberg et al., 2014). This represented a conditional (weak) recommendation based on low-quality evidence. With respect to SSRIs, they found that pooled estimates from 5 RCTs of 6- to 12-week duration showed no improvement in global relief symptoms. Also, four RCTs of 6- to 12-week duration showed no improvement in abdominal pain, with the risk of important adverse effects being minimal. The AGA suggested against using SSRIs for patients with IBS. This represented a conditional (weak) recommendation based on low-quality evidence (Weinberg et al., 2014).

The relative risk of symptoms not improving with intervention compared to control in 11 clinical trials of TCAs (n = 744) in FGIDs was stated to be 0.66 (0.56–0.79); the gain of symptom improvement over control 20%; and the number needed to treat (NNT) = 4 (3–6) for IBS-D only. Findings for SSRIs (7 trials, n = 356) in patients who had comorbid depression or anxiety were stated to be similar (Chey et al., 2015; Linedale and Andrews, 2017). Antidepressants represent a low-cost option.

Opioid antidiarrheals—(codeine, diphenoxylate, loperamide). Opioid receptors are found throughout the gastrointestinal tract. Opioid receptor agonists act to reduce pain perception and slow intestinal transit. Loperamide acts on μ-opioid receptors to reduce stool frequency and increases stool consistency. It can be used prophylactically when diarrhea is anticipated. It is preferred as it does not cross the blood–brain barrier (Chey et al., 2015). The AGA found that available data investigating the use of loperamide specifically for the treatment of patients with IBS-D, as opposed to symptomatic relief of diarrhea for other disease states, were very limited. Two older RCTs that had enrolled 42 patients failed to show a significant benefit in global relief of IBS-related symptoms. However, the quality of evidence from these trials was deemed very low due to methodological concerns and sparse data. There was, however, a large body of indirect evidence from a variety of other settings that showed the efficacy of loperamide in reducing stool frequency. Therefore, because of low cost, wide availability, and minimal adverse effects, loperamide could be viewed as a useful adjunct to other IBS-D therapies. The AGA "suggested" using loperamide (over no drug treatment) in patients with IBS-D. This represented a conditional (weak) recommendation based on very low-quality evidence (Weinberg et al., 2014). In practice, bile acid sequestrants such as cholestyramine have been used to treat diarrhea, although they have not been rigorously evaluated (Chey et al., 2015).

Eluxadoline influences bidirectional brain–gut signaling through the endogenous opioid system. Enteric opioid receptors μ, κ, and δ are involved in the regulation of gut motility, secretion, and sensation. The μ-opioid activation has an inhibitory effect on motility and secretion and is the primary mechanism through which loperamide exerts its effects. Expression of the κ-opioid receptor is increased in states of chronic visceral hypersensitivity, thought to play an important role in the abdominal pain component of IBS. Antagonism of the δ receptor counteracts the constipating effects of μ-opioid activation resulting from increased sphincter tone and inhibition of colonic peristalsis while enhancing the μ- and κ-opioid receptor-mediated effects on visceral sensation. Eluxadoline, a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist, was developed with the intention of utilizing this mixed opioid profile to treat both the diarrhea and abdominal pain associated with IBS-D (Barshop and Staller, 2016). It has been shown to be effective in simultaneously relieving the symptoms of abdominal pain and diarrhea in IBS-D. The most common side effects noted were constipation, nausea, and abdominal pain and the most serious was risk of spasm in the sphincter of Oddi, which may result in pancreatitis (Fox, 2016).

Asimadoline, a k-opioid antagonist, that does not cross the blood–brain barrier, may have peripheral analgesic effects and therefore be effective for abdominal pain associated with IBS (Halland and Saito, 2015). It has been stated to reduce sensation in response to colonic distention and to increase sensory thresholds. It had no significant effects on gastrointestinal transit or colonic motility, unlike μ-opioid receptor agonists, which relieve pain but retard gastrointestinal transit (Camilleri, 2012b).

Antibiotics—Antibiotics might benefit patients by altering gut flora, which may be inherently different from that of people without IBS. Or they may simply reduce the number of colonic bacteria, thereby reducing the amount of intestinal gas (Halland and Saito, 2015). Rifaxamin is a nonaminoglycoside semisynthetic poorly absorbed antibiotic derived from rifamycin. It inhibits bacterial RNA synthesis. It has a broad antimicrobial spectrum against gram positive and negative and aerobic and anaerobic bacteria. The AGA stated that pooled data from 2 RCTs showed a small but beneficial effect based on the combination of improvement in abdominal pain plus improvement in stool consistency in patients treated with rifaximin. Three RCTs demonstrated an improvement in IBS-related global symptoms. Additionally, these studies showed small improvements in abdominal pain and bloating, although these were of uncertain clinical significance. It was important to note that patients were treated for 2 weeks only and there is no evidence to support repetitive treatment. Although side effects were minimal, the cost of treatment for many patients may be quite high. At the time of publication of the AGA guidelines, rifaximin was not approved by the FDA for the treatment of IBS-D. The AGA suggested using rifaximin (over no drug treatment) in patients with IBS-D. This represented a conditional (weak) recommendation based on moderate-quality evidence (Weinberg et al., 2014). Rifaximin rarely causes drug interactions as it is not absorbed from the gastrointestinal tract. However, as it is a P-glycoprotein substrate, using it with strong P-glycoprotein inhibitors (e.g., amiodarone, carvedilol, various macrolides, and verapamil) may increase the systemic concentration of rifaximin. Clinical implications of this are unknown (Australian Medicines Handbook, 2018).

Bile acid binders—In some studies, approximately 30% of patients with IBS-D have increased bile acid levels in the stool (Corsetti and Whorwell, 2016). The presence of chenodeoxycholate in the stool of healthy subjects has been associated with accelerated colonic transit, increased stool frequency, and decreased stool consistency. It has therefore been hypothesized that the use of bile acid sequestrants (e.g., colesevelam, cholestyramine, colestipol, or a farnesoid X receptor agonist such as obeticholic acid) could be useful in the treatment of patients with IBS-D. Because bile acid diarrhea appears to be so common in patients with IBS-D, it has been suggested that a trial of a bile acid sequestrant could be first-line treatment to exclude this possibility (Corsetti and Whorwell, 2016; Halland and Saito, 2015). In the future, a biomarker-therapeutic combination that includes a screening blood test (e.g., serum C4 or serum FGF19) would identify patients who have an abnormality in bile acid homeostasis or synthesis. This may offer a diagnostic approach to identify bile acid diarrhea among patients presenting with IBS-D. A combined diagnostic and therapeutic approach will indicate the optimal treatment for the individual patient who has bile acid malabsorption rather than empirically treating all patients and hoping for the best (Camilleri, 2017).

Drugs under development—At least three therapeutic agents are now being developed (Camilleri, 2017):

- A sodium/hydrogen exchanger inhibitor (tenapanor) indicated for patients with IBS-C. Tenapanor works by inhibiting sodium uptake in the colonic mucosa to alter the fluidity of content in the bowel.
- A neurokinin-2 receptor antagonist (ibodutant) that employs a visceral analgesic approach in patients with IBS-D.
- A histamine H1-receptor antagonist (ebastine) that works as a visceral analgesic.

Fecal Microbiota Transplantation (FMT)—FMT has been practised in an uncontrolled manner for many years and has often been viewed with scepticism. However, since demonstration of superior efficacy compared to conventional treatment for recurrent *Clostridium difficile* infection, interest in the utilization for FMT in other gastrointestinal conditions has intensified. Currently, there have been no randomized, well-designed, controlled trials of this approach in IBS, although there have been case reports of its benefit. The possible management of gastrointestinal conditions by FMT needs a significant amount of research. There are questions to be answered over the safety of donor material, the dose, and the best route of administration of the material to the recipient (Pearson and Whorwell, 2017).

Role of the Pharmacist

What to Tell the Patient

After listening to what the patient has been told about IBS, it could be explained that there is no definitive diagnostic test and no clear abnormality can be shown for your symptoms. Current medical knowledge cannot provide all the answers we need. This does not mean that we know nothing about the causes of your symptoms, which we believe are related to disturbances in several body systems. More than one of these disturbances may occur at the same time. Although there are many possible causes for your symptoms, the risk of your doctor misdiagnosing IBS is rare when he/she makes sure there are no dangerous symptoms present like bleeding or weight loss, when a small number of recommended tests are negative, when physical examination is normal and when certain criteria for IBS are satisfied. These criteria are called "ROME IV" criteria. We do know that IBS does not turn into some other condition or make another condition (such as cancer or inflammatory bowel disease) more likely. We also know that IBS causes no permanent damage to your body.

We believe that there is a strong connection between the gut and the brain. Sometimes what is going on in the gut affects the brain, and sometimes the brain can affect gut function. For example, stress can affect your gut, and changes in the bacteria in the gut (called the "microbiome") can send messages to your brain. Your gut may be more sensitive to what you eat and drink compared to people who don't have IBS. This may cause it to spasm and hurt, or to hurry up or to slow down. If you can identify the factors that cause your symptoms and change or avoid them, you may not need to take any medicine at all. Or you may need to take medicine

only during the times it is most troublesome. If you tell me the symptoms that cause you the most discomfort, I can tell you the medicines that are most effective for them.

If your doctor has explained that all the appropriate steps have been taken to be sure of the diagnosis, then searching for other explanations for your symptoms or diagnoses is not necessary. It may cause you frustration, take lots of time and money, and you may end up buying medicines or herbs that have not been shown to work.

General recommendations that are made include minimizing or avoiding life events that trigger symptoms, identifying dietary triggers and regular exercise, which moves the gut along and elevates mood. This encompasses the concept of putting ones' health first rather than other lifestyle activities like ones' job. It also means looking after oneself to best cope with a condition that can affect other parts of the body besides the gut.

It is likely that there is more than one cause for your symptoms, which means that treatment may need to address different aspects simultaneously.

You may know that probiotics have been used to treat IBS. We know that the microbiome may be significantly altered in patients with IBS. However, at present, there appears to be no useful way of identifying specific disturbances in the gut microbiota. In the future, it may be possible to develop designer probiotics containing organisms that are known to have an impact on symptoms, rather than the current trial and error approach. It is true that in some people, probiotics reduce symptoms, depending upon the strains of bacteria contained in them.

We know that certain treatments can be very beneficial, such as psychological therapies. They obviously cannot cause the side effects that often occur with medicines, and they address the brains considerable contribution to causing gut problems. There use will depend upon finding a psychologist and establishing a good rapport. We also know that diet can be very important. A dietician can advise about exclusion diets, assess fiber intake, and assess the need and supervise a special type of diet (called the FODMAP diet), which has been shown to help.

Some types of herbal medicines have also been shown to reduce symptoms, such as one called "iberogast" or STW 5, a multiherbal preparation. Unfortunately, the quality of trials testing herbal products has generally been poor. In addition, purity and consistency concerns and lack of a clear understanding of the active ingredients has occurred.

What the Pharmacist Should Know

- Multiple comorbidities may occur in up to two-thirds of patients with IBS consisting of somatic symptoms, pain syndromes, other gastrointestinal disorders and psychiatric disorders. Multiple medication intolerances or adverse effects may also occur.
- Doctors may have limited awareness of the effect of IBS on patients' lives or patient beliefs about the causes of IBS.
- Patients may have misconceptions about IBS. For example, they may believe that some discrete event in their past caused it.
- Patients may care more about triggering factors than etiology. They may be more interested in how to manage the symptoms and minimize their effect on daily life.
- General recommendations include regular exercise, stress management, and dietary considerations.
- Explanation and enthusiasm for psychological therapies may convince the patient to try them or retry them with a different psychologist. Direct referral to a psychologist or referral through the patients' general practitioner should be considered.
- Explanation of the benefit of consultation with a dietician. Direct referral or referral through the patients' general practitioner should be considered.
- The placebo response rate in IBS treatment trials has been found to be 30%–40%.
- Personal factors as warmth, empathy, duration of interaction, and the communication of positive expectation might indeed significantly affect clinical outcome
- A therapeutic trial of a bile acid sequestrant could be useful in the treatment of patients with IBS-D.
- Evidence for the use of antidepressants, antispasmodics, and motility agents appear to be poor.

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Management of Wounds and the Pharmacist's Role: Woundcare

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Wounds, whether acute, postsurgical, or chronic, are a growing area of practice, and it is important to review the current methods of management and developments in diagnosis, assessment, and treatment. How do you define "wound management" what is wound management ?

"The provision of the appropriate environment for healing by both direct and indirect methods together with the prevention of skin breakdown" (Sussman, 2014).

To clarify this definition, no longer should we look on wound management as the application of a dressing to an acute or chronic wound dressings don't heal wounds they optimize local environment for healing.

Wound management is, and must be, a holistic approach to the patient to ensure the best practice is applied in treatment. This approach is best expressed as "treat the whole patient and not just the hole in the patient" (Sussman, 2014).

Pharmacy and the pharmacist continue to play an important role in the delivery of wound management to their customers. No longer must the profession see their role as only the supplier of products but as a clinical service. Quality wound care is multidisciplinary and it involves Medicine, Nursing, Pharmacy, Podiatry, etc. Pharmacy is the supplier of therapeutic products, but wound management involves therapeutic decision making some products required are prescription-only medicines. Many drugs impact on wound healing by both stimulating and retarding healing, and some drugs even cause wounds. Wound management and wound pharmaceuticals are as much the responsibility of Pharmacy as are drugs.

Wound management is a stimulating practice, but the problem of both chronic and acute wounds an underestimated problem. The prevalence is increasing at a rapid rate due to the ageing of the population and the significant increasing rates of diabetes worldwide.

Patient-Centered Care

The patient has the wound and is a partner in the discussions and decisions about treatment and other activities. The patient is treated holistically, and you must consider the wound, whole body, personal values and experiences, and environment (social, occupational, familial, etc.).

Best Practice Resources

The benefits of using best practice resources is that we are all working on same page, evidence-based, patient-focused, interprofessional, this will achieve cost-effectiveness, streamline and simplify services, and provide consistency of care across settings and location.

The Basic Principles of wound management

1. Define etiology.
2. Control factors affecting healing.
3. Select appropriate dressings.
4. Plan for management (Grey et al., 2006; Sussman, 2001).

Define Etiology

Wounds are either acute or chronic in nature and the approach to each type can be different.

Acute wounds	*Chronic wounds*
Higher risk of infection	Lower risk of infection
Due to debris contaminating wound	Symptom of underlying condition
Inflammation occurs	Heal by secondary intention
May heal by primary intention	Not sterile
May require antiseptic use and systemic antibiotics	May be sloughy and exudative

Wound Healing Principles

Wounds heal either by primary intention or by secondary intention.

Primary Intention

Involves the apposition of the wound edges and the reunion of tissue structures and should result in minimal scaring.

Secondary Intention

Open gaping wounds where there is loss of tissue, or infected closed wounds, heal by the formation of granulation tissue (vascular and fibroblast proliferation), which fills the defect and by contraction of the wound edges. Healing by secondary intention is slow and can result in a large distorted scar.

Physiology of Wound Healing

There are three phases of wound healing—inflammatory (destructive), proliferative (regenerative), and maturation (reparative). During all of these phases, there are a number of cells that are essential to the healing process including platelets, neutrophils, macrophages, and fibroblasts. Some of the cells are only present for one particular phase; however, most are there from the very beginning of the wound, through to the ultimate healing of the wound.

The critical thing is that the phases of healing are parts of a continuum. Each phase continues on in a steady process merging with the next phase. In fact, one wound may be in more than one phase at one time (Grey et al., 2006; Sussman, 2001, 2016).

Phases of Healing

The Inflammatory Phase

The inflammatory phase is normally the shortest, a wound is either surgically created, caused by trauma or some other reason. There will be bleeding and a clot will develop to induce hemostasis. Wound exudate is often manifested during the inflammatory phase.

The most important cells are the platelets whose task is not only hemostasis but also the production of a growth factor. During this phase, the neutrophils are involved in phagocytosis of bacteria as well as aiding in the extracellular release of proteases, enzymes used by the body for the destruction of necrotic tissue (Grey et al., 2006; Sussman, 2001; Sussman, 2016).

The Proliferative Phase

During this phase, the new vascular bed is formed by angiogenesis, collagen is deposited by the fibroblasts the essential framework for the connective tissue which will eventually fill the wound. The collagen realigns itself by cross-linking, resulting in tensile strength in the wound. During the proliferative phase wound contraction occurs pulling the wound margins together. Contraction and granulation are the processes by which the wound becomes smaller. During the latter stage of the proliferative the epidermal cells over the surface of the granulation tissue, a process which is completed most efficiently in a moist, clean environment (Grey et al., 2006; Sussman, 2001; Sussman, 2016).

The Maturation Phase

The maturation phase is the final stage of healing. During this stage, the fibroblasts decrease in number, vasculization decreases, and the tensile strength of the wound increases. Maturation is the most misunderstood phase of healing. It is assumed that a wound is healing once the epithelium has closed the surface of the wound. Tensile of strength of the wound may, in fact, take quite a considerable time and in some patients it can take up to 12 months. The lack of tensile strength in a wound will increase the risk of breakdown that may be related to tension the tissue below the surface.

Moist Wound Management

Traditional theory has always held that wounds should be kept clean and dry so that a scab forms over the wound, the wounds should be exposed to the air and sunlight as much as possible, and where tissue loss is present, the wound should be packed with gauze to prevent surface closure before the cavity is filled, and then the wound should be covered with dry dressing.

The disadvantages of these principles are that the scab, which is made up of the dehydrated exudate and drying dermis, is a physical barrier to healing, because the epidermal cells cannot move through the scab and this may ultimately result in a poor cosmetic result, even scarring. Exposure to the air reduces the surface temperature of the wound and further delays healing causing peripheral vasoconstriction affecting the flow of blood to the wound. This lower blood flow will also affect the supply of oxygen, nutrition, and other factors to the wound. Air exposure will also cause the wound to desiccate and form a scab (Sussman, 2014).

Where a wound is packed with dry gauze, the quality of healing is impaired due to the adhesion of the material to the surface of the wound causing it to dry out. Equally, covering the wound with a dry dressing that adheres to the wound surface may traumatize the wound surface on removal.

Wounds covered by an occlusive dressing do not form a scab, so epidermal cells are able to move rapidly over the surface of the dermis through the exudate that collects at the wound/dressing interface. The application of a totally occlusive or semipermeable dressing to a wound can also prevent secondary damage as a result of dehydration. It facilitates wound cleansing, since the wound exudate is part of the healing cascade and it also protects granulation and encourages epithelialization. It has now been shown to carry a number of growth factors essential to the healing of wounds (Grey et al., 2006; Sussman, 2001).

There are a number of factors that affect the healing of a wound both intrinsic and extrinsic,

The Intrinsic factors that influence healing (Guo and Dipietro, 2010; Thomas Hess, 2011).

Health Status

This includes the circulation, because without good arterial and venous circulation, healing becomes a problem. Anemia, regardless of type, reduces the capacity of the blood to provide oxygen to the tissues, since hemoglobin transports oxygen to the cells. As a number of other blood cells are critical to the healing process both directly and indirectly by their production of growth factors or other functions—anemia may certainly be a problem.

Immune Function

Normal immune system function is required for the inflammatory phase and the cleansing phase of healing. A reduction in immune function slows the cleansing of the wound bed and reduces the ability of the body to fight invading pathogens. This is likely to be due to a reduction of the number and activity of the white blood cells.

Diabetes

Diabetes is one of the major problems for chronic wounds. Diabetics have a delayed capillary response to injury, reduced cellular function at the injury site, and defects in collagen synthesis and wound strength. This can be attributed to age, obesity, malnutrition,

and vascular disease; however, hypoglycemia caused by reduced insulin availability and increased insulin resistance appears to be major predisposing factors in delaying healing in diabetic patients.

Age Factors

As we age, our skin and tissue change. First, we lose the sensory cells, and then we lose the secretary cells which are so essential for the maintenance of skin moisture and flexibility. We lose the vasculature within the skin, and we lose the hair follicles. The skin becomes far more prone to destruction either by physical or by chemical means.

Body Build

Because of the adipose tissue being poorly vascularized, an obese patient will have a great deal of trouble healing due to the inability to deliver oxygen and nutrients to the wound site. Underweight individuals may also experience difficulties in the healing process.

Nutritional Status

Nutrition is one of the most important factors in the healing of wounds. Proteins, vitamins, carbohydrates, fats, and fluids all play a vital role in wound repair. Of the vitamins and trace elements, vitamins C, A, K, and B are particularly essential in the maintenance of bodily function and consequently wound healing.

Trace elements, such as iron, copper and zinc, are all necessary for a cell proliferation and tissue regeneration. Iron is necessary for hemoglobin synthesis, and deficiency can lead to anemia. Copper is necessary for collagen synthesis. Known zinc deficiency will show a retardation in the synthesis of collagen and a reduction in epithelialization.

Extrinsic factors that influence healing (Guo and Dipietro, 2010; Thomas Hess, 2011).

Mechanical Stress

When a patient is immobile and pressure is exerted locally, especially over a bony prominence for more than 2 h, at a pressure exceeding 30 mm of mercury, localized microvascular ischemia will occur, ultimately leading to tissue destruction both at the surface and deeper into the wound, leading ultimately to a pressure sore. Equally, shearing forces and friction occur when the tissue below the skin is forced to move while the skin itself is restrained by contact to a surface such as the bed sheet. This is particularly evident in the patientsr' heels.

Debris

Debris, such as slough, eschar, scab, wound dressing residues, gauze fibers, sutures, will impede wound healing. Their presence will prolong the inflammatory phase, as well as predisposing the wound to infection. They are act as a physical barrier to the healing process. Debris should be removed, either surgically or by the use of hydrogels, proteolytic enzymes, or hydrocolloids.

Temperature

The optimum temperature for the growth of human cells is 37°C. It is therefore essential to maintain the wound environment at body temperature. A drop in body temperature will lead to peripheral vasoconstriction, affecting the flow of blood through the wound, and it will markedly reduce the activity of growth factors and proteases.

Desiccation

If a wound dries, healing is either delayed or will cease. Exposed, dry wounds are more inflamed, painful, and itchy and have more scab material during the early stages of wound healing. Desiccated wounds present several barriers to efficient wound healing, which can be overcome by maintaining a moist environment.

Maceration

Maceration may be caused by incontinence, perspiration, or excessive exudation. If there is maceration, this will cause the destruction of tissue and slow down the healing process. It is essential to maintain the moist environment without excessive exudation.

Infection

The presence of erythema, discharge, fever, pain with elevated white blood cell count, and sometimes odor is evident that the wound is infected. If clinical signs of infection are present, the use of systemic antibiotics is mandatory. If there are no clinical signs of

infection, there is little reason to use either systemic or topical antibiotics. An exception to this may be the use of very specific topical antibiotics in very specific cases to reduce the level of bacteria in wounds of compromised patients.

Chemical Stress

Iodine, peroxide, chlorhexidine, alcohols, hypochlorites, and acetic acid are commonly used antiseptics and cleansing agents. Use of these agents is often responsible for delayed healing, since they are nonselective in their activity and will kill healthy cells as well as bacteria. It is preferable to avoid the prolonged use of these products on a granulating wound. Their use even in infected wounds is somewhat dubious, they may reduce the surface load of bacteria in an infected wound, they do not penetrate below the surface, and have no real effect on the infection in the tissue itself. They may be of use in dilute forms when applied to some chronic wounds and left in place for no more than 5 min and then washed off.

Systemic Medications

There are a number of drugs that will affect healing, and these include the anti-inflammatory drugs. The use of steroids or non-steroidal anti-inflammatory drugs reduces the normal inflammatory response, which is necessary to prepare the wound for subsequent healing (Karukonda et al., 2000a, 2000b; Pollack, 1982; Sussman, 2007).

Chemotherapeutic agents, such as cytotoxic drugs kill cancerous cells but will also affect and delay the inflammatory phase, suppress protein synthesis, and inhibit cell reproduction. Immuno-suppressive drugs will reduce white blood cells, while penicillin may prevent efficient cross-linking of collagen thereby reducing the tensile strength of wounds. In infected wounds, however, antibiotics enhance the wound healing as they kill infecting organisms and allow wound healing to proceed (Karukonda et al., 2000a, 2000b; Pollack, 1982; Sussman, 2007).

If possible, avoid drugs that inhibit healing, even if this is possible only for the short term. If this is not possible, realize that the wound may never heal; at best, it can be managed so that there is as little pain and discomfort as possible.

Lifestyle

Smoking

The adverse effects of smoking and the potentiation of cancer in various parts of the body have been understood for many years. However, it is clear that the toxic constituents of smoking such as nicotine, carbon monoxide, and cyanide have a dramatic and inhibiting effect on healing (Sussman, 2005). Nicotine will diminish red blood cells, fibroblast, and macrophages and increases platelet adhesiveness. This will produce cutaneous vasoconstriction. Carbon monoxide has an affinity for hemoglobin 200 times that of oxygen. This will have a major effect on the oxygen-carrying capacity of the blood and will lead to a potential ischemia. Hydrogen cyanide inhibits enzyme systems necessary for oxygen transport at the cellular level, as well as oxidative metabolism. Smoking can therefore be a major cause of the nonhealing of wounds (Sussman, 2005).

Alcohol

Excessive and/or *chronic alcohol* intake can lead to health problems affecting wound healing. Alcohol-induced digestive problems may lead to malnutrition and anemia. Liver damage can result in chronic disturbances due to a reduction in platelet levels, and subsequent circulatory damage that may reduce required for wound healing.

Wound Assessment

Patient Assessment

When assessing the status of the patient, the areas to be addressed should include a general health status, medication review, nutritional status assessment, and an evaluation of the awareness and involvement of the patient's family concerning wound care (Grey et al., 2006).

Wound Assessment

After patient assessment, the next step is to carefully assess the wound. Wound assessment includes the wound's etiology, its location, and its size and depth. A thorough wound assessment also includes evaluation of the wound bed in terms of type of tissue present, observation of the quality and amount of exudate, and determination of the presence or absence of infection. It also involves assessment of the condition of the peri-wound area and evaluation of any past and current treatments (Grey et al., 2006).

Wound assessment is now based on the principles of wound bed preparation this clarifies the need to examine all of the aspects of the wound and to address an ongoing debridement phase, management of exudate, and the resolution of bacterial imbalance. From this, the TIME acronym was developed. This consists of the **T**issue, the presence of inflammation/**I**nfection, the level of **M**oisture and the importance of wound, Edge/**E**pithelialization. This simple principle enables a wound to be assessed for most of the important aspects of the wound this enables the health professional to consider the factors for healing or delayed healing and what must be considered in the choice of treatment (Rodrigues et al., 2016; Sibbald et al., 2000).

Wounds are dynamic and as such the choice of dressing will vary and will change as the Wound changes. The product you may commence treating the wound with initially will in many, cases change as the wound itself changes. The choice should be based on a three simple rules. C.D.E. This indicates the three major aspects of any wound Color, Depth, and Exudate.

Color

The Pink wound is in the final stages of healing with new epithelium covering the wound, the major aim is to protect this very delicate tissue, prevent the wound from drying out so as to maintain a moist environment, and to insulate.

The Red wound is a granulating wound with new tissue filling the deficit and with some islets of epithelium present. The aim is to absorb any excess educate, maintain a moist environment, and protect the wound.

The Yellow wound contains a level of slough. This is nonviable tissue that must be removed or healing will not take place. The methods of removal are surgical, re-hydration with dressings such as hydrogels or hydrocolloids. The aim is slough removal by rehydration and absorption of exudate.

The Green wound is most likely infected; this should be confirmed by microculture from the wound to establish the infecting organism. The other signs of infection include

The Black wound has an outer layer of thick hard eschar; this must be removed to commence the healing process. The fastest and most effective method is by surgical removal. The use of dressings such as hydrogels to aid autolytic debridement will at best be slow.

Depth

The wound may be superficial, partial thickness deep, or a cavity. The product choice will depend on the shape, position, and type of wound.

Exudate

Most wound will contain some exudate; this will vary from very little to copious levels. The choice of both primary and secondary dressing will depend on this level and the depth of the wound.

Peri-Wound Area

Assessment of peri-wound skin, or wound margins, can give indications of problems. Erythema of the wound margin can signal infection. A blue-gray or blanched margin can indicate an undermined area. White margins can result from maceration. Stained, dry, cracking, inflamed areas should be noted and documented.

Complex and Chronic Wounds

A large proportion of wounds seen in clinical practice are chronic in nature. The epidemiological studies indicate that one percent of the population has a chronic wound, and of that group some twenty percent have had the wound for more than 2 years. Chronic wounds may be classified into the following groups: (Grey et al., 2006; Sussman, 2014).

Leg ulcers Pressure wounds Chronic infected wounds

The difficulty in the management of any chronic wound is that there is always an underlying physiological cause of the wound that must be treated, but many patients have multifactorial shortages, as discussed earlier. For best results, the basic cause of the problem must be attacked, and the negative factors altered.

It must be understood that some patients may never heal due to the basic pathophysiology of the disease process and our inability to alter some or all of the major factors influencing the nonhealing of the wound. However, even in the most extreme cases, good wound care can be a great help in minimizing the worst effects of such chronic wounds (Sussman, 2014). The complications of leg ulcers include neoplasia, calcification, infection, and hemorrhage.

The main leg ulcers are venous leg ulcer due to venous insufficiency, arterial ulcer due to PVD, mixed venous/arterial, and then atypical ulcers such as vasculitic ulcers (Australian and New Zealand, 2011; Grey et al., 2006; Sussman, 2014).

The Diabetic Foot

Many diabetics may have small and minor skin breakdown, which they may not consider important; however, due to their disease, these minor wounds have the potential of becoming serious. Minor tissue injury was reported as the pivotal event in 86% of cases resulting in amputation every 30 s someone loses a leg to diabetes (Green, 2013; Rodrigues et al., 2016). The pharmacist is in a

unique position as they know their diabetic customers as they dispense their medication and they are able to discuss measures to help the prevent foot ulcers and if necessary treat early skin breaks.

How does Diabetes affect wound healing

- Diabetics have a fivefold risk of infection.
- Diabetics have the inflammatory response impaired.
- Diabetes is associated with atherosclerosis (small vessel disease).
- Diabetes will damage the nerves, which diminish pain sensation and nerve response.

Management of diabetic wounds will depend on diagnosis either a neuropathic or ischemic ulcer. It will involve other health professionals, e.g., a Podiatrist as off-loading to reduce direct pressure is essential.

A simple diabetic wound should be treated with a topical antiseptic, e.g., Cadexomer Iodine and covered with a foam dressing. If there is ischemia present, then urgent referral is critical as surgical intervention may be required (Schwartz, 2013). The pharmacist need to work with the patients GP, Podiatrist, and other health professionals fort the best outcome.

Pressure Injury

Pressure wounds may be as simple as the blister most of us may have experienced over the years from footwear to the extensive pressure sores experienced by bedridden patients suffering from stroke, spinal injury, multiple sclerosis, or dementia. A pressure injury develops when the capillary blood flow to the skin and tissue over a bony prominence is decreased for a sufficient period of time. The consequence of this restricted blood supply is a reduction in oxygen supply and nutrition to the tissue, accompanied by the problem of waste products not being removed from the site (Australian Wound Management Association, 2012; Brink et al., 2006; Lyder, 2003).

The result of this is hypoxia, tissue acidosis, increased capillary permeability, which allows intravascular fluid to escape causing edema and cell death. The main causes of pressure wounds are pressure, friction, and shear.

Risk Assessment

The most important management principle in pressure wounds is to identify any patient at risk of developing such a wound. There are a number of assessment tools that may be used to aid in the identification of such patients. The most commonly used assessment tools are Norton, Waterlow, and Braden. They rate the patient against criteria such as mobility, incontinence, activity, physical condition, mental status, and nutrition (Lyder, 2003; International Wound Infection Institute (IWII), 2016)

Evidence shows nutrition support can prevent pressure ulcers in at risk groups: "Nutritional support, particularly high protein oral nutritional supplements, can significantly reduce the risk of developing pressure ulcers (by 25%)" Nutrition is also an important factor in both prevention and management of pressure wounds (Australian Wound Management Association, 2012; Brink et al., 2006).

Incontinence-Associated Dermatitis

This is skin damage cause by urine or feces and this is sometimes confused with stage 1 or 2 pressure injury. This is in fact a skin damage issue and needs to treated as such gentle cleansing with a cleanser with pH range similar to normal skin, moisturization to maintain the skin's normal barrier function, and application of a moisture barrier product, e.g., a petrolatum-based, dimethicone-based, zinc oxide-based, or liquid film-forming acrylates (Doughty et al., 2012).

Wounds and the Older Person

As a person ages, changes in the skin, such as loss of dermis, collagen, sebum, and sweat production, are reduced. The epidermal layer separates more easily from the dermis, and elastin fibers decrease in number but increase in size, thus making the skin stiff. There is also a decrease in Langerhan cells impacting on the immune system functions. Small blood vessels diminish by 40% and become fragile. There is a loss of vitamin D production, lower migration of capillary epithelial cells, and less epidermal turnover.

Skin tears are the most common simple wound found in older people.

The management of skin tears will include surface contact dressings, e.g., Silicone Tulles, with a secondary dressing of a Silicone Foam dressing, as a general rule never stick any product in the skin of an older person as its removal with most likely cause a new skin tear. It is important to identify patients at risk of skin tears and to institute prevention practices (Sussman and Golding, 2011; Sussman, 2016).

The other issue is maintaining good skin tone by the use of appropriate moisturizing agents to ensure suppleness and to minimize the drying effects of the ageing process on the skin. Recent studies in the *British Journal of Dermatology* have shown that

aqueous creams have a significant increase in transepidermal water loss, and another study reported impacts on cellular and molecular level of the skin. Soap should also never be used as most common soaps are alkaline and have pH from 9 to 12, which will have impact on both permeability barrier formation and skin antimicrobial defense. There are newer liquid detergents with pH in the available acid range (Carville et al., 2014; Mohammed et al., 2011; Tsang and Guy, 2010).

Acute and Simple Wounds

Most wounds resulting from trauma can be managed and treated as part of everyday practice. The critical aspect of emergency first aid is to be aware of your own limitations and know when to refer on to the local medical practitioner or hospital. There are some simple rules for the management of such wounds, covering decontamination, cleansing, hemostasis, wound closure, and dressings bandages.

The types of wounds most commonly seen in pharmacy practice fall into the following categories:

- Lacerations cuts: minor lacerations, major lacerations.
- Grazes.
- Bites: Insect/animal bites.
- Burns: sunburn scalds; superficial burns, partial thickness or full thickness.
- Postoperative wounds: hospital setting or home setting.

Management of Simple Trauma Wounds

In most of the trauma, stop the bleeding by either direct pressure or by the application of a hemostatic alginate dressing, e.g., Kaltostat™, then clean the wound with water or saline, dry and apply a simple waterproof island dressing. If the injury is contaminated, then after cleaning the wound apply a topical antiseptic, e.g., povidone iodine, leave on for 3–4 min, and wash off and apply the dressing. In the case of a laceration if necessary apply several strips, e.g., Steri strips™ to hold the edges in place. If the laceration is large or deep, dress the wound and then refer the patient to a GP or hospital.

Burns

Many burn injuries are minor in nature. They involve pain, discomfort, and disruption to the patient's normal routines of life. Most minor bums will heal spontaneously without any major consequences.

On the other hand, major bums are different, in that they are associated with scarring functional defects, psychological problems, cost to the community, and contractures. It is essential with major burns to establish an accurate diagnosis as to the cause and extent of damage.

Primary Requirements

It is most important to obtain

- type of burn thermal burns, chemical burns, cold injuries
- depth and area of burn
- general medical status of the patient.

Pathophysiology of Burns

The degree of injury will depend on the temperature of the burning agent and the duration of application. The site of the burn (with regard to thickness of skin/keratin layer) will also influence the resultant injury. Certain agents are more likely to cause deeper burns, in particular, electrical burns or flame. Likewise, it is possible for a partial thickness burn to convert into a full thickness burn even when the source of the burn is removed unless the area is cooled then the dynamic heat in the burn will cause deeper damage.

First Aid

Removal from the burning agent is essential first aid in the case of electrical bums. Flush with cold running water for 30 min in order to cool the burn tissue wash away any chemical agents. Care with hypothermia in the young and the elderly do not use ice. Wrap the burned area in a clean, absorbent dressing sterile if possible (e.g., foam). If the burn area is greater than 15% in adults, or 10% in children, it is advisable to transfer the patient to a burns unit. Medical assistance is necessary in major burns of all sizes.

In simple burns, after the cool water treatment apply either a sheet or amorphous hydrogel to maintain the coolness to the burn. In some cases, it may be necessary to apply a silver dressing as the major issue with the burn is infection (Cuttle and Kimble, 2010)

Infection Versus Contamination

It is important to determine if a wound is infected before treatment is initiated. Most chronic wounds with tissue loss are contaminated, but this contamination only becomes significant when local defences can no longer contain the bacterial growth. Therefore, culturing is of little use unless true signs of infection are present. Many strains of bacteria will be found, but this is not an indication of true infection, only contamination (International Wound Infection Institute (IWII), 2016).

The following signs and symptoms of infection are well known:

- Induration
- Fever
- Erythema
- edema

Monitoring for infection in acute wounds, such as surgical wounds and burns, is of great importance. Wounds that are considered contaminated by virtue of their location and procedure are at particularly high risk. In these cases, prophylactic antibiotics are indicated. For management, see antibacterial dressings (International Wound Infection Institute (IWII), 2016; Sussman and Weller, 2006).

Wound Dressing and Bandages

The choice of dressing will depend on the wound it is to be applied to and what the dressing is required to achieve. Once a correct diagnosis of the wound is done, then the wound condition, wound type, exudate level, depth, and potential bacteria are considered and the choice will depend on the ability of the product to address these issues.

Passive Dressings

For many years, the products used were of the "passive" or the "plug and conceal" concept including gauze, lint, nonstick dressings, and tulle dressings and fulfil very few of the properties of an ideal dressing, have very limited (if any) use as primary dressing, but some are useful as secondary dressings (White, 2006). It is clear that there are a number of negative aspects in the use of gauze.

- Gauze a fibrous material sheds readily to contaminate the wound.
- Gauze is absorbent and will tend to dry the surface of the wound
- Gauze is permeable to bacteria, and moist gauze does tend to be an environment for the growth of bacteria.
- Gauze is also adherent and will further traumatize the wound on removal risking damage to granulating tissue and pain.

In addition to gauze, lint, and cotton dressings, other simple modified absorbent pads covered with a perforated plastic film to prevent adhering to a wound such products include Melolin,™ Cutilin,™ and Telfa™ are used both as primary and secondary dressings. They are used in minor and low exudating wounds.

Modern inert more absorbent dressings, e.g., Exudry™, Mesorb™, and Zetuvit plus ™ are products with a highly absorbent pad and a nonstick nonshear surface. It can be used as secondary dressing over moderate to highly exudating wounds (White, 2006).

Tulle Dressings

These are nonabsorbent passive dressings, e.g., paraffin gauze (tulle) dressings are among the earliest dressings, the older style of these dressings are no longer considered appropriate as they are open weave in construction and allow tissue to pass though causing them to stick to the wound and cause trauma on removal they may lead to maceration in that exudate may not pass through and be trapped within the wound. They also require a secondary dressing. They are also used as a primary dressing over skin grafts. Newer forms of Tulle have been developed by changing the composition to synthetic fibers tightly meshed and impregnated with materials that allows moisture to pass through minimizing maceration, e.g., Adaptic™ and Cuticerin™, and Atrauman™ (White, 2006). There are also silicone-coated forms for fragile skin, e.g., Mepitel, adaptic silicone.

Interactive Dressings

These dressings help to control the microenvironment by combining with the exudate to form either a hydrophilic gel or by means of semipermeable membranes, controlling the flow of exudate from the wound into the dressing. They may also stimulate activity in the healing cascade and speed up the healing process.

There are six classes of interactive dressings and are classified according to their functionality (White, 2006).

Film Dressings (for Wounds With no to Low Exudate)

These dressings consist of a thin, polyurethane membrane coated with a layer of acrylic adhesive and island version with a pad

- waterproof
- gas/vapor permeable
- flexible, transparent
- protects from shear, friction, chemicals, microbes
- spread tension forces

They are useful in superficial, clean wounds and in the prevention of breakdown and preulcers in pressure wounds. They are also used as a postoperative dressing over sutures and to reduce subtissue tension over closed sutured wound after removal of the sutures or clips, e.g., clued Opsite,™ and Tegaderm,™. If there is a small amount of exudate in the wound, then an Island film that include a nonstick pad is the best, e.g., Opsite post op and™ Tegderm™ with a pad (White, 2006).

Absorbing Dressings

Hydrocolloid Dressings (for Wounds With Low Exudate)

Hydrocolloids are a combination of polymers held in a fine suspension and often contain polysaccharides, proteins, and adhesives. When placed on a wound, the polymers combine with the exudate and form a soft, moist gel-like mass. They also encourage autolysis to aid in the removal of slough from a wound.

- *flexible, thin available (transparent), waterproof*
- provide physical barrier
- gel with exudate
- debriding
- no secondary dressing

Hydrocolloids should be applied over the wound with at least 3–4 cm extra product greater than the size of the wound. The skin should be dry and free from creams, ointments, or oil to ensure good adhesion. The dressing should be placed 1/3 above the wound and 2/3 below it, this will prolong the wear time of the dressing. The dressing can remain in place for up to 7 days, the removal will depend on the level of exudate and are removed when strikethrough has occurred, i.e., the exudate has migrated to the edge of the dressing. Please note that these dressing are contraindicated in diabetic wounds. Hydrocolloid products are used in low exudating wounds, including ulcers and granulating wounds. The paste or powder forms are used in a deeper ulcer or cavity. These convert to the same hydrophilic gel and are covered with the normal hydrocolloid wafer, e.g., Duoderm®/Comfeel™ and Hydrocoll® (White, 2006).

Foam Dressings (for Wounds With Medium to High Exudate)

These products are soft, open celled hydrophobic/hydrophilic nonadherent dressings that may be single or multiple layers and meet many of the properties of an ideal dressing,

- Absorbent allows the passage of exudate through the nonadherent surface to be absorbed in the main body of the product
- maintain a moist environment
- Thermally insulating
- Cushioning
- Nonadherent
- Nonresidual

Foams are mainly used in moderate to heavily exudating wounds, including ulcers, donor sites, and minor burns, and they act as a secondary dressing, particularly as a covering with the use of amorphous hydrogels

In addition to standard and waterproof foams, there are also shaped cavity devices, which may be inserted into cavity wounds or dehisced surgical wounds, e.g., Lyofoam Max™, Allevyn™, and PermaFoam®.

Foams are also available with a soft silicone coated surface, this allows the dressing to adhere to the skin but are able to be removed without trauma this of particular importance in patients with fragile skin reducing the risk of trauma on removal, e.g., Allevyn Life™ and Mepilex® (White, 2006).

Hydroactive Dressings *(Foam-Like)* (for Wounds With Medium to High Exudate)

These multilayered highly absorbent polymer dressings some with a surface adhesive are similar to foams; however, instead of absorbing exudate by a simple syphon action, the exudate is trapped within the product itself allowing the polymer to swell, they are

- highly absorbent polymer dressing maintain a moist environment.
- waterproof
- expandable
- nonresidual

Hydroactive dressings are indicated for use in highly exudating surface and cavity wounds including leg ulcers and pressure wounds. They are particularly useful over joints such as elbows, knees, fingers, and toes due to their ability to expand and contract without causing constriction. Hydroactive dressings are not indicated for dry or lightly exudating wounds, e.g., Cutinova Hydro™, Biatane™, Tielle™, and TenderWet Active® (White, 2006).

Alginate Dressings (for Wounds With Medium to High Exudate)

Alginates are the calcium or sodium/calcium salts of alginate acid, obtained from seaweed. There are two forms the gel produce with be either firm or soft. When applied to a wound, the sodium salts present in the wound exchange with the calcium in the alginate to form sodium alginate a hydrophilic gel. This gel has the ability to absorb exudate into itself while maintaining a moist environment.

- highly absorbent
- form gel with exudates
- moist interface
- easily removed
- hemostatic (some)

Some alginates are used on donor sites, bleeding sites, e.g., Kaltostat® and Algisite M™, and also in exudating wounds, e.g., Kaltostat®, Algisite M™, Sorbsan™, and Comfeel Seasorb™ (White, 2006).

Alternate Fiber Dressings (for Wounds With Medium to High Exudate)

These dressings have some of the properties of alginates, and they come as a fiber rope or dressing that forms a firm gel in contact with fluid.

- Synthetic fibrous mat—forms a firm gel in contact with exudate
- highly absorbent
- no lateral wicking—protects peri-skin

Aquacel™ Durafiber®, Exufiber® (White, 2006)

Hydrogels (for Dry or Sloughy Wounds)

Hydrogels have the properties of both rehydrating dry tissue and absorbing certain amounts of fluid into themselves. They are provided as either amorphous gels or sheet forms. They are used to help rehydrate slough and necrotic tissue to aid in the autolytic debridement. They are also used in the management of burns, including sunburn, scalds, and other partial thickness burns. Amorphous hydrogels have also been used in the management of chicken pox and shingles, and are applied to the eruptions three to four times a day. They provide a moist environment and relieve the discomfort of the lesion and also reduce the probability of scarring. Hydrogels are also available in sheet form consisting of a cross-linked polymer and water held in a backing. These products are particularly useful in the management of burns and also to aid the management of in pressure wounds, e.g., IntraSite gel™, Purilon Gel™, Solosite™, DuoDERM Gel®, Solugel™; Nugel Hydrogel Sheet, e.g., Hydrosorb™, Nu-gel™ (White, 2006).

New Hydrogels

Flaminal® hydrogels are based upon gelled alginate and not on other polymers Flaminal® hydrogels use the enzymes glucose oxidase and lactoperoxidase to control the bioburden and acts as an important natural antimicrobial (Banks et al., 1986). They have been shown to be bacteriostatic against Gram-positive organisms and exhibit pH-dependent bactericidal action against Gram-negative organisms in the presence of hydrogen peroxide and thiocyanate (Fleischer and Reimer, 1997; Vandenbulcke et al., 2006).

Antibacterial Dressings

Antiseptics are completely nonselective and have the potential to damage all cells. These compounds can be bactericidal or bacteriostatic, and they may inhibit reproduction, inhibit metabolic activity, change pH, and liberate oxygen—mechanical effects. They come as both organic and inorganic compounds.

In open wound, there is some risk of systemic absorption. There are a number of specialized antibacterial dressings for use in particular wound types (International Wound Infection Institute (IWII), 2016).

Iodine

Iodine in its various forms has been used as a topical antiseptic since 1840.

The newer forms of iodophores have been used since the 1950s. Most of these new forms combine iodine in a complex with a polymer, e.g., Povidone and Cadexomer, which slowly release the iodine. Iodine is active against bacteria, mycobacteria, fungi, protozoas, and viruses. There is no evidence of resistance to iodine (Leaper and Durani, 2008; Sibbald et al., 2011).

Cadexomer Iodine Dressings

This is a nontoxic iodophor that combines iodine with a polysaccharide polymer. When applied to the wound, the iodine is released over 72 h at 0.1% (not cytotoxic). The iodine and absorbes exudate—forms gel, breaks down slough, kills bacteria, and stimulates wound healing.

It is used for sloughy/infected wounds, diabetic wounds, recalcitrant wounds, and may stimulate growth factors, e.g., Iodosorb®/ Iodoflex® (Fitzgerald et al., 2017; Leaper and Durani, 2008; Malone et al., 2017; Mertz et al., 1999; Schwartz, 2013; Sundberg, 1997).

Inadine

This dressing consists of a low adherent knitted viscose fabric impregnated with a polyethylene glycol (PEG) base containing 10% povidone iodine; equivalent to 1.0% available iodine.

Inadine® dressings are designed to protect the wound, even if infected. Inadine® is indicated for the management of ulcerative wounds and may also be used for the prevention of infection in minor burns and minor traumatic skin loss injuries (Sibbald et al., 2011; Sibbald and Elliott, 2017).

Povidone-Iodine

A commonly used antimicrobial agent is povidone-iodine, a complex of iodine, the bactericidal component, with polyvinylpyrrolidone (povidone), a synthetic polymer. The most common commercial form is a 10% solution in water yielding 1% available iodine. Povidone-iodine is available as a surgical scrub or skin cleanser with a detergent base (0.75% available iodine) or in other forms, e.g., Betadine® (Durani and Leaper, 2008; Fleischer and Reimer, 1997; Sibbald et al., 2011).

Silver

Silver has been used for many years, and it has proven to have a broad-spectrum antimicrobial activity, and they inactivate most bacteria including MRSA and VRE.

No documented cases of bacterial resistance have been reported.

Silver has been used in particular in the treatment of burns as a silver sulphadiazine cream. This cream has also been applied to some wounds. Contemporary silver dressings allow for continued release up to 7 days. The difficulty is that the cream must be formulated to be applied to intact skin. When applied to a wound, it encourages the development of muscilagenous slough on the wound surface and is now not used as frequently.

The level of silver contained in the various dressings varies greatly. Their mode of action also varies some release the silver into the wound and some partly release the silver and hold some in the dressing and some keep the silver within the dressing. The choice of dressing will depend on the level of infection, the size, depth, and amount of exudate. Silver dressings may be based as high-density polyethylene dressings, foam dressing, alginate dressing, hydroactive dressing, hydrofiber dressing, or tulle dressing, e.g., Acticoat®, Mepilex Ag®,Biatain Ag®, Aquacel Ag™, and Urgotul SSD (Lansdown, 2002a; Lansdown, 2002b).

New Antiseptics

Polyhexanide methyl biguanid (PHMB) is related to chlorhexidine but has superior antimicrobial effect to other cationic biocides. As with the biguanides, PHMB was shown to bind rapidly to the envelope of both Gram-positive and Gram-negative

bacteria, and in doing so displaces the otherwise stabilizing presence of Ca++. It is available as a cleaning solution in combination with a surfactant or as a topical dressing as a foam or a sheet gel, e.g., Prontosan® (Andriessen and Eberlein, 2008; Butcher, 2012; Hübner, 2010).

Dialkylcarbamoylchloride Coated Fiber (DACC)

DACC is presented as a fiber coated with a fatty acid DACC that has selective binding of microorganisms and only binds pathogenic microorganisms. This is a rapid action binding bacteria and fungus within 15–30 s, continues to bind and does not become saturated. Bacteria and fungus bind to surfaces via hydrophobic interaction. As this product does not contain any antiseptics, it is a natural process with no risk of resistance. No known side effects and no negative environmental effects. This product comes as a sheet, ribbon, gel, goam, high absorbent dressing, and a silicone dressing, e.g., Sorbact® (DACC, 2017; Ljung et al., 2006; Meuleneire, 2012).

Octenidine

Octenidine dihydrochloride is a cationic surfactant, with a gemini-surfactant structure, derived from pyridine, active against Gram-positive and Gram-negative bacteria. Octenidine is not absorbed through the skin, nor through mucous membranes, or wounds. It is available as a solution or gel, e.g., Octenaline® (Braun et al., 2014; Hämmerle and Strohal, 2016)

Hypochlorites and Hypochlorous Acid

Sodium hypochlorite was used for many years as an antiseptic, for example, being EUSOL and Dakins Solution. Its use has mostly been discontinued due to its toxicity. Hypochlorous acid is a more recent form of chlorine/oxygen antiseptic that is considered as less or nontoxic, e.g., Microdacyn® (Cheryl, 2016).

Other topical antiseptics have been used in clinical practice including hydrogen peroxide, acetic acid, citric acid, and clorhexidine with or without cetrimide. Most have only limited use.

For recommendation for antiseptic use see **Table 1**

Most topical antiseptics are cytotoxic to tissue and cells; this must be considered when choosing an antiseptic for application to a wound. In the case of acute wounds, they are best applied left in place for 3 to 4 min then washed off. In the case of application to a chronic wound, then the choice should be to use a nontoxic or minimally toxic product (Kempf et al., 2011; Zhong, 2015).

Bandages and Bandaging

Bandages may be used for a number of purposes: keeping a dressing in place (retention), supporting an injured joint (support), assisting venous return in the lower leg (compression), providing a pressure gradient to encourage the flow of blood back to the heart and reduce edema and swelling by compression, as a prophylactic in sports to prevent injury, as a pressure bandage to help control bleeding, and postsurgically to help control venous oozing (Sussman, 2003; Thomas, 1990).

Table 1 General rules for the topical use of antiseptics

Wound Type	*Management*
Cut/laceration	Clean the area with water or saline. If there is any contamination use a surfactant antiseptic, e.g., Savlon® or Betadine scub® to remove any foreign material that may be a focus for infection. Apply an antiseptic around the area and cover with a simple dressing, e.g., a film dressing
Graze	Due to the presence in most grazes of dirt, gravel And other material, scrub the area with a surfactant antiseptic, e.g., Savlon® or Betadine scrub®. Apply an antiseptic around the wound and cover With either a film dressing or an Island Film dressing.
Burn	Most minor burns do not require the use of a topical antiseptic. The use will depend on the depth of the burn and if there is damaged and necrotic tissue present. If there is, then the use of a silver dressing is considered appropriate in the early management. If the burn is minor and there is little tissue damage, e.g., minor blisters then apply an amorphous or sheet hydrogel
Chronic wounds, e.g., Leg ulcers and Pressure wounds	The most important issue with any chronic wound is to clearly identify the underlying cause. In general chronic wound need to be managed by a wound specialist. The pharmacist role is to help with product selection using the rules above and identify the need for recommending specialist help if the wound is not progressing.

Retention Bandages

The role of the retention bandages is effectively to hold a dressing in place. For this purpose, for many years, cotton crepe bandages have been used to hold dressings in place. However, today, there are a number of more effective and appropriate bandages that may be used to hold a dressing in place. The first is the light weight conforming cohesive bandages coated with a thin latex. As a result of this coating, the bandage sticks to itself but not to skin, hair, or clothing. You only require a very small length to hold the dressing in place, compared with using a complete roll of a standard crepe bandage. This type of bandage comes in widths that are appropriate for fingers and toes and also for limbs and larger size for the head. The bandage becomes very cost-effective in that you do only need to use a small amount each time when holding the dressing in place. Examples of this type of bandage are Handigauze Cohesive® and Easy Fix Cohesive® (Sussman, 2003; Thomas, 1990).

The other type of product is the elasticized tubular bandage available in a light weight form that may be cut to the size required and be placed over the dressing, again holding it in place. An example is Tubi Fast®.

Support Bandages

Support bandages are of a heavier construction and are made from both natural and synthetic fibers. They achieve their stretch by the use of high twist yarns and the heavier construction. The main role of strong support bandages is the support of joints in strains and also in the management of muscular injuries. Examples of this type of bandage are the heavy duty crepe bandage, such as Elastocrepe® and Handycrepe®; however, they are of limited use as they do not maintain compression heavier weight cohesive bandage that are able to provide the support with only a few layers and provide about 25 mmHg of compression, e.g., Coban®, Coplus®, and Handygrip® (Sussman, 2003; Thomas, 1990).

Tubular Compression

There are two types of tubular compression bandages: straight or shaped.

Straight tubular compression provides approximately 8 mmHg, and the shaped tubular compression provides between 18 and 20 mmHg at the ankle.

To apply either bandage, invert a length of the bandage equivalent to the length of the patient' foot. Slide the bandage on up to the ankle. Grasp the dangling end of the bandage and in one motion slide the rest of the bandage over the foot and up to the knee. Multiple layers of straight tubular bandage are used for compression, e.g., Tubi Grip®, Handyplast Tubular®, and Tensogrip® (Sussman, 2003; Thomas, 1990).

Compression Bandages

Compression bandages are used as one of the main treatment modalities in the management of venous disease, especially where there's an association between venous ulcers and varicose veins both to aid the healing of the ulcer and ultimately in the management of the venous return to help prevent reformation of a venous ulcer. Effective therapeutic compression starts with a subbandage pressure of 18 mm of mercury at the ankle. Anything lower, while appropriate for support, is not considered appropriate for the treatment of venous leg ulcers or their prevention. The primary aim of compression is to reduce the pressure in the superficial veins to encourage venous return to the heart by increasing the velocity flow in the deep veins, also discouraging edema by reducing the pressure difference between the capillaries and the tissue. The most effective method is to apply graduated compression from the toe to the knee. The highest pressure should be exerted at the ankle, gradually falling to about 50% at the knee. The accumulated fluid and waste products are removed from the affected tissue by the accelerated rate resulting from the application of the pressure bandage. Compression bandages are also used in the management of lymphedema and in sport soft tissue or joint injury (Sussman, 2003; Thomas, 1990).

There are two types of compression bandages are available

High Stretch Compression Bandages

These have an extensibility from 130% to 200%, have high elasticity, high to medium resting pressure, and high to medium working pressure. They exert their effects mainly superficially in working combination with the muscles, and they are indicated for the treatment of venous edema and the management of venous ulcers. Examples of high stretch compression bandages include Tensopress®, Setopress®, Surepress®, and Eloflex®. High stretch must only be applied with a spiral technique with a 50% overlap of layers. These bandages apply compression of between 30 and 40 mmHg at the ankle (Sussman, 2003; Thomas, 1990).

Short Stretch Bandages

These have an extension from 30% to 90%, low elasticity, low to slight resting pressure but high to very high working pressure. They exert their effects mainly deep within the limb and they are indicated for both venous edema and lymphedema. Examples of short stretch bandages are Comprilan® and Tensolan®, which may also be applied in figure of eight manner (gives more compression and stays in place better). These bandages only apply pressure when the wearer is active and the calf muscle is being used. If inactive, little extra pressure is applied (Sussman, 2003; Thomas, 1990).

Other Forms of Compression

The other forms of compression garment include the straight tubular bandage. When used for this purpose, it is usually applied in multiple layers commencing with a full bandage from toe to below knee, a second from toe to mid-calf and a third from toe to ankle. This type of product is also available in a shaped version, which provides the graduated compression. The application of a single layer of shaped tubular bandage will produce from 18 to 24 mm of mercury, and this may also be used in multiple layers. To apply bandage, invert a length of the bandage equivalent to the length of the patient's foot. Slide the bandage on up to the ankle. Grasp the dangling end of the bandage and in one motion slide the rest of the bandage over the foot and up to the knee. When applying three layer straight tubular bandage use the following method; Layer one from Toe to Knee, Layer two over layer one from Toe to mid-calf, Layer three over layer two from Toe to just above the ankle bone. This will provide 24 mmHg at the ankle, 16 mmHg at the mid-calf, and 8 mmHg and the knee (Sussman, 2003; Thomas, 1990; Weller, 2012).

Multilayer Bandages

A recent development in bandaging has been the introduction of the Charing Cross fourlayer system. This combines an orthopedic wool, a crepe bandage, a compression bandage, and a cohesive bandage in multiple layers. This combination achieves 40 mm of mercury at the ankle, graduating to 17 mm of mercury at the knee. A number of published studies have shown good healing rates in 12 weeks with this particular system. The example of the multilayer system available is Profore®, Profore Lite®, Coban-2®, and Coban-2 lite® (Sussman, 2003; Thomas, 1990).

Farrow wraps are a newer form of compression that allows a more simple method of application. In cases where the patient is unable to wear compression, then the use of intermittent pneumatic compression devices may be considered.

Contraindication for the Use of Compression Bandages

Great care must be taken before applying compression where there is an indication of arterial disease. It is therefore important that before compression bandages or similar are used on the patient, that their peripheral arterial circulation is checked to ensure that they may not be compromised by the application of compression bandages. Some of the hazards of the use of compression can include skin necrosis, direct trauma, and ulceration from inappropriately applied compression bandaging and ultimately, where used inappropriately leading to amputation. If you do not have a Doppler available to obtain the ABI, then simple observation will help identify potential risk patients. If any of the negative signs are observed, then do not apply compression until a proper vascular assessment is done (Sussman, 2003; Thomas, 1990). All bandages for compression should be applied from the base of the toes to the knee (finishing at the lower edge of the patella). The actual stretch in the bandage for compression begins at the ankles.

Caution

It is essential when applying a compression bandage to a leg, especially where there is unevenness of circumference that the area around the ankle in particular is padded out with orthopedic wool to ensure even distribution of the compression along the leg. This is to reduce the risk of damage from the bandage or if the patient has inverted champagne bottle legs (Sussman, 2003; Thomas, 1990).

Compression Stockings

Compression stockings are used in the management of venous disease post-ulcer healing and in the treatment of lymphedema. Stocking are also used to prevent and treat deep vein thrombosis for many years; antiembolic stockings have been used in hospitals pre and postsurgery to help prevent DVT's More recent studies have questioned their role, and the use of low molecular weight heparin in combination with them or with calf stimulation is seen as a better option. Once the patient is fully ambulating, antiembolic stocking have no role as they only provide 6–8 mmHg compression when the minimum required is 18 mmHg (Kapelle, 2011; Mosti et al., 2011; Patel et al., 2013).

Table 2 Simple leg physical circulation assessment

Observation	*Positive*	*Negative*
Foot temperature	Warm	Cold
Foot color	Pink	White
Toe refill after squeezing	Fast	Slow
Foot pulse	Present	Absent

If a customer is observed to have some of the negative results they may need to be referred for a vascular assessment before compression is used. The application of compression in a patient with arterial disease is generally contraindicated.

Table 3 Recommended levels of compression

Specific condition	*Level of pressure*
Prevention DVT	18–24 mmHg
Superficial/early varices	
Medium varices	25–35 mmHg
Ulcer prevention	
Mild oedema	
Gross varices	35–45 mmHg
Postthrombotic syndrome	
Gross oedema	
Ulcer treatment	
Lymphoedema	35–50 mmHg

Stocking Measurement

The measurement should be taken with the patient standing and as early in the day as possible after the leg has been rested and when any tendency for the leg to swell is a minimum. If this is not possible, and particularly if there is evidence of edema, the limb should be raised in a horizontal position until the swelling has subsided. If the edema is a severe problem, the patient may need to be remeasured for a smaller sized stocking when the initial garment begins to reduce the swelling (Sussman, 2003; Thomas, 1990).

Conclusion

The pharmacist has an important role as a primary health provider in both the areas of wounds and skin diseases. It is essential for them to have a sound knowledge of all aspects of the wound healing process and are in fact the product advisor of treatment (**Tables 2 and 3**)

Web Sites

Wounds Australia www.woundsaustralia.com.au
European Wound Management Association www.ewma.org
Surgical Materials Testing Lab www.smtl.co.uk
Wounds international www.woundsinternational.com
International Wound Infection Institute www.woundinfection-institute.com

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Direct Oral Anticoagulants and the Patient-Reported Outcomes: Synthesis and Advances

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Introduction

Atrial fibrillation is the most commonly seen arrhythmia in patients in Europe. Patients with AF are at an almost four times higher risk of stroke, which is a leading cause of morbidity with significant disability and mortality in the United Kingdom (Kirchhof et al., 2016a). Treatment and prevention of venous thromboembolism is another problem within the United Kingdom requiring anticoagulation, which particularly occurs postorthopedic surgery of due to prolonged hospitalization stays (Miesbach and Seifried, 2012). Vitamin K antagonist, warfarin, has previously been the standard treatment of venous thromboembolism and prophylaxis of stroke from atrial fibrillation. The introduction of novel direct oral anticoagulants in the past decade has transformed anticoagulant treatment providing alternatives to the complicated monitoring and resource intensive warfarin treatment. Patient-reported outcomes (PROs) are a distinctive method of evaluating patient's response to health care or treatment, such as patient satisfaction, adherence, and quality of life. The chapter aimed to analyze the impact of PROs in patients on DOAC treatment using a systematic searching of PUBMED, CINAHL, EMBASE, SCOPUS, Google Scholar, and Springer Link databases.

Twenty-one original studies (6 controlled trials and 15 observational studies) were included from 3231 screened studies. Health-related quality of life (HRQoL) was assessed by 6 (n = 1 for controlled trials and n = 5 real-world studies) studies and reported that HRQoL scores were similar in patients on DOACS and warfarin. Patients prescribed with DOACs presented higher HRQoL scores, which were attributed to lack of intense monitoring required compared with warfarin but this was not statistically significant. The majority of studies (n = 5 for controlled trials and n = 9 for real-world studies) investigated patient-reported satisfaction indicating greater satisfaction with DOACs with significantly lower burden and increased benefit scores for patient on DOACs. Patient-reported expectations, compliance, and adherence were similar for patients on DOACS and warfarin. Patients appear to prefer treatment with DOACS versus warfarin. This has been exhibited by the higher QoL, satisfaction, and adherence described in the studies. This enhanced patient preference of treatment would in turn increase adherence, thereby significantly reducing costs associated with the complications.

This chapter provides an overview of the use of PROs in anticoagulant treatment and has categorized an increasing body of evidence to establish the importance of PROs in patients treated with DOACs.

Advances in Anticoagulants Use

Vitamin K antagonist, warfarin, has been the mainstay of treatment for venous thromboembolism (deep vein thrombosis and pulmonary embolism) and nonvalvular atrial fibrillation for prevention of stroke. The introduction of new (or direct) oral anticoagulants over the past decade has revolutionized the treatment and thromboembolic conditions. These direct oral anticoagulants (e.g., apixaban, rivaroxaban, dabigatran, and edoxaban) have made rapid progress in revolutionizing anticoagulation and been extensively investigated and researched in clinical trials for their clinical effectiveness and safety profile in comparison with standard treatment (Brunton et al., 2018).

Use of warfarin effectively is associated with a significant reduction in the risk of stroke and mortality associated with AF (Brunton et al., 2018). However, warfarin use is limited by its narrow therapeutic index requiring regular monitoring of INR,

multiple drug interactions, and dietary restrictions (Gomez-Outes et al., 2013). DOACs have also been recognized as a safe and effective treatment option in thromboprophylaxis postorthopedic surgery. However, these agents have been known to carry a potential risk of bleeding with no actual method of anticoagulation reversal (Miesbach and Seifried, 2012; Saliba, 2015).

Vitamin K antagonist (warfarin) was first approved for human use in 1954 and proved to be a cornerstone in the treatment of atrial fibrillation and stroke prevention (Pirmohamed, 2006). Until recently, warfarin has been the mainstay of therapy and was recognized as being the only oral pharmacological treatment option available for long-term management of nonvalvular atrial fibrillation and prevention of ischemic stroke.

Direct (or new) oral anticoagulants were introduced to the UK market in the past decade. Dabigatran was the first agent approved for use for patients with nonvalvular AF and stroke prevention. It exerts its activity through competitive direct inhibition of thrombin (Miesbach and Seifried, 2012). Dabigatran was first approved for use within the United Kingdom for AF and VTE in 2011 following results of the RELY trial (Connolly et al., 2009). Rivaroxaban, apixaban, and edoxaban exert their effects by reversible and direct inhibition of Factor Xa in the clotting cascade. Rivaroxaban approval followed showing noninferiority to warfarin for the prevention of AF and VTE in the ROCKET AF study in 2011 (Patel et al., 2011).

The ARISTOTLE trial led to the licensing of apixaban in 2012 showing that apixaban was superior to warfarin in preventing stroke in AF patients and VTE (Granger et al., 2011). Edoxaban was approved in 2015 after the result of the ENGAGE-AF trial displaying noninferiority of edoxaban to warfarin (Giugliano et al., 2013). These clinical studies emphasized the clinical efficacy of the DOACs versus warfarin with the enhanced benefit of a reduced intracranial and major bleeding however showed a higher risk of GI bleeding. Nevertheless, the European society of Cardiology and NICE have recommended DOACs as a suitable option for nonvalvular AF over warfarin (Kirchhof et al., 2016b; NICE, 2016). DOACs are accredited with a number of advantages over warfarin. These include the achievement of rapid onset of action negating the need for bridging anticoagulation. DOACs have a relatively short half-life, therefore allowing ease of anticoagulation control. There are little food–drug and drug–drug interactions with DOACs therefore reducing dietary and other medication restrictions.

The principle benefit of DOAC treatment is the predictable pharmacokinetics displayed by these agents therefore removing the need for blood monitoring and dose adjustment. Hence, these agents are fast becoming the anticoagulation treatment of choice for prescribers in order to enhance patient satisfaction and adherence (Miesbach and Seifried, 2012). In comparison to warfarin, however, DOAC treatment is significantly more expensive, and the lack of monitoring has led to questions of adherence and ensuring clinical effectiveness. This has led to the establishment of patient-reported outcomes in anticoagulation and is an optimal method to assess patient adherence and overall clinical effectiveness of the treatment.

Patient-Reported Outcomes

PROs offer a unique perspective of treatment effectiveness without the invasive blood testing and monitoring requirements associated with warfarin. These can often be more reliable that physiological parameters and informal interviews through the use of optimal validated tools as a method of categorizing and measuring patient outcomes (Valderas et al., 2008).

PROs are testimonies from the patient about how they feel about any particular condition or treatment they are receiving without any intervention or bias from the clinicians (Green and Higgins, 2005). PROs include any evaluation of treatment or outcome directly from patient interviews, questionnaires, or specifically developed tools to capture and enable analysis of valuable patient-reported data. PROs provide valuable data from the patient's perspective and are sometimes used as primary outcomes from clinical trials. However, more often PROs are conveyed as subanalyses after the initial trials have been published (Doward and McKenna, 2004).

Tools for Measuring Patient-Reported Outcomes

PROs are subjective measures relating to patent experience and quantify assessment of patient satisfaction, adherence, or HRQoL (Kingsley and Patel, 2017). HRQoL can be defined as an evaluation of impairment, disability, or handicap (Doward and McKenna, 2004; Wang et al., 2015). Patient satisfaction determines perceived burden or benefits of the perceived treatment being appraised (Doward and McKenna, 2004).

PROs can be collected using validated tools or instruments to ensure the data obtained are valid and reliable. A number of tools have been developed and utilized to quantify or measure PROs. These include the EuroQol 5-dimension 3 level, (EQ-5D-3L), Visual Acuity Score (VAS), and the Sawicki questionnaire to assess HRQoL (Devlin and Krabbe, 2013; Sawicki, 1999; Wang et al., 2015). The Anticlot Treatment Scale (ACTS), Treatment Satisfaction Questionnaire for Medication (TSQM), and Perception of Anticoagulation Questionnaire (PACT) are tools used to assess satisfaction (Atkinson et al., 2004; Cano et al., 2012; Prins et al., 2009). The Duke Anticoagulation Satisfaction Scale has been specifically developed to measure both satisfaction and HRQoL (Samsa et al., 2004; Wild et al., 2008). Patient-reported adherence can be evaluated using self-report scales, such as the Morisky 4- or 8-item adherence scale (Tan et al., 2014). These tools measure disease or treatment-specific objectives describing severity of symptoms, benefit, adverse drug effects in order to capture the patients' well-being and experience with the intervention. Such tools have been developed to measure PROs in patients-receiving anticoagulation and have been scrutinized and validated prior to use.

DOACs and Patient-Reported Outcomes: Evidence Synthesis Method

The review process was conducted by applying the eligibility criteria to examine abstracts of original journal articles published in English that (1) PROs and (2) new or direct oral anticoagulants (DOACs), namely, apixaban, rivaroxaban, dabigatran, or edoxaban were included. Finally, abstracts had to report PROs based on a recognized PRO tool with measurable outcomes. The following types of studies were excluded: review articles, observational studies, and articles on compliance or persistence, which focussed on tablet count or prescription monitoring (Appendix 1).

For population attributes, studies were included that assessed PROs in adults being treated with a DOAC. The search was restricted to studies involving humans and original journal articles. Titles and abstracts were screened to remove studies that were irrelevant to the aim of the review, and full texts of the remaining studies that analyzed the required data but did not utilize a recognized PRO tool were excluded.

The following databases were searched between September 2018 and October 2018 with no filters set on publication date: PubMed (United States National Library of Medicine), Cumulative index to Nursing and Allied Health Literature (CINAHL—Elsevier, Amsterdam, Netherlands), MEDLINE (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online), Embase (Excerpta Medica database) from 1974 until September 2018, SCOPUS, and Springer Link databases. Google scholar was also searched to identify articles not indexed in scientific databases. References cited in the reference list of each identified original research were scanned for any additional articles that would be relevant to this review; these were subsequently also scanned for reviews and studies, which may have been relevant and which were subject to the same eligibility evaluation.

The search strategy identified original research on patient-reported outcomes associated with the use of new or direct oral anticoagulants. Search terms were Anticoagulant* OR oral anticoagulant* OR novel oral anticoagulant* OR Non Vitamin K antagonist oral anticoagulant* (NOAC) OR vitamin K antagonist oral anticoagulant* OR coumarin* OR dabigatran OR rivaroxaban OR apixaban OR edoxaban OR warfarin OR direct factor Xa inhibitor* OR direct thrombin inhibitor* AND Patient reported outcomes OR patient reported satisfaction OR patient reported adherence OR quality of life.

After possible studies were identified, all retrieved titles were screened to determine their potential relevance. The abstracts were assessed against five inclusion criteria: (1) original research studies, (2) recognized and validated tool to measure PROs, (3) patients were taking a DOAC for >4 weeks, (4) adult subjects (≥19 years of age), and (5) reported in English.

The data from all the retrieved studies were subsequently collected and tabulated using a form developed by the lead author that were verified by the second reviewer. Extracted information from studies is mentioned in **Table 1**. The extracted information included study design, study participants and settings, objectives of the study, and main findings of the study.

The outcome measures were categorized into three main groups, namely, HRQoL, patient-reported satisfaction, and patient-reported adherence/compliance or expectations related to anticoagulation treatment with DOACs.

DOACs and Patient-Reported Outcomes: Search Results

The search yielded 1964 unique abstracts from PubMed, CINAHL, Medline, and EMBASE with an additional 1321 abstracts from SCOPUS, Springer Link, and Google Scholar were identified. After removal of duplicate records, 3231 abstracts were screened. Of these, 3104 studies were excluded. Of the remaining 127 articles, 97 were excluded as they did not describe original research or did not illustrate patient-reported outcomes or focussed on warfarin alone. The search yielded 19 articles that were excluded because they involved investigations on adherence or persistence based on pill taking patters, tablet counting or prescription fill analysis rather than patient-reported outcomes.

A total of 21 studies were ultimately included in the review, 6 controlled trials and 15 observational studies (Appendix 1). The 21 studies evaluated patient-reported outcomes or quality of life, using a validated tool, associated with the use of DOACs. The controlled trials (n = 6) included 5 randomized and 1 nonrandomized trial (**Table 1**). Controlled trials were used as they provide larger-scale trials within controlled environments, however, due to being sponsored by industry often may contain an element of bias and not present the full patient overview. Real-world observational and cross-sectional studies provide actual patient experience and use of the treatment in practice. Of the 6 controlled trials, 5 were conducted in multiple countries (including the United Kingdom, the United States, Canada, the Netherlands, France, Germany, and Italy) (Bamber et al., 2013; Coleman et al., 2016; Hohnloser et al., 2016; Monz et al., 2013; Prins et al., 2015), and one was conducted in Japan (Koretsune et al., 2017). The observational studies (n = 15) used the following study designs: 11 prospective studies conducted in Spain, France, Canada, Japan, the United States, Australia, and Europe. Four of the studies were cross-sectional studies conducted in Spain, France, and Canada (**Table 1**).

Patient-Reported Satisfaction

Greater satisfaction with DOACs was reported in five of the included studies using the ACTS tool. These studies showed a significant reduction in the burden score and a higher benefits score illustrating more satisfaction with DOAC treatment (Bamber et al., 2013; Coleman et al., 2016; Hanon et al., 2016; Okumura et al., 2018; Prins et al., 2015; Suarez Fernandez et al., 2018). One study demonstrated a reduced ACTS burden score but stable or no change in the benefit score (Koretsune et al., 2017, 2018). Only two studies showed increased satisfaction in the DOAC group based on the PACT Q2 tool (Benzimra et al., 2018; Larochelle et al., 2018).

Table 1 Summary of controlled trials and observational studies

Author-year of publication	*Data collection period*	*Treatment/population*	*Study details*	*PRO assessment*	*Main findings of the study*
Randomised controlled trials					
Monz et al. (2013)	December 2005 to December 2007	*Treatment*: Dabigatran versus dose adjusted warfarin *Population*: for nonvalvular AF *Mean age*: 71.5 years *Female*: 36.4%	*Design*: RCT Subgroup of RE-LY population RE-LY = Prospective, randomized open-label, blinded end point evaluation *Setting*: 44 countries and 951 clinical centers	Patient-reported health-related quality of life using EQ-5D utility and visual analog VAS scores, assessed at baseline, 3 and 12 months	*HRQoL*: No statistically significant difference between dabigatran groups or warfarin groups Utility weighted scores for Dabigatran 150 mg BD ranged from 0.805 to 0.811 for dabigatran 110 mg BD and did not change over the 1-year observation period. No difference between dabigatran and warfarin group except dabigatran 150 mg at 3 months None of the in-groups or between-group analyses were significant
Bamber et al. (2013)	March 2007 to Sept 2009	*Treatment*: Rivaroxaban vs enoxaparin/warfarin for *Population*: patients with DVT *Mean age*: 56.8 years *Female*: 42.4%	*Design*: RCT Substudy analysis of EINSTEIN DVT study *Setting*: Conducted in seven countries (the United States, the United Kingdom, Canada, the Netherlands, France, Germany, and Italy)	Patient-reported treatment satisfaction using ACTS score, assessed at 12 months of treatment	*Satisfaction*: Clinically significant reduction in ACTS burden (55.2 vs. 52.6, $P < 0.0001$) and improvement in ACTS benefit (11.7 vs. 11.5, $P = 0.006$) in rivaroxaban group (compared with warfarin)
Prins et al. (2015)	March 2007 to March 2011	*Treatment*: Rivaroxaban vs standard therapy (enoxaparin/warfarin) *Population*: patient with PE *Mean age*: 58 years *Female*: 44%	*Design*: Subanalysis of EINSEIN PE study, *Setting*: conducted in seven countries the United States, the United Kingdom, Canada, Netherlands, France, Germany, and Italy	Patient-reported treatment satisfaction using ACTS and Treatment satisfaction questionnaire for Medication Ver II, assessed at 1, 2, 3, 6, and 12 months	*Satisfaction*: Rivaroxaban group reported statistically significant increase in ACTS benefit (11.9 vs. 11.4, $P < 0.0001$) and less ACTS burden (55.4 vs. 51.9, $P < 0.0001$) Statistically significant improved TSQM II scores in the rivaroxaban group $P < 0.0001$ for all four factors, effectiveness, side effects, convenience, and global satisfaction
Hohnloser et al. (2016)	October 2012–September 2013	*Treatment*: Rivaroxaban vs standard therapy for cardioversion *Population*: Patients with AF requiring cardioversion *Age range*: 18–65 years *Female*: 52.7%	*Design*: RCT Post hoc study of X-VERT trial, *Setting*: conducted in seven countries the United States, the United Kingdom, Canada, Netherlands, France, Germany, and Italy	Patient-reported treatment satisfaction using User Treatment Satisfaction Questionnaire for medication Version II, completed after 42 days of treatment	*Satisfaction*: Rivaroxaban group reported increased score for convenience (81.74 vs. 65.78), effectiveness (39.41 vs. 32.95), and global satisfaction (82.07 vs. 66.74), $P < 0.0001$
Coleman et al. (2016)		*Treatment*: Rivaroxaban for stroke prevention *Population*: Patients with nonvalvular AF prescribed rivaroxaban *Mean age*: 71 years *Female*: 36.3%	*Design*: Nonrandomized controlled trial Xantus ACTS substudy prospective international noninterventional phase 4 study, *Setting*: 308 investigational sites in 21 countries	Patient-reported treatment satisfaction using ACTS implemented at baseline and 3 months after switch	*Satisfaction*: Baseline ACTS burden and benefit scores 50.51 and 10.30, respectively, scores improved after 3 months to 54.5 and 11.4, respectively
Koretsune et al. (2017)	September 2015 to October 2016	*Treatment*: patients switched from warfarin to apixaban *Population*: Patients with nonvalvular AF *Mean age*: 76 years *Female*: 37.9%	*Design*: RCT Prospective short-term multicenter single-arm observational study AGAIN study *Setting*: 149 institutions in Japan	Patient-reported treatment satisfaction using ACTS, implemented before switch and after 12 weeks of treatment with apixaban	*Satisfaction*: No significant changes in ACTS benefit scores (10.5 vs. 10.4) but significant changes in ACTS burden scores vs baseline (55.6 vs. 49.7, $P < 0.0001$)

(*Continued*)

Table 1 Summary of controlled trials and observational studies (*cont.*)

Author-year of publication	*Data collection period*	*Treatment/population*	*Study details*	*PRO assessment*	*Main findings of the study*
Observational studies					
Alegret et al. (2014)	1st February to 30th June 2012	*Treatment*: on VKA or NOAC *Population*: Patients with AF undergoing electrical cardioversion *Mean age*: 62 years *Female*: 19%	*Design*: Prospective study Patients included in the CARDIOVERSE study *Setting*: conducted in 67 hospitals in Spain	Patient-reported HRQoL in patients on oral anticoagulants using Sawicki Questionnaire, assessed at baseline and 6 months	*HRQoL*: No significant differences seen at baseline between the two groups. At baseline general treatment satisfaction score was significantly lower in the NOAC group (better HRQoL). Global score was also lower indicating better HRQoL in NOAC group (10.3 vs. 9.6). No significant differences seen at 6 months between the 2 groups
Carrothers et al. (2014)	May 2010 to December 2011	*Treatment*: Patients prescribed rivaroxaban *Population*: VTE prophylaxis following lower limb arthroplasty *Mean age*: 66 years *Female*: 61%	*Design*: Prospective study *Setting*: conducted in single orthopedic center in Canada	Patient-reported compliance using self-administered questionnaire, administered 14 days postsurgery and 6 weeks after treatment at the follow-up appointment	Compliance: Majority of patients were compliant with rivaroxaban treatment (83%), noncompliance was associated with older age, smaller BMI, and lower preoperative hemoglobin
Castellucci et al. (2015)	September 2012–September 2013	*Treatment*: Patients on oral anticoagulants (VKA, rivaroxaban, dabigatran, and apixaban) *Population*: VTE and AF patients *Mean age*: 63 years *Female*: 42.7%	*Design*: Cross-sectional survey *Setting*: conducted in 1 anticoagulant clinic in Canada	Self-reported anticoagulant adherence using 4-item Morisky score, administered once	*Adherence*: Self-reported adherence using the 4-item Morisky scale was 56.2% on VKA and 57.1% on DOAC. Adherence was similar in both groups
Hanon et al. (2016)	April 2013 to June 2014	*Treatment*: patients previously treated with warfarin and switched to rivaroxaban *Population*: Nonvalvular AF patients *Mean age*: 74.8 years *Female*: 37%	*Design*: Prospective, observational study *Setting*: conducted in French multicenter	Patient-reported treatment satisfaction using ACTS, administered at baseline, 1, 3, and 6 months	*Satisfaction*: At 3 months, statistically significant patient satisfaction with rivaroxaban compared with VKA warfarin. Mean ACTS burden score (46.5 vs. 54.9, $P < 0.001$) and benefit scale (10.4 vs. 10.9, $P < 0.001$) between rivaroxaban and VKA
Marquez-Contreras et al. (2017)	May 2013 to April 2015	*Treatment*: patients on rivaroxaban *Population*: Patients with nonvalvular atrial fibrillation *Mean age*: 75 years *Female*: 50.3%	*Design*: Observational, prospective, multicenter, longitudinal study *Setting*: Conducted in 160 primary and specialty care centers in Spain	Patient-reported quality of life using Sawicki Questionnaire, administered at baseline and at 6 and 12 months	*HRQoL*: Global compliance was 84.1% and 80.3% at 6 and 12 months, respectively. Average QoL rating was 112.85 in noncompliant and 111.80 in the compliant group ($P > 0.05$). After 12 months, 124.67 in noncompliant group and 83.47 in the compliant group ($P < 0.0001$) showing a significantly improved QoL
Keita et al. (2017)	July 2014 to July 2015	*Treatment*: Patients prescribed warfarin or switched to DOAC or initiated on DOAC treatment *Population*: VTE patients *Mean age*: 60.4 years *Female*: 46%	*Design*: Observational descriptive study, *Setting*: Conducted in multicenter in France	Patient-reported adherence, satisfaction, and quality of life using Morisky Medication Adherence Scale, MMAS-8, EQ-5D, perception of anticoagulation questionnaire part 2, administered after 3 months treatment, and 6 months treatment	*HRQoL*: VKA patients reported more negative experience than DOAC group in EQ-5d questionnaire. No significant difference in overall quality of life in favor of DOAC group (71 vs. 65, $P < 0.063$) *Satisfaction*: Satisfaction with PACT-Q2 >90% of patients were satisfied with their VKA or DOAC treatment *Adherence*: Adherence with MMAS-8 7.2 in VKA group vs 7.7 in DOAC group greater adherence in DOAC group, especially after 6 months' treatment

Contreras Muruaga et al. (2017)	September 2014 to March 2015	*Treatment*: *Population*: Patients with nonvalvular atrial fibrillation *Mean age*: 75 years *Female*: 44.2%	*Design*: Observational cross-sectional study *Setting*: 63 neurology departments in Spain	Patient-reported satisfaction, QoL and perceptions of VKA versus DOACs (only QoL included)	*HRQoL:* Mean EQ-5D 3L score was 75.9 Patients taking VKA with longer time in therapeutic range were more satisfied. DOAC = 76.26 and VKA = 75.05—showing no significant difference in HRQoL. HRQoL for all 3 DOACs were comparable
Stephenson et al. (2018)	October 2011 to June 2014	*Treatment*: Patients prescribed warfarin, dabigatran, rivaroxaban, or apixaban *Population*: Patients with nonvalvular AF *Mean age*: 65.6 years *Female*: 39.4%	*Design*: Hybrid US observational study *Setting*: conducted in 14 institutions in the United States	Patient-reported adherence using Morisky Medication Adherence Scale MMAS-8 duke anticoagulation treatment scale, administered at baseline, and at 4, 8, and 12 months	Adherence: Mean MMAS scores were similar among all four groups in the initial and follow-up surveys *Satisfaction*: DASS scored were lower for dabigatran and rivaroxaban cohort indicating greater treatment satisfaction
De Caterina et al. (2018)	2012 to 2013	*Treatment*: On stable VKA or switched to NOAC (rivaroxaban, dabigatran, or apixaban) *Population*: Patients with atrial fibrillation *Mean age*: 72 years *Female*: 37%	*Design*: Prospective study PREFER in AF Registry Substudy *Setting*: Conducted in 7 European countries	Patient-reported quality of life and satisfaction using PACT-Q2 and EQ-5D-5L questionnaires, administered at baseline and at 1 year follow-up	*Satisfaction*: Switched patients more often reported bruising or bleeding, dissatisfaction with treatment, mobility problems, and anxiety/depression traits with VKA that may have influenced the switch to NOAC
Koretsune et al. (2018)	April 2012	*Treatment*: Rivaroxaban in patients previously on warfarin *Population*: Nonvalvular AF patients *Mean age*: 73.6 years *Female*: 35.5%	*Design*: Postmarketing surveillance study of a prospective study *Setting*: Conducted at 124 sites in Japan	Patient-reported treatment satisfaction ACTS and treatment satisfaction questionnaire for Medication Ver II, administered at baseline and at 3 and 6 months	*Satisfaction*: Statistically significant improved TSQM scores in the rivaroxaban group at 3 and 6 compared to baseline in all 4 domains ($P < 0.001$). Significantly ($P < 0.001$) less burden at 3 months (54.6) and month 6 (54.5) vs baseline (51.0), and benefit remained stable in the rivaroxaban group
Larochelle et al. (2018)	February 2013 to December 2014	*Treatment*: Patients newly prescribed an oral anticoagulant (either warfarin or DOAC, apixaban, rivaroxaban, or dabigatran) *Population*: Patient with nonvalvular atrial fibrillation *Mean age*: 71.35 years *Female*: ~60%	*Design*: Prospective, observational study *Setting*: Conducted in hospitals in Canada	Patients expectations and satisfaction with oral anticoagulation treatment using PACT Q1 and PACT Q2 questionnaires, administered before treatment and at 3 and 6 months postdischarge	*Expectations*: No significant differences in treatment expectations, patients prescribed warfarin had a slightly higher expectation of having side effects *Satisfaction*: Convenience scores were similar at 3 months but much higher in DOAC group at 6 months (86.29 vs 90.97, $P < 0.05$). Satisfaction scores were similar between both groups

(*Continued*)

Table 1 Summary of controlled trials and observational studies (*cont.*)

Author-year of publication	*Data collection period*	*Treatment/population*	*Study details*	*PRO assessment*	*Main findings of the study*
Benzimra et al. (2018)	June 2013 to November 2015	*Treatment*: Patients receiving oral anticoagulants VKA/DOAC (dabigatran, rivaroxaban, or apixaban), or switched treatments *Population*: patient with atrial fibrillation *Mean age*: 74.3 years *Female*: 41%	*Design*: Real-life observational descriptive cross-sectional study *Setting*: Conducted in various recruitment sites in France	Quality of life, treatment satisfaction, and adherence using 3 validated questionnaires-Euro-QoL 5 dimensions 3 levels visual analog scale EQ-5D, Perception of anticoagulation treatment Questionnaire PACT-Q2, 8-item Morisky Scale Medication Adherence Scale MMAS-8, administered once over the phone to patients for at least 3 months treatment	*HRQoL*: HRQoL—EQ-5D scores were similar in all groups but higher in the DOAC group Overall QoL on the EQ-5D VAS tended to be better in the DOAC group but this was not statistically significant. *Satisfaction*: Convenience and satisfaction scores were high in all 3 groups but significant difference in favor of the DOAC group ($P < 0.001$) *Adherence*: Adherence scores were high for all 3 groups with no significant difference between the groups
Okumura et al. (2018)	September 2013 and December 2015	*Treatment*: Patients on anticoagulation (VKA/DOAC) *Population*: Patients with nonvalvular atrial fibrillation *Mean age:* 72 years *Female*: 22.6%	*Design*: Substudy of SAKURA AF registry Questionnaire-based prospective study *Setting*: Conducted in 40 institutions in Japan	Patients satisfaction with anticoagulant treatment using ACTS and Treatment Satisfaction questionnaires for medication II, administered once	*Satisfaction*: There were no significant differences in the TSQM II questionnaire between the 2 groups. The ACTS burden scores were significantly higher for the DOAC group than the warfarin group showing greater satisfaction with treatment
Suarez Fernandez et al. (2018)	*ALADIN Study*: September 2014 to March 2015 *ESPARTA Study*: October 2015 to March 2016	*Treatment*: Patients prescribed VKA or DOAC *Population*: Patients with nonvalvular AF *Mean age*: 78.5 years *Female*: 48.95%	*Design*: 2 different cross-sectional studies combined (ALADIN and ESPARTA studies), *Setting*: Conducted at various departments in Spain	Patient satisfaction with anticoagulant treatment using ACTS questionnaire, administered at regular single visit, patients on at least 3 months treatment	*Satisfaction*: Overall satisfaction with oral anticoagulation was high Patients taking DOACs showed a lower perceived burden with anticoagulation therapy (48.8 vs. 53.1, $P < 0.001$) Perceived benefits were higher in DOAC group (11.06 vs. 11.99, $P < 0.001$)
Obamiro et al. (2018)	Not specified	*Treatment*: Prescribed oral anticoagulants *Population*: Patients with atrial fibrillation *Age range*: 18 to >65 years *Female*: 68%	*Design*: Secondary analysis of the Australian oral anticoagulation survey *Setting*: Conducted through online recruitment in Australia	Predictors of adherence and patient-related factors of adherence using Morisky Medication Adherence Scale (MMAS-8), anticoagulation knowledge tool and PACT Q1 and Q2 questionnaires	*Adherence*: No significant difference in adherence seen between patients taking warfarin and DOACs Patients in the high adherence group showed a higher anticoagulation knowledge *Satisfaction*: Satisfaction scores were greater in the medium adherence groups

Another study that used the PACT Q2 tool showed high satisfaction in both anticoagulation groups, VKA and DOAC (Keita et al., 2017). One of the studies reported inconclusive results or dissatisfaction with DOAC therapy; however, these patients had been switched from warfarin, and the questionnaire may correlate to the patients' experiences of warfarin treatment (De Caterina et al., 2018). Three of the studies that utilized the TSQM questionnaire reported greater patient satisfaction with DOAC treatment scores (Hohnloser et al., 2016; Koretsune et al., 2017; Prins et al., 2015). Okumura et al. (2018) reported no difference in satisfaction when utilizing the TQSM score. Stephenson et al. (2018) used the Duke anticoagulation treatment scale, which confirmed patient satisfaction with DOAC treatment. Satisfaction with VKA versus DOAC was also analyzed by Contreras Muruaga et al. (2017); however, the patient population was the same as another study (Suarez Fernandez et al., 2018), and therefore these results were excluded from this review to avoid duplication.

Health-Related Quality of Life (HRQoL)

HRQoL was investigated by six different studies, which utilized either the Euro Qol 5 dimension of the Sawicki questionnaires. All six studies reported that HRQol was similar among patients on VKA and DOACs (Alegret et al., 2014; Benzimra et al., 2018; Contreras Muruaga et al., 2017; Keita et al., 2017; Marquez-Contreras et al., 2017; Monz et al., 2013). Contreras Muruaga et al. (2017) demonstrated that a higher QoL was associated with longer time in therapeutic range and better INR control. Four of the studies described a higher HRQoL score in the DOAC group, but this was not statistically significant (Alegret et al., 2014; Benzimra et al., 2018; Keita et al., 2017; Marquez-Contreras et al., 2017). Keita et al. (2017) showed that this higher QoL score can be attributed to the lack of blood monitoring associated with DOACs. Marquez-Contreras et al. (2017) highlighted that a significantly higher QoL score was confirmed in patients with established compliance after 12 months of treatment.

Patent-Reported Expectations, Compliance, or Adherence

Larochelle et al. (2018) used the perception of anticoagulation treatment questionnaire to determine patient expectation with anticoagulation treatment prior to initiation. The study found that there was no statistically significant difference between the groups; however, there was a greater expectation of adverse effects in the warfarin group.

Patient-reported compliance was explored by Carrothers et al. (2014) using an investigator developed questionnaire and showed that the majority of patients prescribed rivaroxaban were compliant with the treatment.

Patient-reported medication adherence was investigated by five studies using the 8-point Morisky Medication Adherence Scale (MMAS-8) (Benzimra et al., 2018; Keita et al., 2017; Obamiro et al., 2018; Stephenson et al., 2018). Castellucci et al. (2015) used an abridged 4-point version of the MMAS tool. All five studies indicated that adherence was similar among patients treated with VKA and DOACs. Obamiro et al. (2018) highlighted that a higher adherence score was observed in the patient group that exhibited a higher knowledge of anticoagulation treatment.

Patient Acceptance and Preferences

Warfarin and DOACs are equally as effective in the prevention or treatment of VTE and stroke (Sindet-Pedersen et al., 2015). DOACs are associated with less bleeding risk and net benefit when compared to warfarin (López-López et al., 2017). However, the simple medication regime and lack of therapeutic monitoring associated with DOACS are likely to result in more patients and physicians opting and preferring DOAC treatment with proven satisfaction, adherence, and likely HRQoL. Satisfaction has been reported with warfarin treatment that comprises less complicated regimes and monitoring and management methods including self-monitoring, pharmacist inclusion, or single point of testing at home (Carris et al., 2016; Hixson-Wallace et al., 2001; Meyer et al., 2013).

Near patient testing and self-monitoring with warfarin have shown improved satisfaction rates than standard clinic monitoring with warfarin treatment. Studies have shown an improved quality of anticoagulation in patients who self-monitor and self-adjust their doses, which results in an overall reduced incidence of VTE by around 50%, a 33% reduction in major hemorrhage, and a reduction in mortality from all causes (Heneghan et al., 2006).

The World Health Organization has reported that half of the patients prescribed regular medication for chronic illness do not adhere to their prescribed regimes (Brown and Bussell, 2011). Factors that affect adherence are multiple and complicated in nature. Factors of nonadherence can be patient-related (lack of literacy, involvement, or engagement), physician-related (prescribing of complex regimens or ineffective communication), or can be health-care system related (Brown and Bussell, 2011). Barriers to adherence and medication taking behavior are complex and challenging to overcome therefore patient satisfaction to treatment plays a fundamental role in enhancing patient concordance, experience, and overall preference for taking their medications for chronic conditions. Further evidence suggests that enhanced patient knowledge about anticoagulation treatment results in enhanced patient satisfaction therefore pharmacist are best placed experts in medicines to provide thorough counseling to patient through effective communication (Obamiro et al., 2016; Sahm et al., 2011; Wang et al., 2014).

Therefore, health-care professionals play an elemental role in educating and motivating patients to engage with their treatment plan to ensure maximum adherence with medication. Empowering and motivating patients as well as involving them in the decision making process is likely to provide profound benefit to the patient and overall health-care economy due to reduced incidence of complications and costly hospitalizations. A clear link has been established between greater treatment satisfaction resulting in

enhanced adherence to treatment for chronic conditions (Barbosa et al., 2012). Patients reporting greater satisfaction, improved quality of life, and therefore higher adherence to DOACs they are more likely to concord with DOAC treatment, resulting in successful treatment, fewer complication of stroke or VTE, and reduced mortality.

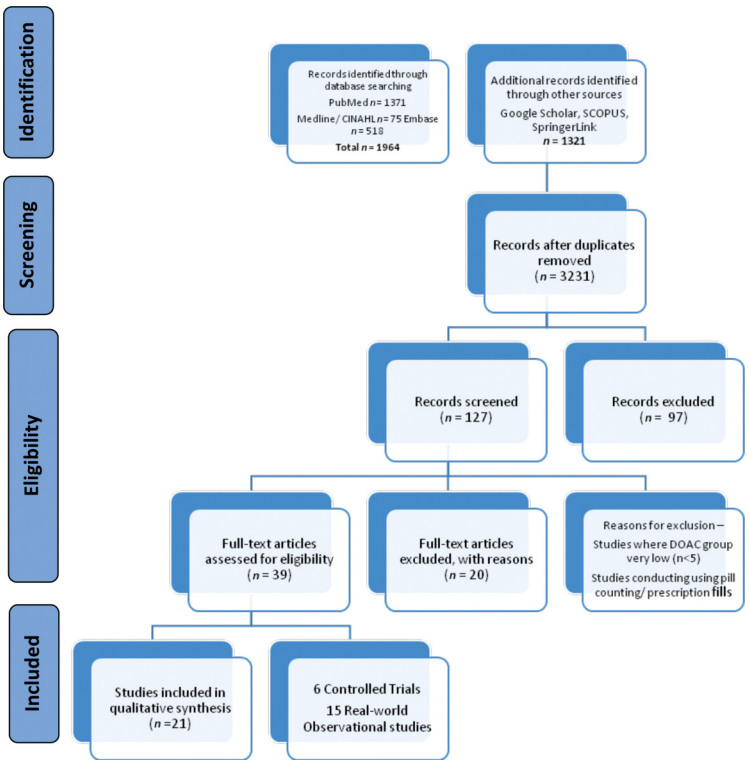
Cost Implications

Warfarin, although an inexpensive drug, requires monitoring and is resource intensive which patients are known to dislike due to the regular clinic appointments and blood tests with up to 13 appointments a year and less than 65% of time spent in therapeutic range with a consequent increase in risk of stroke (Anticoagulation UK, 2018). DOAC on the other hand are costly drugs, and this has been a nature of debate in order to achieve the most cost-effective anticoagulant treatment available on the NHS.

Various studies have demonstrated that treatment with DOAC compared with dose-adjusted or genotype-adjusted warfarin is as economically beneficial in the long term despite higher short-term costs involved (Carles et al., 2015). High-dose edoxaban versus dose-adjusted warfarin in nonvalvular AF showed that cost of treatment with edoxaban was economically beneficial compared to the monitoring requirements associated with warfarin and a similar risk of stroke (Nguyen et al., 2016). However, another study by Carles et al. demonstrated that self-monitoring of warfarin is as effective as dabigatran; however, short-term costs were lower (Carles et al., 2015). Janzic and Kos (2014) investigated treatment with DOACS versus genotype-guided dose adjustment warfarin, which showed that satisfaction with warfarin treatment was dependent on warfarin therapeutic control and method of monitoring (Janzic and Kos, 2015). Cost-effectiveness of DOACs is highly dependent and directly related on the costs of the alternative, VKA, with the associated adequate quality of monitoring and therapeutic control (You, 2014). However, this can be balanced with the enhanced patient preference of no monitoring with DOACs, therefore indicating higher satisfaction, preference, and overall QoL with DOACs.

It is well-known that costs of hospitalization due to VTE or stroke place a profound burden on the NHS (Xu et al., 2018). In the United Kingdom, stroke is one of the leading causes of death and disability costing the NHS £3.6 billion for the first 5 years of treatment after occurrence of the event and accounts for approximately 5% of the NHS budget, which shows the significant long-term investment required for stroke patients in order to provide an adequate quality of life (Saka et al., 2009). Hence, reducing the incidence of avoidable stroke caused by AF through well-managed anticoagulation is a priority for NHS England. NICE estimates that implementing recommendations to initiate DOAC treatment can lower the stroke burden by about 69% and around 10,000 strokes per year (NICE, 2014). Accordingly, designing medication regimes for anticoagulation in AF which patients prefer and are satisfied with is of primary importance to ensure adherence and decrease the incidence of stroke and associated complications. Furthermore, it is estimated approximately 58,000 incidents of VTE occur in the United Kingdom every year costing the NHS almost £340 million showing the clear burden placed on the NHS (NICE, 2015). NICE have shown that using appropriate treatment and prophylaxis with DOACs can result in a 60%–80% reduction in this burden, leading to considerable cost savings as well as a reduction in morbidity and mortality.

Appendix 1: Study Selection Process, PRISMA Flow Chart



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VOLUME 3 – Part B

Clinical Pharmacy Education

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CONTENTS OF ALL VOLUMES

VOLUME 2

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Louise Curley is a pharmacist and Senior Lecturer in Pharmacy practice at the School of Pharmacy. Louise's area of research focuses on the effects of recreational drug use in humans. She began her research as an undergraduate by investigating the subjective and electrophysiological effects of the Party Pill drugs using electroencephalography (EEG) and graduated with a PhD in pharmacy in 2012. Her thesis investigated the effects of the main constituents of "Party Pills" benzylpiperazine (BZP) and trifluromethylphenylpiperazine (TFMPP) on executive functioning and reward using functional magnetic resonance imaging (fMRI). Currently, her focus is developing new fMRI paradigms to investigate different aspects of risk, specifically by comparing populations of dependent versus non-dependent participants. Louise also has an interest in pharmacy practice research including innovative methods of teaching undergraduate students using different technologies and evaluating the effects of these innovations. She has recently been awarded the Butland Teaching Award: Innovation in Teaching.

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Dr. sc Arijana Meštrović, MPharm, FFIP has been working as a community pharmacist and she was responsible for education, services, and competency development in the biggest pharmacy chain in Croatia. She is now independent consultant and educator in Pharma Expert international agency, providing lectures and workshops in CPD programs for pharmacists, pharmacy technicians, medical representatives, implementing new services in pharmacy chains, and teaching Social Pharmacy and Pharmaceutical Care at universities in Croatia and Cyprus as Assistant Professor. Her Doctor's degree is in biomedical sciences—competency development in pharmacy. Arijana serves as member of the International Services Program Advisory Group the Accreditation Council for Pharmacy Education (ACPE, USA), member of PCNE (Pharmaceutical Care Network of Europe), ExCo member of FIP (Pharmaceutical International Federation) Academic section, and WHO international expert consultant in Pharmaceutical care field. She used to serve as Co-Chair of the FIP World Congress Programme Committee, Expert Member of the Board of Pharmacy Practice at FIP. In Croatia, she is a leader in Croatian Pharmaceutical Society and Croatian Chamber of Pharmacist as a Lecturer and Co-author of New services model in community pharmacy practice. Arijana is dedicated to promoting competency-based education in CPD cycle, so her teaching usually addresses all components of competencies—knowledge, experience, and motivation. In collaboration with ACPE International Services, she has founded and implemented SMART Pharmacy CPD model for pharmacists in more than 12 countries all over the world. She was invited speaker and consultant in more than 40 countries.

Kath Ryan

Kath is Professor of Social Pharmacy at the University of Reading, and Visiting Professor at Bournemouth University, United Kingdom. She has 45 years of experience as a pharmacist in the pharmaceutical industry, community practice, and academia. She has held posts at the University of Otago, New Zealand; Bournemouth University, United Kingdom; La Trobe University, Melbourne, Australia; and the University of Reading, United Kingdom. She also has experience in academic nursing and midwifery. Her research interests include extended roles for pharmacists, especially in general practice; application of the behavioral sciences to pharmacy practice; personal experiences of health and illness; and public and patient involvement, engagement and participation in research, and the education of health professionals. She has expertise in quantitative, qualitative, and mixed methods research. She also has an interest in infant feeding,

particularly breastfeeding research, promotion and support, from lay, professional, and academic perspectives. She has been a health advisor to La Leche League International and La Leche League New Zealand. Kath has been on Scientific Committees for the International Social Pharmacy Workshops and the Australasian Pharmaceutical Sciences Association. She has consulted for the National Institutes of Health, USA; Canadian Forces; Health Technology Assessment, NHS UK; and the NZ Ministry of Health.

Kath has over 100 publications in peer-reviewed journals and several book chapters and reports. She produced two multimedia, online resources for Health Talk: women's experiences of breastfeeding in the United Kingdom, and people's experiences of ageing in Australia. She was a Founding Co-Director of Health Talk Australia.

FOREWORD

This first edition of the Encyclopedia of Pharmacy Practice and Clinical Pharmacy is one-of-a-kind and the most comprehensive amalgamation of an inclusive range of topics relevant to the pharmacy profession brought together to ensure safe and effective provision of pharmaceutical care across the world. Professor Zaheer Babar is a Professor in Medicines and Healthcare at the University of Huddersfield and also a global expert in pharmacy practice and pharmaceutical policy. He has united over hundreds of researchers and practitioners from across the world in a collaborative endeavor to provide a unique insight into current best practice and strategies for the future for the profession of pharmacy and its practice.

As patient care becomes more complex with advances in medicines and new developments in practice, including pharmacogenomics and pharmacoeconomics, there is an ever-evolving demand for practice and policy to keep pace. This encyclopedia contains 180 chapters, from all fields of pharmacy practice and clinical pharmacy, providing an in-depth coverage of modern approaches to the practice of pharmacy and highlighting the directions that will enable advancement to continue.

This encyclopedia includes definitions, concepts, theories, and applications of clinical pharmacy and pharmacy practice, providing background knowledge of the area that will provide valuable information for students of pharmacy practice. By providing relevant and topical summaries on a broad range of subjects, this book is also an excellent resource for those seeking information beyond their specific areas of expertise. In addition, the information contained in this book and its communication is of importance to a range of stakeholders, such as physicians and other healthcare professionals, health regulatory authorities, and the pharmaceutical and health industry, in addition to patients and their caregivers.

This encyclopedia also provides an excellent insight into pharmacy practice research and methods, as well as pharmacovigilance, pharmacoeconomics, social and administrative pharmacy, public health pharmacy, pharmaceutical systems research, the future of pharmacy, and new interventional models of pharmaceutical care. In addition, new treatments, algorithms, standard treatment guidelines, and pharmacotherapies regarding diseases and disorders are also covered.

The six key strands around which this encyclopedia is arranged pay testament to the complex and broad nature of the topic and are key topics of interest in pharmacy today and drivers of change for the future, for the benefit of public health across the world.

1. Pharmacy practice
2. Pharmacy practice research methods
3. Clinical pharmacy education, professional standards, and workforce
4. Clinical pharmacy and pharmacotherapy
5. Pharmacoepidemiology and pharmacovigilance
6. Socio-behavioral and administrative pharmacy

Topics range from the education and training of pharmacists, technicians and assistants to counterfeit medicines, pharmaceutical pricing policies, and implementation of change. As pharmacy practice evolves to meet the ever-more-complex health and medicines needs of patients, practitioners need an understanding of the social, political, and economic contexts across the world, noting particular highlights and challenges in developing countries to reach high standards. While it is acknowledged that there are differences between countries in terms of legislation, regulations, and guidelines (as detailed in individual chapters), the vision for the profession must be for a world in which everyone can access safe, effective, and affordable medicines and pharmaceutical care. The chapters include many examples of innovation and best practice in delivering health

services for the future, embracing additional roles beyond the supply of medicines in a robust manner underpinned by scientific and evidenced practice. Quantitative, qualitative, and mixed methods of pharmacy practice research are presented alongside expanded and evolving roles for pharmacists and where technology may take us. More quality research and coordinating efforts will bring a range of theoretical concepts and an evidence-based practice to the forefront of our activities, to focus a global workforce to meet the challenges of this exciting new era for pharmacy practice. This timely volume exemplifies the willingness and ability of the profession to work collaboratively on global issues, representing an unprecedented opportunity to shape the future of pharmacy practice.

With ever-increasing demands on healthcare systems, alongside growing financial pressures, it is essential that we work collaboratively with other pharmacists and the wider public health workforce who have the expertise, opportunity, and capacity to support and inform development.

In this context, this encyclopedia is an important resource with far-reaching impact on global healthcare community, and I hope this will be well liked by students, researchers, and academics.

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March 2019

PREFACE

Encyclopedia of Pharmacy Practice and Clinical Pharmacy

This encyclopedia has 180 chapters in total and it covers all domains of pharmacy practice and clinical pharmacy, including pharmacy practice research, socio-administrative and behavioral pharmacy, pharmacy education, pharmacoepidemiology, and the pharmacotherapy. One main question being asked is the need for this work. *What encyclopedia of pharmacy practice and clinical pharmacy adds to the current body of literature and what it means for global pharmacy community?* The answer to that is, though there were a number of books available on pharmacotherapy, however, current landscape lacks material comprehensively covering aspects, such as pharmacy practice, pharmacy practice research, social pharmacy, pharmacoepidemiology, pharmacy education, and the linking of clinical pharmacy with the health system. This encyclopedia aims to provide a collection of chapters on the above-mentioned areas. It also developed, synthesized knowledge, and provided policy guidance in the areas where there were gaps in the literature. For example, filling the gaps and including chapters on health systems, pharmaceutical policy, evidence and impact in pharmacy practice research, and on pharmacy education.

Here is a brief summary of what is being covered in its three volumes: Volume 1, 2, and 3.

Volume 1 includes chapters on pharmacy practice and pharmacy practice research. The pharmacy practice section starts with the historical evolution of pharmacy practice, medicines management, expanded roles of pharmacists, cognitive pharmacy services, community, and ambulatory pharmacy practice, ethics and regulation, and the new models of pharmaceutical care. There are also chapters on prescribing standards, practices, and competencies, interpersonal communication, evidence-based medicine, models on patient counseling, innovative pharmacy services, technology in pharmacy practice, and the pharmacist's role in substance misuse. The case studies chapters include pharmacy practice in high, low, and middle-income countries; United Kingdom, Western Europe, Australia, New Zealand, China, India, Gulf States, Philippines, and Portugal.

It is vital to understand and discuss the quality of evidence in pharmacy practice research, for example, how the evidence is produced and how it could impact on health outcomes. This is a niche section in the encyclopedia covering chapters on quantitative and qualitative methods in pharmacy practice research, quality of qualitative research, philosophical perspective and theories applied in pharmacy practice research, meta-synthesis, mixed methods research, discrete choice experiments, and the use of network meta-analysis in pharmacy practice. There are also chapters on evolution and definition of practice research, evidence, impact, and gaps in pharmacy practice research in low- and middle- and high-income countries.

Volume 2 covers pharmacovigilance, pharmacoepidemiology, and the socio-behavioral and administrative aspects of pharmacy and medicines use. The knowledge regarding pharmacoepidemiology and pharmacovigilance significantly impacts on medicines safety. The chapters included are on definitions, principles, and application of pharmacoepidemiology, descriptive and drug utilization studies, case-control and cohort studies, methodological challenges in epidemiological studies, data sources, and the issues related to medicines safety and comparative effectiveness research.

The socio-administrative and behavioral pharmacy section covers two broad aspects, namely, social pharmacy and pharmacy administration. Social pharmacy section covers concepts, development, and theories related to social pharmacy, public and patient engagement, sociology for pharmacists, implementation of change in pharmacy practice, and the social perspectives in addiction. There are also chapters on medicines adherence, compliance, and concordance, medication narratives, investigating medicines use among elderly

from a sociological perspective, changing nature of pharmacy as a profession, the impact of culture and religion on medicine use, and the issues related to disease mongering.

The understanding of health system is vital when promoting access and the use of medicines, hence in this context understanding administrative aspects of pharmacy are crucial. This section explores the dynamics between public policy, pharmaceutical policy, pharmacy practice, health systems, and patient-health outcomes. It covers a range of pharmaceutical policy and health system issues including access to biosimilars, access to high-cost medicines, counterfeit medicines, factors influencing pharmaceutical policy implementation, funding mechanisms for community pharmacy services, generic drug policies, national medicine policies, essential medicines list, pharmaceutical company sponsored medication assistance programs, and the pharmaceutical pricing policies.

Volume 3 covers clinical pharmacy education and pharmacotherapy. Pharmacy education training and the workforce have a great impact on global health. There are 25 chapters or more on pharmacists' training, and certification exploring the relationship between education, regulation, and practice. This is one of the largest collection of chapters covering pharmacy education and regulation at the global level. This includes chapters on pharmacist workforce, competency standards for clinical pharmacists, quality assurance in the pharmacy education, developing and evaluating clinical skills, continuing professional development, experiential education, inter-professional learning, leadership in pharmacy education, and the needs-based education. There are also case studies chapters on clinical pharmacy professional standards in the United States of America, Canada, the European Union, and in the low- and middle-income countries.

The pharmacotherapy section covers over 70 chapters discussing standard treatment guidelines, pharmacist's role in the central nervous system, infectious diseases, cardiovascular disorders, skin and endocrine disorders, musculoskeletal disorders, neurology, gastrointestinal disorders, and the respiratory disorders. The other key chapters include clinical pharmacy concepts, history, and development, clinical governance principles, pharmacokinetics, therapeutic guidelines, end of life care, palliative care, long-term care, fundamentals of pharmaceutical care planning, health outcomes and quality of life, the role of the pharmacist in the military and prisons, and the pharmacotherapy and deprescribing.

It has been a challenging task to complete this encyclopedia within a short span of 2 years. However, I am very thankful to the support of my section editors, reviewers, and hundreds of authors from all over of the world to come together and to contribute to this exciting project.

I hope you will like this effort and it will serve its purpose.

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Encyclopedia of Pharmacy Practice and Clinical Pharmacy

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Becoming A Pharmacist: Education and Training

A Stepwise Approach to Competency-Based Pharmacy Education

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Introduction

The pharmacy profession has been adapting to an ever-changing external environment (Bonanno et al., 2012). From creating and preparing medicines to counseling on their proper usage, to optimizing health outcomes, the profession's identity has been in a state of flux, and so has been the underlying education. Today, pharmacists are increasingly expected to provide direct patient care (cognitive services) aimed at optimizing patient's usage of medicines, to improve safety and efficacy (Saseen et al., 2017). We are seeing an expansion of the scope of practice for pharmacists in several countries, as the health-care system is increasingly under economical pressure, physicians are overwhelmed with increasing and aging populations, and medication therapy increases in complexity. It is important for the initial pharmacy education to keep abreast of the population needs and the professional expectations in order to provide a relevant workforce (Anderson et al., 2012; Bader et al., 2017a). The pace at which each country has embraced and implemented these changes, both at the professional and educational levels, probably explains the rather heterogeneous landscape of pharmacy education today. Recently, the International Pharmaceutical Federation (FIP) proposed educational statements (The Nanjing statements) in an effort to try to provide a reasonably homogenous "template" for pharmacy educators of different countries to align better with each other (Bader et al., 2017a). Anyone contemplating a revision of their curriculum should review and aim to satisfy these statements.

To add to the complexity related to the timing of professional and curricular changes worldwide, the current transition, from a predominantly scientific-based pharmacy education to the one that includes more clinical sciences and experience is conducted with a plethora of denominations and length of studies (see **Table 1**). Since 2000, North America, with the United States as a lead, has embraced the PharmD (doctor of pharmacy) avenue, which requires 6–7 years (2–3 prepharmacy + 4 pharmacy) of education. Other countries are following in this path, including examples in Asia, Middle East, and Africa. In the European Union in general, the directives require at least 5 years of training, including at least 6 months of residency in a pharmacy setting. This can be done as a single program (leading to master) or as two separate programs of Bachelor and Master. The qualification's expectations are similar, irrespectively of the name or structure, to allow pharmacists mobility within the Union (Atkinson and Robinson, 2011). The United Kingdom has chosen a 4-year MPharm (Master of Pharmacy) path, with a 1-year residency performed afterward in order to be eligible for practice. Other countries, like Australia, continue to offer Bachelor of Pharmacy degrees to access the profession (**Table 1**). Some countries even graduate pharmacists with a degree in pharmaceutical sciences. For the unexperienced outsider, the landscape is very confusing, especially when professional graduate programs are added to the mix.

Although program names differ, the name is not what defines the preparation of future pharmacists, it is what the curriculum contains. Indeed, Baccalaureates in pharmacy (BPharm) can incorporate as much clinical pharmacy education as PharmD

Table 1 Examples of pharmacy curriculum length and structure across the world

		Structure of requirement for pharmacy practice			
University	*Country*	*Prepharmacy*	*Duration of the pharmacy program*	*Posteducation practice training*	*Notes*
Monash University	Australia	3 years Requires a bachelor's degree in sciences Or none	2 years BPharm +Master degree Or 4 years BPharm +Master degree	1 year internship	Pharmacy education normally takes 5 years in Australia (including the internship)
National University of Singapore (NUS)	Singapore	None Either GCE-A level, or equivalent examinations	4 years Bachelor of Science (Pharmacy) degree. Includes 6 months preemployment competency training	12 months preregistration training	Registered pharmacists may also study a full time 2-year PharmD program for advanced clinical care
University of California San Francisco (UCSF)[3]	United States	3–4 years Requires a bachelor's degree in sciences	3 years (year-round) PharmD program	None	Pharmacy education normally takes 6 years (2 + 4) in North America
University of Nottingham	United Kingdom	None Requires A-level courses for admission	4 years Master of pharmacy (MPharm) program	1 year pre-registration training, followed by the GPhC[a] exam to become a qualified pharmacist.	The University also offers an MPharm (with Integrated preregistration), which is 5-years and at the end the graduate is ready to be a UK pharmacist
Utrecht University	Netherlands	None Requires a diploma or an A- level for admission	3 years Bachelor of science followed by 3 years Master's degree (MSc) in Pharmacy		The EAFP[b] states that 5 years is the minimum for pharmacy education in Europe

Universities were selected based on their region and their ranking in the QS pharmacy and pharmacology classification and are presented in alphabetical order.
[a]GPhC, General Pharmaceutical Council.
[b]EAFP, European Association of Faculties of Pharmacy declaration in 2008.

programs, as is the case in Australia. As often required by accreditation bodies, most curricula will contain courses in biomedical sciences (anatomy, biochemistry, microbiology, physiology, pathophysiology, and molecular biology), pharmaceutical sciences (medicinal chemistry, pharmaceutics, biopharmacy, pharmacokinetics, pharmacodynamics, toxicology, biotechnology, and pharmacogenomics), social and administrative sciences (biostatistics, pharmaco-epidemiology, pharmaco-economy, ethical and professional standards, health systems, practice management, laws and regulations, and cultural diversity), and clinical sciences (pharmacotherapeutics, medication therapy management, clinical pharmacokinetics, health promotion and disease prevention, public health, medication and patient safety, self-care, and primary care) (Anonymous, 2014). The proportion of each discipline and their integration within a curriculum varies widely and there is no easy way of summarizing the situation (Atkinson and Rombaut, 2011), except to say that obtaining the right balance between the scientific and clinical influences is a current preoccupation for most schools of pharmacy (Fielding and Regehr, 2017).

Generally, clinically oriented programs will include more time for trainees to gain experience by engaging into practice sites supervised by preceptors. In the PharmD model, the experiential training component is integrated within the curriculum to offer a transition between theory, laboratory practice, and real-life experience. This learning continuum has required a very strong collaboration between the faculties and the professional environment, to allow all students to have a very significant amount of hands-on training. In a 4-year PharmD (accessible after 2 preparatory years), the early pharmacy practice experience (EPPE) and advanced pharmacy practice experience (APPE) normally account for more than a full academic year (Anonymous, 2015). In other programs, such as the MPharm of the United Kingdom, graduates are generally required to complete 1 year of prelicensure experience before they can obtain their independent license to practice the profession. Thus, although some programs may appear longer to complete (such as a 2 + 4 PharmD), the mandatory year of practice experience requested by registrars is actually included within the university coursework.

Another aspect that cannot be determined from the name of the degree is the method by which education is provided. Like the pharmacy profession, education as a whole has also undergone major transformations. The past 100 years has witnessed three generations of higher educational reforms, from a scientific-based focus, through a problem-based approach, to professional competency development (Frenk et al., 2010). As regulatory and accrediting authorities move toward competency frameworks to define the expectations of a graduating pharmacist, the way by which students are taught has to follow suit in order for them to be competent, and not just knowledgeable (Anonymous, 2014, 2015; Saseen et al., 2017). With the support of information technologies, offering a massive amount of information available in a split second, the time is probably ripe to move toward learning to use information rather than memorizing it (Summers, 2012).

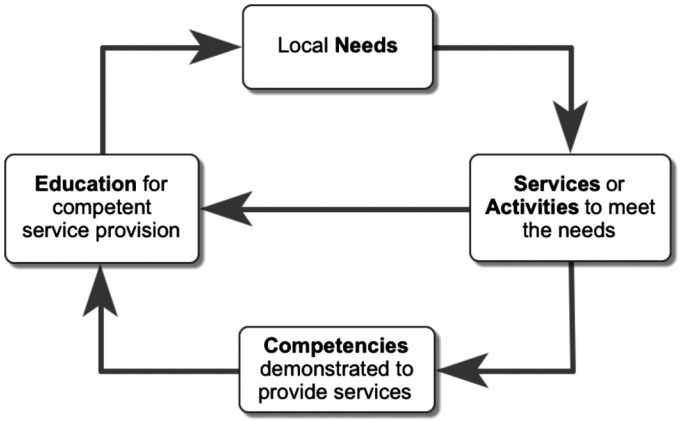

Figure 1 Needs-based professional educational model. *Source: Adapted from Brock, T., Brown, A.N., Rennie, T., Rouse, M.J., 2012. Global pharmacy education: are we nearly there yet? Int. Pharm. J. 28(1) (2012) 4–11. An arrow from Services to Education was added from the original model (see text for details).*

Needs-Based Education

In an ideal setting, there should be a very strong alignment between a professional practice and the underlying education so that graduates are optimally prepared, accelerating their integration to serve the population efficiently (Hawkins et al., 2015; Saseen et al., 2017). According to the recent literature, it seems that the gap between education and practice is unfortunately widening rather than narrowing (Frenk et al., 2010). As health-care professionals are expected to competently address the increasingly complex and changeable needs of the population, education has not followed and seems to be rooted in a pattern of discipline-based structure that allows for very little flexibility and adaptation (Noble et al., 2011). According to the Lancet commission, current professional education has not kept pace with emerging challenges and has created a gap between the graduate competencies and population needs; in addition, it has failed to nurture team working skills, has fostered narrow technical focus, and has contributed to the fragmentation of care (Frenk et al., 2010). Thus, education continues to evolve; however, its evolution trajectory and speed is not in sync with the practice evolution. Considering the years required for a freshman to graduate, universities should feel an urgent motivation to reform their education in order to improve health-care outcomes in the not too distant future. Currently, discipline-based curricula structure drives the learning objectives, rather than learning objectives driving the curriculum (Frenk et al., 2010). This translates into knowledgeable professionals who lack in their ability to solve problems in the real world (Hawkins et al., 2015). As we reflect on what should be the educational framework to prepare the future generations of pharmacists, being accountable to the workforce needs should be a fundamental concern and objective (Bader et al., 2017a; Brock et al., 2012).

Needs-based education brings the local necessities at the forefront of curriculum transformation, instead of relying on a universal curriculum that may prove to be maladapted in countries with different challenges (including educational capacity) and realities (Anderson et al., 2012). In other words, trying to standardize pharmacy education should aim at the outcomes (what is a competent pharmacist in a given community) rather than on the nature of the courses that should compose a pharmacy curriculum. This is further emphasized by the recent International Pharmaceutical Federation (FIP) Nanjing statements that gives direction, but does not determine how to reach the goals (Bader et al., 2017a). The need-based education process first defines the local needs, then the professional activities or services needed to address those needs, followed by the competency required to offer the services and, finally, by the education to prepare a competent workforce (**Fig. 1**). According to Anderson et al., defining a common set of competencies (competency framework) seems easier than anticipated, even in countries with different needs (Anderson et al., 2012). To support an outcomes-based education transformation, the FIP has proposed a global framework to guide schools of pharmacy to develop their education with this new mind-set of preparing competent pharmacists (Bruno, 2012). What appears more challenging, however, is translating such list of competencies, organized in a comprehensive framework, into an efficient educational model that will prepare graduates to their professional challenges (Hawkins et al., 2015; Koster et al., 2017).

Competency-based Education

Competency-based education does not have a uniform definition or meaning (Frank et al., 2010). The Competency-Based Education Network has a proposed definition on their website (C-BEN, 2015), while Frank et al. (2010) have proposed the following: *"Competency-based education (CBE) is an approach to preparing physicians* for practice that is fundamentally oriented to*

* The word "physicians" could be substituted by "professionals" or "pharmacists"

graduate outcome abilities and organized around competencies derived from an analysis of societal and patient needs. It de-emphasizes time-based training and promises greater accountability, flexibility, and learner-centeredness."

One of the barriers of progressing toward competency-based education (CBE) is that it involves moving away from traditional discipline-based courses, to knowledge integration and competency development in practice-relevant contexts (Hawkins et al., 2015). It is a huge shift that requires courage and trust that the outcomes will be better for the students and, ultimately, for the patients. This is often the question that allows a certain opening to new ideas, as discussion with stakeholders often confirms that current curricula have important deficiencies, as outlined by the Lancet Commission (Frenk et al., 2010). To be successful, such a bold shift in the educational vision for the profession requires leadership, expertise, and skilled change management.

In addition to affecting the teaching culture from disciplinary to integrated and patient-focused, CBE will also affect the teaching and learning methods used. Indeed, one does not develop competencies the same way one acquires knowledge. The science clearly demonstrates that students fare much better when they can actively engage in learning, rather than passively receiving what the instructor has prepared for them (Dean Jr and Kuhn, 2007; Kober, 2014; Waldrop, 2015). In his article about the science of teaching science, Waldrop concludes that knowing the consistent message of the literature regarding the benefits of active learning, lecturing should be unethical, just like it is unethical to put a patient on an old medicine when evidence overwhelmingly confirms that the new medicine is safer and more effective to obtain the therapeutic goals (Waldrop, 2015).

Finally, assessments have to adapt to measure the degree or level of competence that the learners have achieved after a certain time during their education. Competencies take time to mature, and expectations at the beginning of the curriculum cannot be the same as the expectations at the end. These "levels and ranges" are therefore necessary to make sure that students are progressing appropriately, and that remediation can be started when students show signs of deficiency in core competencies early in the program. Defining expectations at different time points within the curriculum is another challenge brought about by CBE. This is over and above the development of new assessment methods that must be devised and mastered to assess student's proficiency. These may include Objective Structured Clinical Examinations (OSCE), mini-Clinical Evaluation Exercise (mini-CEX), or other methods that evaluate students in action (observation), a sharp departure from relying solely on multiple-choice and short-answer questions.

CBE seems to be the way to go forward, but it comes with an array of challenges and educational practice changes that meet strong resistance and impede a more enthusiastic shift toward what appears as the holy grail (Hawkins et al., 2015; Koster et al., 2017). However, it brings the opportunity of having a more flexible educational approach that can be tailored to the local expansion of the scope of pharmacy practice within a specific country or region (Brock et al., 2012). Considering the shifts that are currently happening in pharmacy practice worldwide, there is a need for more open, flexible, and adaptable learning architectures that can evolve together with the local development of pharmaceutical services.

Competence and Competency

Competence can be defined by having a complete repertoire of competencies (Brown et al., 2012). There are several definitions of a competency, and Nash et al. published a whole list of possibilities in their review of the use of competency standards in pharmacy education (Nash et al., 2015). We propose a combination of previous definitions to define competency as: knowledge, skills, behaviors, and attitudes that an individual accumulates, develops and acquires through education, training and work experience that can be mobilized to perform job-relevant tasks effectively within a given professional context. Thus, competency defines effective action in a certain context. Competencies describe what graduates should be able to do in practice rather than simply what they should know or the skills being able to demonstrate during training (Thistlethwaite et al., 2014). Accordingly, a competency framework, or the list of competencies expected from a graduate, represents the abilities of the professional at the outcome of the program (ten Cate, 2013). Clearly, then, competency implies a sense of professional judgment that goes beyond theory. This resonates with a suggestion to put students regularly in gray zones, similarly to their future professional career, as patient care is not black or white (Noble et al., 2011). In a knowledge-based curriculum, we stack knowledge and skills separately for each discipline and we expect students, as they progress, to combine them to solve problems, using their judgment.

Unlike knowledge and skills, competencies take time to develop, and the pace of acquisition varies between students. When a knowledge or skill element comes again in a curriculum, students complain of redundancy and it can be corrected by tweaking the curriculum, often to make room for even more knowledge. But unlike knowledge and skills, competency development needs several iterations and most of the time, different levels of expectations over time. Redundancy is crucial, but context can vary. This gradual appropriation of a competency has a profound impact on a CBE program, as time must be devoted to use the knowledge and skills in meaningful and context-relevant learning activities. Some may object by saying that there are so many things a pharmacy student needs to know that there is no time for revisiting competencies on multiple occasions. However, one should consider that if, as research shows, students retain only 10%–20% of what is being taught after the exam period by conventional methods, cramming even more knowledge will just be detrimental to the major concepts that are professionally relevant (Waldrop, 2015). By using active learning methods, and time and space to practice becoming competent using these major concepts, retention will be much better, and learning will be improved (Dean Jr and Kuhn, 2007; Waldrop, 2015). Pharmacy

educators must move away from the compulsion of covering everything to embrace the expansion of the key concepts underpinning the professional activities.

The knowledge acquired during the pharmacy program rapidly becomes obsolete, due to the advancement of science, medicines, and practice. In that context, active learning and competency development provide a foundation for life-long learning, in addition to helping students develop their autonomy, judgment, confidence, and leadership. Guiding the students to find the right sources of information and making sound interpretation is much more important than providing a snapshot of today's wealth of knowledge, especially in this day and age where information can be retrieved quickly (Summers, 2012). The debate between covering "all" knowledge and allowing students to construct their own knowledge as they become competent has to occur before CBE can be considered.

Numerous universities are already developing CBE programs to bridge the gap between education and practice (Hawkins et al., 2015; McIntyre-Hite, 2016). Few competency-based pharmacy education (CBPE) initiatives have been reported so far, if one looks at published accounts (Nash et al., 2015). The jury is still out as to how one can translate a competency framework into an effective curriculum that will graduate competent health-care providers (Lurie and Garrett, 2017). One approach for CBPE development and implementation has been recently proposed by Koster et al. (2017). In this chapter, it is our intention to propose an alternative (although often similar) stepwise approach for developing a student-centered CBPE curriculum in the context of a patient-centered care role for pharmacists, relying on a solid scientific foundation.

A Model for Competency-Based Pharmacy Education

Guiding Principles

The creation or the major overhaul of an existing curriculum into an entity that is radically different from past experiences is a major endeavor. It requires the collaboration of all faculty members and stakeholders. Because the efforts are significant, the planning process should not be underestimated or rushed. Initial efforts should be aimed at defining internal and external needs and expectations to devise a visionary curriculum that will be relevant to the population it serves for years to come. Before embarking on external consultation, it is worthwhile to have an internal reflection on the outcomes of the curriculum in its new form. **Table 2** presents the results of such an exercise done at the Faculty of Pharmacy of Kuwait University. A core group of academic staff, representing all departments, were free to express their wishes and expectations in the form of keywords or short sentences. At the end, the keywords were integrated into vision statements. From what was expressed, it became clear that knowledge and skills were not sufficient to fulfill the vision. To be coherent with the outcomes, the new curriculum had to allow the development of a series of competencies. The same group then reflected upon the impact to be anticipated from this new vision on four domains: (1) the global curriculum structure (macro level), (2) the course material and delivery methods (micro level), (3) the assessment and grading modalities, and (4) the University and Faculty rules and regulations for admission and progression. These guiding principles were defined early in the process in order to steer the development of the curriculum towards the vision. They had to be explicit, widely accepted and respected to maintain the desired vision.

As an example of guiding principles for the global curriculum structure, consensus was reached on students developing competencies, working with a locally relevant competency framework, putting experiential learning (labs, projects, and practice experience) as a major component, integrating disciplines toward problem resolution, implementing interprofessional education, and engaging in continuous curriculum assessment and improvements. For the course creation and delivery domain, the guidelines propose that the learning material be context relevant for pharmacy practice, using active learning approaches and to prioritize disease states that are more prevalent in Kuwait. The methods chosen encourage peer teaching, regular feedback, and critical thinking (working in gray zones). In addition, this domain outlines the student support, individualized remediation, as well as the use of technology.

The third domain, concerned with the assessment strategy, dictates that the global assessment framework focuses on higher dimensions of learning (deep learning) and measures the progression towards the expected level of competency. The methods of assessment are to be coherent with the learning objects and incorporate some level of feedback. Formative assessment is mandatory before each summative examination. The fourth and last domain of the guiding principles deals with rules and regulations, such as admissions, number of students, progression criteria for the second year, and conditions for success. They respect the general policies of Kuwait University.

Table 2 Guiding vision statements for the reform of the existing pharmacy curriculum in Kuwait

Each graduate is expected to be a:
1. Patient-centered, collaborative health-care provider
2. Self-guided, lifelong learner using evidence to support decisions and practice
3. Accountable practitioner with reputable professionalism and ethical behavior
4. Community-oriented professional conceiving value-added services and public health promotion activities
5. Engaged professional leader and advocate with significant mentoring and communication skills

From these guiding principles, it was concluded that at least four frameworks had to be created to allow the development of a curriculum aligned with the vision. The main steering committee focused on the development of the competency framework and three subcommittees were formed to work on an active learning framework, an assessment framework (later combined in an integrated active learning and assessment framework), and an experiential training framework defining capacity building and preceptor training. Using several subcommittees was also part of the change management strategy, as individuals involved in the change process are less likely to resist it (Kotter, 1996).

Needs Assessment

Several competency frameworks are available and can be used as a starting point for curriculum development (Koster et al., 2017). Ideally, however, a thorough local needs assessment should be conducted in order to set the stage for competency identification and professional requirements (Anderson et al., 2012). The external stakeholder consultation is also a recommended tool to inform and involve the pharmaceutical community to the curriculum reform. The FIP Pharmacy Education Taskforce, together with the WHO, published a needs-based education development model that can be used as a template for linking population needs to education development (**Fig. 1**) (Anderson et al., 2012; Bruno, 2012). Needs-based education requires the identification of local needs as a basis for the development of a relevant curriculum (Anderson et al., 2012). Then, services to fulfill those needs are identified and competencies in order for pharmacists to provide those services are delineated. In this way, the curriculum becomes relevant to the needs of the local population.

Knowledge of the external expectations requires the input from a wide range of stakeholders, and the information has to be gathered in a structured or semistructured focus group setting, with guiding questions, in order to prevent the discussion from straying off into undesired tangents. A stakeholder map, where all relevant stakeholders are identified, is a good exercise to perform at this stage. It is important to be aware of the impact of hierarchy within the study population, which might affect the quality of data generated. Therefore, it is advisable to have homogenous focus groups, where participants with similar backgrounds are grouped together, as this facilitates the discussion and is more productive in terms of depth of discussion and participation of group members (Krueger, 1994).

In order to make sense of these focus groups, two simple questions were asked. The first one dealt with the current population needs (or pharmacy services) that are currently met by pharmacists in Kuwait. The second asked what needs were currently not met by pharmacists, according to the experience of the stakeholders. For each need identified (met or not met), expectations for pharmaceutical services were discussed with a strong emphasis on the competencies that pharmacists should hold to deliver each service in a professional and effective manner. During such diverse focus groups interviews, it is vital to define certain terms in the introduction to ensure that discussions are consistent. In our experience, the following terms were defined: competencies, pharmaceutical care, and medication therapy management. At the end of the session, stakeholders were also asked to discuss barriers that they felt could limit the development of certain services within the country. This was aimed at guiding our work to bridge the gap between the curriculum and the regulatory framework of the practice.

During each focus group, notes were taken with an emphasis on collecting and clarifying needs, services, competencies, and barriers. This aided in organizing the content by combining entries that had a similar meaning. Population needs, whether met or unmet, were quantified in terms of the number of times they were discussed within a focus group. This was then linked with the services proposed by the participants to meet those needs, as well as the competencies needed to fulfill those services. This formed the basis of the competency framework (see below). We identified five population needs that were further defined in terms of fifteen currently offered or expected pharmaceutical services. **Fig. 2** presents the relationships between needs and services.

Competency Framework

As alluded to previously, several pharmacy-related competency frameworks have been developed and can guide the development of a local set of competencies (Nash et al., 2015). Our needs assessment yielded a series of competencies supporting the provision of pharmaceutical services. The most frequent competency domains mentioned for any service (total occurrences from 8 focus groups) were communication (33 times), patient-centered care (18), life-long learning (16), Intra- and interprofessional collaboration (12), professionalism (12), and information access and critical appraisal (11). Interestingly, there was a very strong alignment between what the steering committee had in mind in terms of graduates (educational outcomes, **Table 2**) and the competencies that were identified by our external stakeholders.

The global occurrence for the competencies, and the service they were part of, became a guide to develop our competency framework. Starting from this list of competencies, a series of competency frameworks and national pharmacy standards of practice were reviewed to identify the elements of competencies that would define, at a more comprehensive level, the expected outcomes. The following five competency documents were considered very much aligned with our initial results and were used for that purpose: (1) the core competency framework for pharmacists by the Pharmaceutical Society of Ireland (Anonymous, 2013), (2) the CAPE pharmacy education outcomes (Medina et al., 2013), (3) the FIP global competency framework (Bruno, 2012), (4) the Educational outcomes or the Association of Faculties of Pharmacy of Canada (Brown et al., 2010), and (5) the professional competencies for Canadian pharmacists at entry to practice by the National Association of Pharmacy Regulatory Authorities (NAPRA) (Anonymous, 2013). Of these five documents, the competency framework developed by NAPRA had the greatest coherence with our competencies and pharmacists' activities identified and was used as a reference tool to delineate our

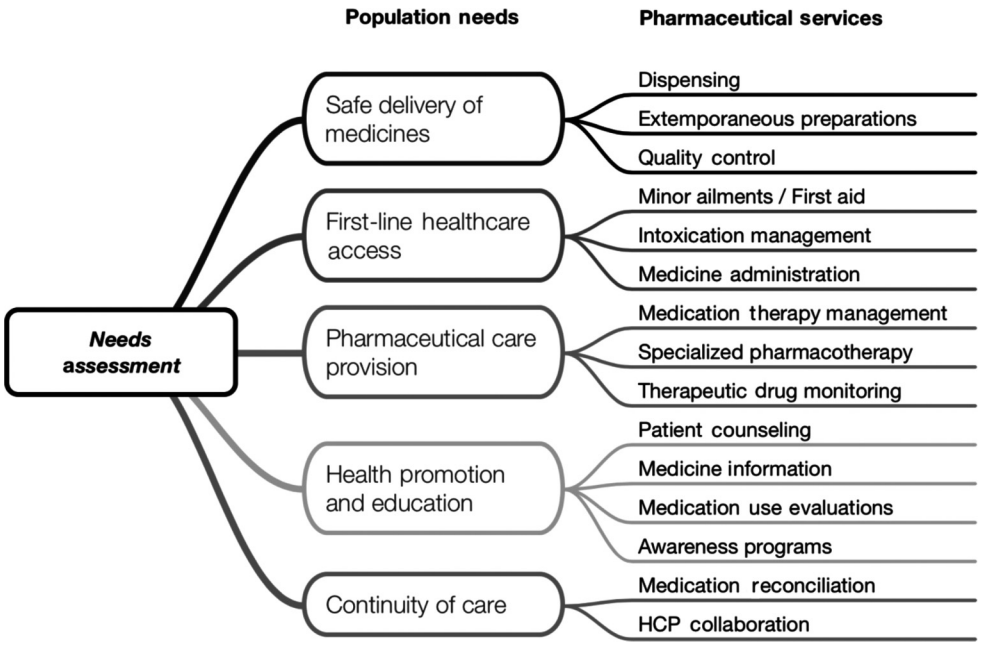

Figure 2 Results of the needs assessment in terms of population needs (*boxes*) and pharmaceutical services expected to be provided, by pharmacists, to fulfill the population needs. *HCP*, Health-care professionals.

competency framework, including definitions of competency domains. Other frameworks were then used to refine and finalize our competency element statements.

We ended up with eight transversal (or generic) competencies and three professional competencies. However, instead of using a linear model to describe and detail them, we used a matrix that crosses the professional competencies with the transversal competencies to define the elements of competencies (Table 3). Indeed, after reviewing several competency frameworks, we realized that there were several redundancies by using a linear model. As an example, communication was detailed in terms of elements of competency, as it constitutes a major transversal competency, but communication skills were also part of delivering direct patient care, managing the operations and providing educational activities, which are professional competencies. Thus, communication was expected to be developed both as a stand-alone competency and as part of professional competencies related to practice. The matrix model went through several rounds of revisions to reduce redundancies to a minimum and making each

Table 3 Matrix competency framework for Kuwait

	Provide pharmaceutical care	*Engage in health promotion and education*	*Manage pharmacy practice*
Communicate	• Develop and maintain a professional relationship with the patient by using effective communication and having a caring attitude • Listen actively to and assess the patient's health, needs and goals for their medication therapy • Obtain all needed information using appropriate interview techniques with patients, caregivers and HCP +3 others	6	2
Access and critically appraise information	3	2	1
Solve problems and make decisions	7	3	3
Collaborate	3	1	3
Engage in lifelong learning	2	2	1
Act professionally	3	2	5
Manage	4	2	8
Are proactive	2	3	3

Three professional competencies intersect with eight transversal competencies. The first intersecting cell is partially detailed in terms of competency elements. The number in the other cells represents the number of competency elements.

HCP, Health-care professional; *MTP*, Medication therapy plan.

element as specific as possible. It also allows the assessment of transversal competency proficiency in the context of professional competence (and vice versa).

Pharmaceutical Services

The need-based education model suggests that the competency framework underpinning expected professional services is translated in an education curriculum to complete the circle to fulfill the population needs (**Fig. 1**). According to Thistlethwaite, "competency frameworks should promote the alignment of competencies with appropriate activities and subsequent assessment to verify that learners have attained the competencies (Thistlethwaite et al., 2014). For educators, this is a significant challenge, since competency-based education is not widespread and there are few examples (Koster et al., 2017). Relying on an experienced consultant to guide curriculum development may be a wise thing to do. The main challenge is to transform a list of competency elements into meaningful learning activities that will allow time and space for knowledge acquisition, skills practice, and competency development. As Koster et al. described it, competence is contextual, developmental, and multidimensional, meaning that it has a significant impact on curriculum design (Koster et al., 2017).

How can competency development be integrated within knowledge and skills? What is the best approach to allow students to become competent? How can all the competency elements be visited and revisited until mastered? One could rely on the pharmaceutical services identified during the needs assessment (**Fig. 2**). The provision of each service (or professional activity) requires a unique subset of competency elements (a "competency profile") that form the framework. An example of the competency profile for medication reconciliation is provided (**Table 4**). Students can then practice and gradually master each competency element by practicing the delivery of a complete service. In other words, services contextualize the learning activities so that the students can focus on achieving specific results while developing their competencies.

This approach resonates with what is a current trend in work-based assessment. Indeed, in the medical education field, the apparent disconnect between competency frameworks, defining the abilities of the graduates, and professional activities, defining what a professional does, has been the source of an interesting development (Mulder et al., 2010). To reconcile the two in the context of work-based assessment, ten Cate et al. have conceived that professional activities that trainees can be trusted to perform (entrustable professional activities or EPA) actually uses a subset of the competency framework (ten Cate, 2013). In other words, performing a single professional activity will require students to mobilize only a part of the global list of competency elements (what we defined as a competency profile). Each professional activity will have its own subset of competency elements, and by combining different professional activities, all competency elements should be covered. Some competency elements may be needed only by one professional activity, while others may be common to several ones. If a competency element is not covered by any service, maybe it is not central to the professional development of the students, or may be it is something that can be acquired after graduation, in a continuing professional development strategy.

By using the EPA model to guide the curriculum, graduates would be able to perform all the expected professional activities and services in a competent manner. This idea is also set forward by Koster et al. in their model of CBPE (Koster et al., 2017). Focusing on services rather than on disciplines within a profession allows the desired integration of knowledge, skills, and competence. The number and definition of professional services become the backbone of the curriculum, rather than disciplinary knowledge. This is where the local influence will be apparent, as some countries may need more emphasis on developing a medicine distribution service, while others may focus on drug manufacturing and quality assurance services. This new paradigm allows for a wide range of professional activities to be included in the curriculum and also for new or emerging ones to be added at a later stage.

In our experience, it is worthwhile to define each service and try to limit the overlap between them. For instance, we separated medication therapy management (MTM) from patient counseling, as combining the two was redundant, increased the number of

Table 4 Competency profile for the medication reconciliation professional service

Professional competency domain	*Transversal competency domain*	*Competency element description*
Provide pharmaceutical care	Communicate	Develop and maintain a professional relationship with the patient by using effective communication and having a caring attitude
Provide pharmaceutical care	Communicate	Obtain all needed information using appropriate interview techniques with patients, caregivers, and HCP
Provide pharmaceutical care	Access and critically appraise information	Assess the relevance, accuracy and completeness of the information in relation to patient-needs, and interpret this information
Provide pharmaceutical care	Collaborate	Engage in and facilitate continuity of care within the pharmacy, with other pharmacists, and with other HCPs
Provide pharmaceutical care	Manage	Maintain complete and accurate patient records to document actions, interventions, and results

This service is defined as: "Performing the necessary actions to verify the completeness and accuracy of a patient's current medicines at critical points (admission, transfer, and patient discharge)."

competency elements, and made the assessment more challenging. Dispensing also had to be defined as a separate entity from MTM. Each professional activity or service has to be performed by students in learning activities. Having a very lengthy competency profile will make the scenarios that have to be developed for students to perform, and instructors to assess, more complex. In our experience, a maximum of 12–15 competency elements should compose the profile of a single professional activity. At the other end of the spectrum, less than 5 competency elements within a profile will make it difficult to discriminate the performance of the students.

Each professional service should be introduced and revisited on several occasions during the curriculum in order to allow students to reach the level of performance expected at the end of the program. When students perform a service for the first time, the level of mastery of each competency element within the profile cannot be expected to be ideal. However, expectations have to be set to a challenging but reasonable level for students to feel confident and build on previous experiences to progress in the mastery of their competencies. By changing the setting or context, students can revisit a professional service, but with some added knowledge that makes the redundancy worthwhile. For example, students could learn about and practice community pharmacy dispensing in a first course, but focus on inpatient dispensing on the second iteration of the service.

Essential Knowledge and Skills and the Curriculum

Most pharmacy curricula are based on a defined list of disciplinary knowledge and skills that allow students to become familiar with each pharmacy-related discipline. For example, the pharmacology department will cover basic pharmacology concepts and then review the pharmacology of different classes of medicines, sometimes even covering the therapeutics aspects for each class. However, professional practice also requires a set of more generic or transversal competencies (often called soft skills) that are seldom the focus of any formal learning activity. Students are asked to present their work and we expect good presentation skills, without providing the theoretical background of what constitutes a good presentation. The same goes for communication, scientific writing, professionalism, leadership, and the list goes on. Soft skills are sometimes addressed in add-on courses that try to reduce gaps in the education.

Thus, one important step in preparing a competency-based curriculum is to define the essential knowledge and skills required to learn about and practice components of all the competency elements that are part of the framework. For example, medication reconciliation includes "Obtain all needed information using appropriate interview techniques with patients, caregivers and HCP" as a competency element (Table 4). This requires knowledge of the techniques of conducting an interview and the skill of conducting an effective interview. These knowledge and skills, combined with those for other competency elements, can then be applied to performing a medication reconciliation service.

After mapping all competency elements with the essential knowledge and skills required, this content should be added to the disciplinary knowledge and skills required to create the scientific and clinical base for pharmacists. With a known set of knowledge, skills, and professional activities (each with a competency profile), one can start to think about the course structure of the curriculum. In our current reform, some pharmaceutical services have actually become distinct courses, while before, they were parts of less structured pharmacy practice laboratories. Courses on dispensing now integrated theory and practice. Courses on extemporaneous preparations include the legal framework as well as the aspects of pharmaceutics. Instead of seeing a course as a disciplinary possession, courses have to become a setting for a professional activity to be introduced (knowledge and skills) and performed (competency development).

The longitudinal (horizontal) iterations allowing students to become competent for each professional service have to be defined within the new curriculum. The second iteration of a service can rely on its first iteration to allow a progression in the challenge offered to the students. One academic staff can be nominated to champion this longitudinal continuity for a given service. Ideally, as the service is revisited, less time is devoted to knowledge and skills, and more time is allowed for practice. This is the reason why theory and practice have to be better integrated, and the two components should in fact be part of the same course for optimal coordination. Also, the integration provides a better platform for the assessment of both surface and deeper learning within a professional context, encompassing different levels of the bloom taxonomy (Bloom, 1956).

Active Learning and Assessment Frameworks

To foster the development of proactive professionals, an environment where the responsibility of learning is shared between the learners and the instructors has to be created. Indeed, passive learning is more likely to generate passive graduates (Kober, 2014). Proactivity is a competency that will develop when students are faced with challenges and allowed to construct their own knowledge. Active learning approaches have been shown to be superior to the more passive teaching that most of us currently use (Dean Jr and Kuhn, 2007; Waldrop, 2015). As Linda Kober puts it in her report: "Applying findings from research on teaching and learning to improve instruction involves the same type of thinking one would use to solve a scientific or an engineering problem in a discipline. Why do outstanding scientists who demand rigorous proof for scientific assertions in their research continue to use and, indeed, defend on the basis of their intuition alone, teaching methods that are not the most effective?" (Kober, 2014).

One important question is whether active learning should be done independently by individual instructors or should be part of a global effort embedded within the curriculum. The educational literature is filled with examples of active learning activities tested in one course within a curriculum. Considering the evidence-based advantages of active learning, we believe that a more structured

approach is more efficient. It will also help the student find a more "predictable" learning environment if there is a global framework for active learning. In other words, each course could be developed by adhering to some guidelines in order for students to focus on the goals they have to achieve and not on learning how they have to behave in an unknown pedagogical environment. The framework needs some flexibility to accommodate variations in disciplinary content and student competency development across the various courses. As alluded to above, a course becomes a learning continuum of theory and practice, prepared by the same instructors with the final goal of competency development in mind. This should challenge the learners sufficiently enough to anchor knowledge for future retrieval and foster optimal application.

This active learning framework can be easily communicated, with workshops and examples, to prepare students for what lies ahead. This will greatly reduce the anxiety of the learners as they embark on this new journey of competency development. The same framework should also be used to train the educators and instructors to develop coherent learning activities. They can take part in workshops and discuss their experiences to help others transition and empower them (Kotter, 1996). By preparing and guiding instructors, we can ease the transition from their current method of teaching to embrace a more open environment of learning through shared responsibilities.

As new learning methods are introduced, assessment tools also have to be adapted and relevant. "Assessment drives learning" is a very powerful statement that should guide our assessment activities. It means that the students will do all they can to pass the assessment, thus making the assessment, and not the learning objectives, the true reflection of their knowledge and competence. Aligning the assessment with the learning objectives will ensure that the students are learning what is really important. For competency-based education, assessment is a significant challenge, because students should be assessed "while performing." The synchronous assessment can be resource intensive, and solutions have to be devised to keep the assessment as closely linked as possible to the performance. This can be facilitated by video recording or paper-based reporting by students (of a case resolution, for example) to allow asynchronous assessment. Objective Structured Clinical Examinations (OSCE) and mini-CEX are examples of methods that can be used to assess competence.

Competency assessment normally has two dimensions. First, one has to determine which competency element has to be assessed. Second, the level of competence has to be defined and will depend on the progression of the student within the curriculum. Expectations should be higher for students in their final years. This implies that for each competency element, different levels of expectations have to be described and the student's performance graded according to the expected level. Thus, if a competency framework has more than 50 competency elements and 3 levels are expected (beginner, intermediate, and expert), then more than 150 definitions of expectations have to be created.

To address the first dimension, one can rely on competency profiles, one for each professional activity, as discussed above. Each profile represents the competency elements that are assessed each time students practice a given service. The level of competence (the second dimension) for each competency element can become quite complicated. However, one can borrow from the evaluation of work-based EPA, which rely on five generic levels, reflecting the level of trust a supervisor has toward a trainee performing a task (Mulder et al., 2010). This concept can be used and modified according to the setting. For example, for laboratory and simulation assessment, we have identified four levels of competence:

- Level 1: not sufficient to perform the activity
- Level 2: sufficient to perform the activity with moderate feedback (dependent)
- Level 3: sufficient to perform the activity without feedback (independent)
- Level 4: sufficient to teach or become supervisor

This generic grading scale is easy to understand and use and allows flexibility for the assessors to ask additional questions or "prompt" students to determine their level of independence. Competency profiles and the expected level are known by the students and the assessors before the learning and assessment activities. The same format can be used as a formative assessment before the summative assessment so that students can get feedback on their performance before it is marked.

In order to detect if a student frequently fails competency elements in the same competency domain, the individual scores of competency elements can be included into a portfolio and revised periodically. The goal is to identify early students with competence shortcomings and help them to get back up to speed.

Developing an appreciation that "knowledge is only as good as its application" is relevant for both the instructor and the learner. It should be the driving force to resist reverting back to old habits of using solely knowledge assessment. Accordingly, programmatic assessment is emerging as a structured way of considering assessment as part of the learning strategy, rather than as an imperfect but necessary tool to determine the extent to which students have achieved their learning objectives (Fielding and Regehr, 2017; van der Vleuten et al., 2012). It includes periods of formative assessment and feedback to allow students to pursue the development of their competencies. Student grading is then based on a collection of assessments (data points) measured on several activities with appropriate examination methods.

Experiential Training

The learning continuum, from theory to practice, has a third component; professional experience (or experiential training). Students have to be confronted to real-world scenarios to ensure that they are ready to take care of patients. Simulations and

case resolutions done within the university setting do not have the emotional range experienced with real patients. The level of responsibility and accountability are clearly not the same. Practice experience is engrained in most pharmacy programs to allow students to test their preparedness and work more in gray zones under supervision from their preceptors. The preceptors provide input on behaviors and attitudes that are difficult to reproduce outside a practice context, even with role-playing.

Although this part of the curriculum occurs outside the university, most often with practitioners that are not faculty members, there needs to be a clear continuity with the curriculum. The learning outcomes become extensions of the ones started within the university. Experiential training can be seen as another form of active learning and can still fit within the active learning framework. The difference would be that the course (the placement) is fully in the competency development mode, and there is very little room for knowledge acquisition. In that context, the assessment of students during their rotation could follow the same model as with the university courses, as they were based on EPA with competency profiles. Entrustable professional activities were in fact developed for work-based assessment to start with (Mulder et al., 2010). Thus, irrespective of the fact that a student practices a professional service in a practice laboratory or in a clinical setting, the same assessment tool, based on the competency profile, can be used. Students will be familiar with the expectations. However, like faculty members, preceptors have to be trained to use the tools by conducting hands-on workshops with them. During the placements, support will have to be provided to make sure that the assessment tools are used properly both as formative (with feedback) and summative instruments.

As it is the case with competency assessment done *intra muro*, different levels of performance can be expected during early pharmacy practice experiences or advanced experiences. A generic grading scale, based on the EPA literature, should be used to facilitate the work of the preceptors who will have to grade students according to their performance for each competency element (Mulder et al., 2010; ten Cate, 2013). To be intuitive, the assessment follows the trust that the preceptor feels when the trainee performs a certain activity or service.

Each practice experience placement within the program will allow students to practice a subset of all the professional services, and one has to make sure that the selected sites are offering these services to allow students to develop as they conduct the activities. Distinct placements will focus on different pharmaceutical services to cover the whole range in a real-life setting. Including the same professional activities (or services) within the practice experience will allow a smooth transition and optimal continuity from the *intra muro* curriculum. Thus, placements become part of the longitudinal competency development structure.

Conclusion

Pharmacy is an evolving profession (Bonanno et al., 2012), and the professional education curriculum must adapt to changing needs and expectations from the population. Its evolution trajectory and speed are not the same in all countries and there is a need for conducting local need-based assessment of what is expected from the graduates (Atkinson, 2014; Brock et al., 2012). Competency-based education is recognized as a model that allows a better alignment to the societal needs, by focusing on the desired outcomes rather than on disciplinary knowledge (Frenk et al., 2010). Because there are not many examples, competency-based education is still difficult to grasp, let alone to develop (Hawkins et al., 2015; Koster et al., 2017). It involves significant changes in basic academic activities, such as the need to move toward active learning methods, discipline integration, direct observation assessment, and experiential learning. There is a need for a longitudinal structure allowing students to reach increasing levels of competence mastery over time.

Although there is a different view on which courses should compose a pharmacy curriculum (and this is expected in countries with different challenges), there is a greater homogeneity on the outcomes expected from the curriculum: pharmacists that are competent to fulfill the local needs (Bader et al., 2017b; Bruno, 2012). The challenge is to translate these outcomes into meaningful learning activities that will compose courses. For too long, we have worked backwards, by defining courses first, then learning objectives and expecting competent pharmacists at the outset (**Fig. 3**). We are proposing a step-by-step approach that starts from the outcomes in the form of a competency framework that, through pharmaceutical services, can be practiced and mastered during the curriculum. This approach was used to develop the new PharmD curriculum at Kuwait University and can be adapted to serve local needs and realities.

To our knowledge, one of the first pharmacy curriculum based on competency development was first offered at the Faculty of Pharmacy of Université de Montréal in 2007 (Mailhot et al., 2006). The impact on the students' confidence and overall preparedness to offer pharmaceutical services was phenomenal (personal observation). We are currently seeing similar outcomes in Kuwait in a competency based 2-year add-on PharmD program. We are thus convinced that beyond knowledge and skills acquisition, CBPE generates change leaders that can have a significant and positive impact on the scope of practice and quality of care. Unless these are not desired outcomes, educators involved in preparing students to "becoming a pharmacist" should seriously consider joining the growing community moving toward competency-based education.

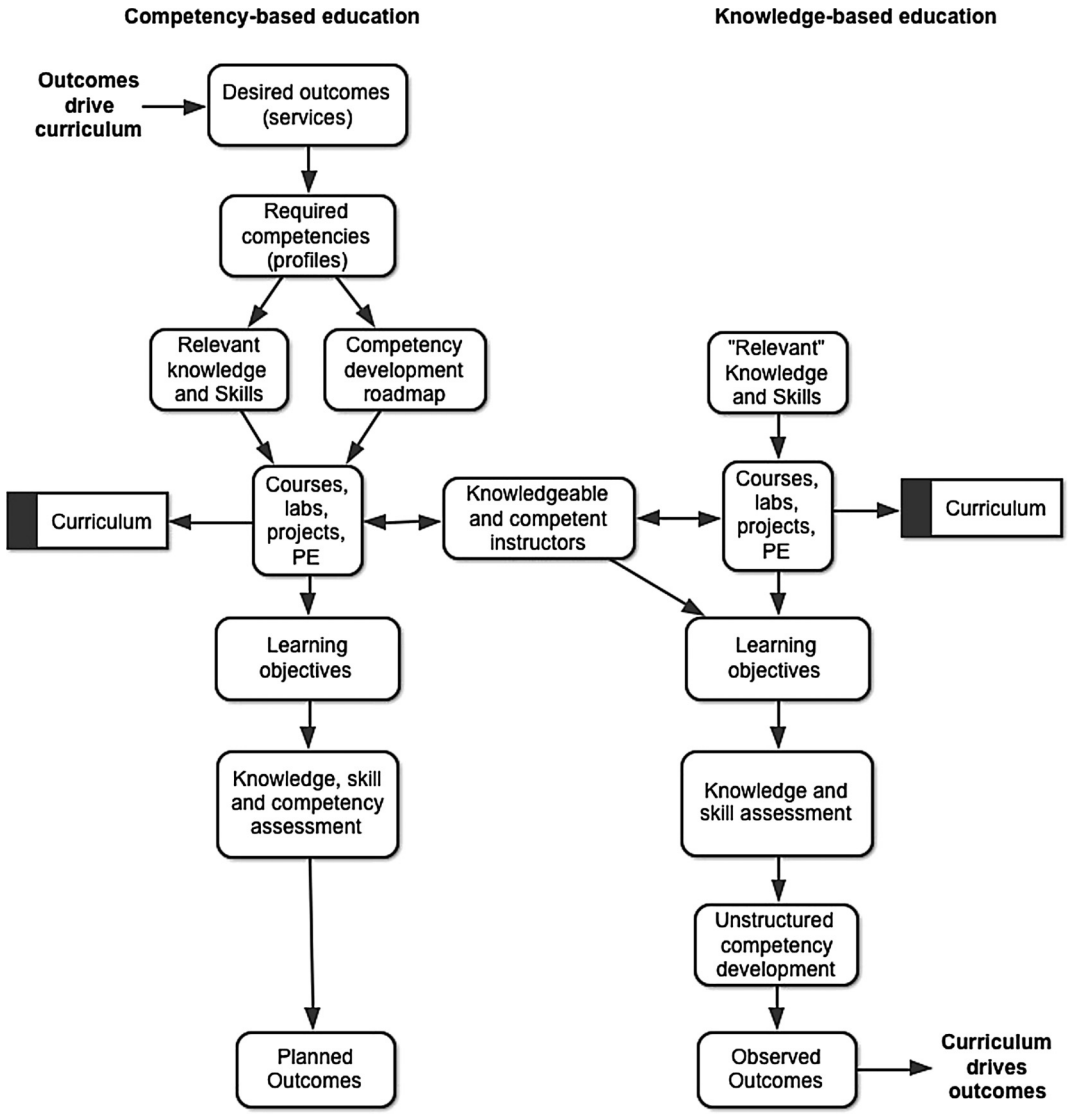

Figure 3 Comparison between competency-based education (*left*) and a more traditional approach to curriculum design (*right*). Both share competent instructors, but in a knowledge-based model, the outcomes are not driving the curriculum, and one should expect only partial preparedness to offer the scope of professional services. PE, practice experience.

Glossary

Active learning: a form of learning in which teaching strives to involve students in the learning process more directly than in other methods (en.wikipedia.org).
Bloom's taxonomy: a set of three hierarchical models used to classify educational learning objectives into levels of complexity and specificity. The models were named after Benjamin Bloom, who chaired the committee of educators that devised the taxonomy (Bloom, 1956).
Competence: having a complete repertoire of competencies (Brown et al., 2012).
Competency: mobilization of knowledge, skills, behaviors and attitudes that an individual accumulates, develops and acquires through education, training and work experience, to perform job-relevant tasks effectively within a given professional context (from the authors, summarizing several definitions from (Nash et al., 2015)).
Competency-based education: an approach to preparing professionals for practice that is fundamentally oriented to graduate outcome abilities and organized around competencies derived from an analysis of societal and patient needs. It deemphasizes time-based training and promises greater accountability, flexibility, and learner-centeredness (Frank et al., 2010).
Competency framework: a list of competencies and competency elements that define a professional (from the authors)

Direct observation (or observational) assessment: Assessing a performance related to knowledge, skills, or competence by observing the participant (from the authors)
Entrustable professional activity: is a key task of a discipline that an individual can be trusted to perform in a given context, once sufficient competence has been demonstrated (www.royalcollege.ca/rcsite/documents).
Experiential learning: is the process of learning through experience, and is more specifically defined as "learning through reflection on doing" (en.wikipedia.org)
Knowledge: facts, information, and skills acquired through experience or education; the theoretical or practical understanding of a subject (Oxford Dictionaries).
Needs-based education: an assessment of the needs of the community and then development, or adaptation, of supporting educational systems accordingly. Implementing such a needs-based approach requires ongoing consultation and cooperative partnerships between all stakeholders within countries and within institutions (Anderson et al., 2012)
Skill: the ability to do something well; expertise (Oxford Dictionaries).

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Becoming a Pharmacy Assistant and Technician: Education and Training

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Introduction

In many professions a support workforce has evolved to assist the professional in the successful completion of their professional activities. In pharmacy this support activity has evolved into the role undertaken by the pharmacy technician. The pharmacy technician functions in the role of assistant to the pharmacist although with the continued evolution of both the roles of the pharmacy technician and that of the pharmacist there is increasing responsibility devolving to the pharmacy technician.

The education and training of the pharmacy support personnel (pharmacy technician) who support the activities of the pharmacist has evolved in response to many factors: the evolution of the role of the pharmacist; legislation; requirement for support personnel certification or registration; and extended roles for pharmacy technicians. This chapter will explore the education and training of pharmacy technicians and the factors influencing the evolution of this education and training.

Influence of the Evolution of the Role of the Pharmacist

With the advent of the concept and practice of pharmaceutical care the role of the pharmacist has evolved from being product (medicine) focused to a patient focus with the pharmacist assuming responsibility for outcomes relating to medicine therapy (Anderson et al., 2009; Toklu and Huddain, 2013). This has required pharmacist activities to shift from the more technical tasks, such as stock control, order entry and distribution, prescription capture and filing, to tasks requiring higher-level cognitive skills such as interpretation and evaluation of the prescription, assessment of possible drug/drug or drug/disease interactions, and patient counseling (Anderson et al., 2009).

In countries such as the United States, United Kingdom, and Australia the driver for a greater utilization of pharmacy technicians is indeed the task shifting of pharmacists toward a more clinical role (Zellmer, 2012). The increased utilization of pharmacy technicians frees the pharmacist for participation in a more clinical role with a higher cognitive demand. However, in countries where the number of pharmacists is lower the situation is more complex. The increased demand for or possibly the more expanded practice of pharmacy technicians is greatly driven by the great need for a larger number of personnel to provide pharmaceutical services in the absence of sufficient pharmacists (Brown et al., 2011; World Health Organisation, 2011) supplemented by the additional driver of the movement of pharmacists to the more clinical role.

Europe has on average >7.5 pharmacists per 10,000 population while the WHO regions of Eastern Mediterranean, Western Pacific, and the Americas have between 5 and 7.5 pharmacists per 10,000 population with South East Asia having between 2.5 and 5 pharmacists per 10,000 population and Africa less than 2 pharmacists per 10,000 population. Interestingly WHO regions of Europe, Western Pacific, Americas, and Africa have more Pharmacy Technicians than pharmacists per 10,000 population while South Eastern Asia has fewer pharmacy technicians than pharmacists (Bates et al., 2016). This indicates that factors other than evolution of the role of the pharmacist and country income play a role in the demand for pharmacy technicians. These factors include absence of supporting legislation.

Legislation

Scope of Practice

The scope of practice of a pharmacy technician is directly linked to education and training as the education must be fit for purpose, i.e., the education and training must provide the knowledge, skills, and attitude required to fulfill the requirements of the scope of practice (Schafheutle et al., 2015).

Scopes of practice for pharmacy technicians vary from country to country (Frost and Adams, 2017; Kohler and Brown, 2017). Areas of greatest variation are: accepting verbal/telephonic prescriptions; performing a final accuracy check for dispensed medicines; supervisory powers; administering vaccinations; participation in medicine reconciliation; and functioning under indirect supervision. Additionally, in some countries such as Canada (National Association of Pharmacy Regulatory Authorities, 2014) and the United States (National Association of Boards of Pharmacy, 2017) the scopes of practice of pharmacy technicians will vary from state to state creating in-country variations.

In Australia the role includes: ordering and unpacking of stock; repackaging stock; preparing dispensing labels; attaching dispensing, cautionary and advisory labels; gathering nonclinical information; collating prescriptions; and compounding of medicines. A pharmacy technician may not offer any information to a patient about the safety and efficacy of medicines. The duties of the pharmacy technician are assigned by the pharmacist and must align to the technicians' education and training as well as experience. A suitably trained and experienced pharmacy technician may compound simple as well as complex medicines but the ultimate responsibility for the compounded medicine lies with the pharmacist. Compounding may only be undertaken under direct supervision of the pharmacist (Pharmacy Board of Australia, 2015; Pharmaceutical Society of Australia, 2003).

In Ontario, Canada pharmacy technicians may prepare a prescription and perform the final technical accuracy check. The technician may also provide information and education to the patient, but, the pharmacist is responsible for the therapeutic assessment and or education relating to the prescription. A pharmacy technician may also compound a medicine required for a prescription and may receive verbal prescriptions (Ontario College of Pharmacists, 2018).

In Denmark the pharmacy technician is known as a pharmaconomist. Activities of the pharmaconomist are undertaken at a higher level of responsibility than that of pharmacy technicians in most other countries. In community pharmacy the pharmaconomist can dispense a prescription including the final check without the input of the pharmacist although the pharmacist must be available (in person or telephonically) to respond to any queries from the pharmaconomist (Hansen and Brown, 2017). More information about and a comparison of the scopes of practice for pharmacy technicians in the various countries in Europe can be found in a survey published in 2017 by the European Association of Pharmacy Technicians (2017a).

In Malawi, largely due to a scarcity of pharmacists, pharmacy technicians work almost entirely without supervision and provide the backbone of personnel involved in provision of pharmaceutical services. In 2008, of the 300 strong pharmacy workforce only 2% were pharmacists. Pharmacy technicians, in the public sector, work mainly in hospitals where they are in charge of all aspects of provision of pharmaceutical services including drug supply management and dispensing services. Pharmacy technicians also supervise pharmacist assistants (a lower level of pharmacy support personnel) who provide pharmaceutical services at health centers (Larsen-Cooper et al., 2017).

Activities of entry level pharmacy technicians in Singapore include supportive roles in stock control and dispensing processes. An advanced role is also envisaged with career progression allowing for participation in supervisory and managerial tasks. Activities associated with an advanced level of practice include involvement in: distribution services including automation processes; compounding of sterile and nonsterile medicines and participation as part of the team for clinical trials; dispensing processes including medicine management and patient education; and quality assurance and medicine safety (Chew et al., 2017).

In South Africa although the scope of practice for pharmacy technicians was published for comment in 2011 the scope has not, to date, been formally legislated requiring pharmacy technicians to practice within the scope of practice of a pharmacist assistant post basic—a lower scope of practice. Activities in the proposed scope of practice for the pharmacy technician include: assist with manufacture, compounding manipulation or preparation of a sterile or nonsterile medicine; packing and re-packing of medicines; picking, packing, and dispatch of medicine orders; management and ordering of medicines; dispensing of medicines; general housekeeping and administrative tasks; supervision of other pharmacy support personnel; and technical support for screening tests. The supervisory capacity and involvement in technical aspects of screening tests is not included in the pharmacist assistant post basic scope of practice (Boschmans et al., 2017).

The role of the pharmacy technician has evolved in two main areas of practice in the United Kingdom, namely, community pharmacy and hospital pharmacy although pharmacy technicians also practice in education and the pharmaceutical industry. Although there are ongoing discussions relating to a greater shift of responsibility in community pharmacy to the pharmacy technician in hospital pharmacy the autonomous role of the pharmacy technician has evolved to a greater extent. Entry level activities for pharmacy technicians include: preparation of medicines for prescriptions and the supply of medicines to patients; compounding and manufacture of medicines; procurement and stock control of medicines; provision of health education; and supervision of other pharmacy staff (Boughen et al., 2016; General Pharmaceutical Council, 2018a).

There is great variation in the role of the pharmacy technician in the different states in the United States. Although the Pharmacy Technician Certification Board (PTCB) has been in existence since 1995 not all states require certification of pharmacists (Pharmacy Technician Certification Board, 2017a). However, generally the role is seen as a supportive one including the following activities: receipt of prescriptions; counting tablets; labeling of medicine containers; administration associated with processing of prescriptions such as updating of computerized patient profiles and submission of insurance claims; stock control; and other administrative functions include answering phones and operating cash registers (National Association of Boards of Pharmacy, 2017).

In summary, activities commonly included in the pharmacy technician scope of practice/role are:

- Prepare prescription;
- Provide information and education (nontherapeutic);

- Compound medicines (sterile and nonsterile);
- Stock control management;
- Ordering and procurement of stock; and
- Participate in health promotion activities.

Activities allowed in certain jurisdictions and not in others include, but are not limited to:

- Accept verbal prescriptions;
- Supervision/delegation;
- Supervision of a pharmacy;
- Administration of vaccines;
- Medicine reconciliation; and
- Technical accuracy check of dispensing process.

Supervision

Three aspects relating to supervision are important influencers of pharmacy technician education and training. These are, the ratio of pharmacy technician to supervising pharmacist permitted, whether the pharmacist supervision is direct (the pharmacist is in the same venue as the pharmacy technician and personally supervises the pharmacy technician's activities) or indirect (the pharmacy technician is operating in a geographically distinct site), and whether the pharmacy technician has supervisory capacity over other pharmacy support personnel. The greater the ratio of pharmacy technicians to supervisory pharmacist ideally the greater the required knowledge and skills base of the pharmacy technician. It stands to reason that the pharmacist will not be able to directly supervise every single activity undertaken by the pharmacy technician if the pharmacist is allowed a greater number of pharmacy technicians to supervise. If a pharmacy technician practices under indirect supervision, especially if there is not a direct video-link facilitating supervision, one would also expect greater autonomy of activity thus requiring a more extensive knowledge and skills base. Lastly if a pharmacy technician is permitted to supervise other pharmacy personnel or perform final accuracy checks the education and training would need to include supervisory practice knowledge and skills and accuracy checking (Kohler and Brown, 2017; White Paper on Pharmacy Technicians, 2002).

Supervisory ratios, for direct supervision, are stipulated by the Pharmacy Board of Australia in the "Guidelines for dispensing of medicines" (Pharmacy Board of Australia, 2015). The ratio that should not be exceeded is two pharmacy technicians to one pharmacist. A pharmacist may, however, motivate for an increased ratio. The Society for hospital Pharmacists of Australia is more conservative and recommends a ratio of 1.5 pharmacy technicians to everyone pharmacist (O'Leary and Allinson, 2009). Generally direct supervision of the pharmacy technician is required. There are some circumstances in remote areas where indirect supervision may be allowed. A video-link is required under these circumstances.

Canada is another country where there are remote areas with inadequate provision of pharmaceutical services. In these circumstances indirect supervision of a pharmacy technician is permitted as long as there is a live audio-visual link and the supervising pharmacist is present in the pharmacy that operates the remote dispensing site. The designated pharmacist is responsible for ensuring that supervision of support staff is appropriate (Ontario College of Pharmacists, 2014).

In Denmark the pharmaconomist functions relatively independently with the requirement that the pharmacist must be available to handle queries either in person or telephonically. Thus, a pharmaconomist does not have to function under direct supervision. The ratio of pharmaconomists to pharmacists is 3.5:1 (Hansen and Brown, 2017).

As a consequence of the need for pharmaceutical services in the rural areas and inadequate numbers of pharmacists ratios for both direct and indirect supervision of pharmacy support personnel have been legislated in South Africa (South African Pharmacy Council, 2016a). A pharmacist may supervise not more than three pharmacy support personnel (irrespective of role played, e.g., pharmacy intern, learner post basic pharmacist's assistant) under direct supervision. When the pharmacy support personnel are functioning at a primary health care clinic under indirect super vision a pharmacist may supervise up to five pharmacist's assistant post-basic. These two supervisory roles are not mutually exclusive.

In the United States the pharmacist to pharmacy technician supervisory ration differs greatly from state to state (Malacos, 2016). Some states do not even stipulate a ratio leaving the decision to be determined by the pharmacist in charge. Examples of some of these states are Delaware, Iowa, Kentucky, Oregon, and Vermont. In states where the ratios are stipulated these ratios vary from two pharmacy technicians to one pharmacist to six pharmacy technicians to one pharmacist. As examples more detail will be provided below on the ratios in a few states with legislated ratios.

California stipulates a ratio of one pharmacist to one pharmacy technician initially, thereafter two pharmacy technicians for each subsequent pharmacist are permitted (California Board of Pharmacy, 2018). This ratio does not include pharmacy support personnel involved in administrative tasks such as filing or cleaning. In a licensed health facility the initial ratio will be one pharmacist to two pharmacy technicians. In addition to direct supervision, a pharmacist in California may also indirectly supervise two pharmacy technicians who are working at a remote dispensing site. Requirements for indirect supervision are a direct audio and video link that allows the pharmacist to clearly observe all steps of the dispensing process and to communicate with the patient in order to provide patient counseling.

Colorado has a much higher ratio, namely one pharmacist to six pharmacy technicians. Pharmacy interns are included in the ratio but the total of six may not include more than two pharmacy interns. Additionally if three or more technicians are on duty at the

same time the technicians must be certified or have passed an accredited exam or have completed at least 500 hours of experiential training (Colorado General Assembly, 2017).

Idaho has one of the higher ratios. Under direct supervision six pharmacy technicians may be supervised by one pharmacist (Adams, 2017).

Mississippi allows a ratio of one pharmacist to three pharmacy technicians (Mississippi Board of Pharmacy, 2017). This ratio also excludes any support personnel involved in administrative duties such as filing prescriptions and general record keeping.

Although Montana also has a ratio of three to one the rule clearly states the requirements for application for a higher ratio (Montana Board of Pharmacy, 2006). The pharmacist must submit a pharmacy services plan illustrating how the standards of providing pharmaceutical care will be maintained. The plan should include information pertaining to the following aspects: design and equipment; information systems; work flow; and quality assurance.

In New Mexico the ratios for both direct (New Mexico Board of Pharmacy Regulation and Licensing Department, 2016) and indirect supervision (New Mexico Board of Pharmacy Regulation and Licensing Department, 2017) may be determined by the pharmacist in charge. Indirect supervision, similar to California, requires the use of audio-visual communication so that the pharmacist can supervise all required aspects of the dispensing process. Additionally the pharmacist may not supervise, directly or indirectly, across more than four pharmacies.

Culminating in 2016, the Tennessee Board of Pharmacy led a process to institute legislation concerning the supervisory ration for pharmacy technicians. The drivers were concerns for safety and quality (Todd et al., 2014). The ratio decided on was that of one pharmacist to every two pharmacy technicians. A ratio of four to one may be allowed if at least two of the pharmacy technicians are certified. The greater ratio would be considered bearing in mind aspects relating to public safety considerations.

In Virginia the ratio may be determined by the pharmacist in charge but may not exceed four pharmacy technicians to one pharmacist (Virginia Board of Pharmacy, 2018). The conditions for direct supervision are clearly delineated. The pharmacist must be physically present (no other means of communication, such as electronic or written, is acceptable) and have personal control over all aspects of the dispensing process.

Registration/Certification of Pharmacy Technicians

Registration or certification of pharmacy technicians leads to standardization of gateway examinations for certification. Standardized examinations prior to registration ensure that pharmacy technicians have the prerequisite knowledge and skills for the expanding roles they are adopting (National Association of Boards of Pharmacy, 2017). Once again there are differences across countries and even within countries with variations between provinces/states.

A pharmacy technician is not required to register in order to practice in Australia (and New Zealand). Although the Pharmacy Board of Australia does require any formal educational qualification to practice as a pharmacy technician there are recommendations that pharmacy technicians complete recommended training courses. There are variations in the recommendations for the technicians practicing in community pharmacy and those in hospital pharmacy.

Prior to 2010 pharmacy technicians in Canada were not registered/certified (Ontario College of Pharmacists, 2018). At the end of 2010, following legislative changes Ontario became the first province to regulate pharmacy technicians and require registration. Eight years later, in 2018, registration is required for pharmacy technicians in all provinces (nine provinces) except for Quebec (Canadian Institute for Health Information, 2018). Additionally, although Newfoundland and Labrador allow unregistered pharmacy technicians to practice this is an interim measure and this province is moving toward registration being a requirement for all pharmacy technicians to practice. In Manitoba pharmacy technicians are regulated but are not registered they are only listed (National Association of Pharmacy Regulatory Authorities, 2018). By 1 January 2018 there were 8185 registered technicians in Canada (Canadian Institute for Health Information, 2018).

Pharmacy technicians or pharmaconomists in Denmark do not require registration as authorization to practice (Hansen and Brown, 2017). The only requirement is the certificate from Pharmakon. Pharmakon, a college of pharmacy practice, is the only academic institution in Denmark that trains pharmacy technicians. Foreign pharmacy technicians are not required to register in order to practice. The permission of the Danish Medicines Agency is required in order to practice as a pharmacy technician (Danish Medicines Agency, 2016).

As of July 2017 there were 283 pharmacy technicians and 242 pharmacist assistants registered with the Pharmacy, Medicines and Poisons Board of Malawi (2018). Registration is a requirement to practice. A pharmacy technician registration examination is administered by the Pharmacy, Medicines and Poisons Board of Malawi. Pharmacy technicians must pass the examination prior to applying for registration as a pharmacy technician.

In Singapore pharmacy technicians are not regulated. However, the pharmacy technician functions under the close supervision of the pharmacist (Chew et al., 2017).

Pharmacy support personnel in South Africa may not practice without registration with the statutory body for pharmacy—the South African Pharmacy Council. Registration for pharmacy support personnel was first introduced in 1987. There were two categories of pharmacy support personnel on the original register: qualified pharmacy assistants and unqualified pharmacist assistants (students who exited from the pharmacist qualification prior to completion) (Boschmans et al., 2017). Currently, there are three categories of pharmacy support personnel in South Africa: pharmacist's assistant basic; pharmacist's assistant post basic; and pharmacy technician. The legislation has not been finalized to allow for a register for pharmacy technicians to be established.

Therefore, graduates from the pharmacy technician qualification are registered in the register of pharmacist's assistant post basic. A preregistration examination will be introduced within the next two years.

Prior to 2011 pharmacy technicians in the England, Scotland, and Wales were not required to register with the Royal Pharmaceutical Society of Great Britain/General Pharmaceutical Council (the General Pharmaceutical Council was founded in September 2010) in order to practice (Boughen et al., 2016). In 2001 the Audit Commission which looked at medicines management in local hospitals recommended that pharmacy technicians should be registered (Audit Commission for Local Authorities and the National Health Service in England and Wales, 2001). Voluntary registration with the Royal Pharmaceutical Association of Great Britain commenced in 2005 and compulsory registration was instituted by the General Pharmaceutical Council in 2011 (Boughen et al., 2016). In order to be eligible for registration as a qualified pharmacy technician candidates must have completed the required educational requirements and have spent a minimum of two years in the practice environment (Rosado et al., 2015).

In the United States certification of pharmacy technicians is undertaken by the Pharmacy Technician Certification Board which was founded in 1995. In order to achieve certification candidates must: have a high school diploma; disclose all criminal and State Pharmacy Board records; comply with Pharmacy technician Certification Board certification policies; and pass the pharmacy technician Certification Examination (Pharmacy Technician Certification Board, 2017c). Successful completion of a training program is not required in order to write the Pharmacy Technician Certification Examination. In 2012 the Pharmacy Technician Certification Board published an additional requirement for writing the certification examination: completion of a Pharmacy Technician Accreditation Commission accredited training program. The additional requirement was to be implemented by 2020. However, in 2017, the decision was suspended to allow for further consultation (Pharmacy Technician Certification Board, 2017d). Postcertification pharmacy technicians are required to participate in continuing professional development.

Certification requirements in the United States differ greatly from state to state. At the end of 2017 there were still five states (Colorado, Hawaii, Michigan, New York, and Pennsylvania) which did not regulate pharmacy technicians (Pharmacy Technician Certification Board, 2017b). Only 23 states and the District of Columbia require certification in order to practice. Twenty-two states regulate pharmacy technicians but do not require national certification. Regulation by the state with required registration with the state board of pharmacy is beneficial in that it allows the board of pharmacy to determine the number of pharmacy technicians practicing in the state.

Basic Education and Training

A requirement for a minimum qualification linked to registration can be a driver for the development and progression of a workforce such as pharmacy technicians. Such a requirement would set minimum standards for education and training required for pharmacy technicians and would additionally serve as a basis for development of advanced roles in terms of both practice and required supporting education and training (Society of Hospital Pharmacists of Australia, 2016). However, the establishment of such a requirement for a minimum qualification linked to registration has not been implemented in all countries where pharmacy technicians participate in the pharmaceutical services workforce.

Legislation in Australia does not enforce any requirement for a formal educational qualification for pharmacy technicians (dispensary technicians). The Pharmacy Board of Australia does, however, recommend that a relevant educational program should be completed by all pharmacy technicians (Pharmacy Board of Australia, 2015). In addition to the initial program the Pharmacy Board of Australia (2015) also recommends ongoing training in areas relevant to the pharmacy technician's area of practice.

There are three routes pharmacy technicians can use toward attaining competence. These are: an appropriate qualification; and/or achievement of specific competencies from within the qualifications; and/or practice experience. A combination of one or more of the three can be used as a measure of the pharmacy technicians' ability to practice. The judgment is made by the supervising pharmacist.

In Australia the Australian Qualifications Framework (AQF) is responsible for standard setting of recognized qualifications. For community pharmacy the AQF accredited Certificates III and IV in Community Pharmacy from the Retail Service Training package are recommended for pharmacy technicians practicing in community pharmacy (Training.gov.au, 2013a). For Pharmacy Technicians practicing in hospital pharmacy the AQF accredited Certificates III and IV in Hospital/Health Services Pharmacy Support from the Health Training package are recommended (Training.gov.au, 2013b). O'Leary and Allinson (2009) reported, in a 2007 hospital pharmacy survey, that only 52% of hospital pharmacy technicians held a postschool qualification. The qualification held by most of the pharmacy technicians was a certificate at level III or IV.

The topics covered in the core community pharmacy modules for Certificate III include: respond effectively to difficult or challenging behavior; comply with infection control policies and procedures; accept prescriptions and return dispensed medicines to customers; support the supply of Pharmacy Medicines and Pharmacist Only Medicines; assist customers seeking to relieve cough and cold symptoms; assist customers seeking to relieve skin and fungal conditions; assist customers seeking relief from gastrointestinal conditions; assist customers seeking to relieve common allergic symptom reactions; assist customers seeking analgesic and antiinflammatory products; apply point-of-sale handling procedures; interact with customers; organize and maintain work areas; communicate in the workplace to support team and customer outcomes; work effectively in a customer service environment; perform stock control procedures; minimize loss; and apply safe work practices (Training.gov.au, 2013a). Whereas the modules in the hospital pharmacy level III certificate include: contribute to effective workplace relationships; contribute to team effectiveness; organize workplace information; promote innovation in a team environment; create and use spreadsheets; interpret and apply medical terminology appropriately; organize personal work priorities and development; facilitate responsible behavior; participate

effectively in the work environment; recognize healthy body systems in a health care context; respond effectively to behaviors of concern; communicate and work effectively in health; work effectively with culturally diverse clients and coworkers; work effectively with Aboriginal and/or Torres Strait Islander people; comply with infection control policies and procedures; maintain pharmaceutical ward stock; pack pharmaceutical products; procure, store, maintain, and distribute pharmaceutical stock; assist with dispensing of prescriptions and medication orders; conduct small scale compounding and labeling of pharmaceutical products; conduct small-scale compounding and labeling of aseptic pharmaceutical products; and contribute to workplace health and safety processes (Training.gov.au, 2013b).

The Canadian Council for Accreditation of Pharmacy Programs is the body in Canada that accredits all pharmacy technician education and training programs. Accreditation of pharmacy technician programs commenced in 2008. All pharmacy technicians must have successfully completed an accredited program. There are 46 providers of accredited pharmacy technician programs. The duration of the programs varies from one to two years (Canadian Council for Accreditation of Pharmacy Programs, 2018).

The programs in Canada must fulfill the requirements of the standards for accreditation of pharmacy technician programs in Canada (Canadian Council for Accreditation of Pharmacy Programs, 2015). Typical content would include modules such as: anatomy and physiology; community pharmacy computers; pharmaceutical calculations; community practice theory; community pharmacy dispensing practice; home health care and nonprescription products; compounding; introduction to pharmacology; aseptic technique principles; institution dispensing; institution communications and operations; advanced pharmacology; and pharmacy management. Work-based placement periods are also included.

In Denmark the qualification for a pharmacy technician (pharmaconomist) is the equivalent of a three year degree course (Raagaard, 2016). There is only one provider of the pharmacy technician qualification, i.e., the Danish College of Pharmacy Practice or Pharmakon in Hilleroed north of Copenhagen. The students spend 23 weeks each year completing coursework at the institution. The remainder of the time is spent in the workplace either community pharmacy or hospital pharmacy. Therefore, the students spend the majority of the three years in the workplace with e-learning and workplace tutoring supplementing the coursework completed at the institution.

The training includes modules on: knowledge of pharmacology; anatomy and physiology; communication; and instructional skills and practical skills acquisition (Danish Association of Pharmaconomists, 2018). Education and training requirements vary across Europe. A useful summary of requirements across European countries is presented by the European Association of Pharmacy Technicians (2017b).

In Malawi the two levels of pharmacy support personnel, pharmacy technician and pharmacy assistant, are required to complete a diploma (pharmacy technician) or certificate (pharmacy assistant) course at an educational institutions. The pharmacy assistant program is of two years duration and covers content such as: anatomy and physiology; first aid, microbiology; parasitology; chemistry; counseling; communication; computer skills; pharmacology; pharmaceuticals; and medicine management (Kasiyamphanje, 2014). During the period of training blocks are spent in the workplace. The diploma course for pharmacy technicians is a three year qualification and covers similar topics but at a higher cognitive level.

The pharmacy technician course in Singapore is a part time program presented on two to three evenings a week over a year (Pharmaceutical Society of Singapore, 2018a). In order to register for the program workplace experience (minimum of six months) is required and the candidate must remain in the workplace for the duration of the course. The program is presented by the Pharmaceutical Society of Singapore and accredited by Workforce Skills Qualifications (WSQ). The content for the Advanced Certificate in Healthcare Support (Pharmacy Support) includes: coach for service performance; assist with procurement and storage; support and guide team members; demonstrate professionalism in work practices; maintain workplace safety and health policies and procedures; solve problems and make decisions at supervisory level; demonstrate understanding of basic pharmacology and drug development process; assist in basic dispensing and good pharmacy practice; assist in compounding of sterile and nonsterile pharmaceutical products; and provide drug information services and use of information and communication technology (ICT) in work activities (Pharmaceutical Society of Singapore, 2018b).

Successful completion of the relevant qualification is a requirement for registration as a pharmacy technician with the South African Pharmacy Council. There are two parallel routes via which the pharmacy technician qualification can be achieved in South Africa, via the: Higher Education and Training (HET) subframework or Quality Council for Trades and Occupations (QCTO) subframework. The HET qualifications are presented by universities while the QCTO qualifications can be workplace based. The qualifications are developed by the South African Pharmacy Council in consultation with stakeholders.

The HET (university presented) qualification consists of two full-time on campus one-year certificate programs (South African Qualifications Authority, 2018a,b). A two year diploma course has subsequently been developed and will be implemented once the required regulations allowing for registration as a pharmacy technician have been legislated (South African Pharmacy Council, 2016b). On successful completion of the university qualification graduates are required to complete a supervised six-month traineeship prior to registration as a pharmacy technician with the South African Pharmacy Council (South African Pharmacy Council, 2017).

The QCTO (work-based) qualification is the Occupational Certificate: Pharmacy Technician. Part qualification exit points exist within the occupational certificate (South African Pharmacy Council, 2016b). After completion of 62 credits (approximately 6 months) the learner can exit and register as a pharmacist's assistant basic. Completion of a further 130 credits (approximately 12 months) will allow for registration as a pharmacist's assistant post basic. Completion of the remaining 152 credits in the Occupational Certificate: Pharmacy Technician will allow for registration as a pharmacy technician. Workplace-based training is included in the occupational certificate therefore, the graduate is not required to complete a period of traineeship prior to

registration with the South African Pharmacy Council. The QCTO occupational certificate will replace the further education and training certificates currently in place for pharmacist's assistant basic and pharmacist's assistant post basic. There is no further education and training certificate for pharmacy technician. Providers have been invited to submit courses for accreditation against the QCTO occupational certificate.

The content of the HET qualifications and the QCTO occupational certificate are similar and cover the following topics: basic pharmaceutics; manufacture of medicines; extemporaneous compounding of medicines (sterile and nonsterile); dispensing of medicines; pharmacy operations and management; communication and counseling; anatomy and physiology; pharmacology; disease management; and relevant legislation.

In the UK, since July 2011, pharmacy technicians have been required to register with the General Pharmaceutical Council (Boughen et al., 2016). In order to register two education and training programs must be completed within a two year period. During the period of enrollment in the programs the pharmacy technician must be employed in a pharmacy environment. The qualifications are: Level 3 Diploma in Pharmaceutical Science (knowledge program) and Level 3 Diploma (NVQ) in Pharmacy Service Skills (competency-based program). The qualifications have been approved by the General Pharmaceutical Council in line with the General Pharmaceutical Council's Initial Education and Training Standards and Criteria (General Pharmaceutical Council, 2010).

Since the publication of the Initial Education and Training Standards and Criteria for pharmacy technicians in 2010 (General Pharmaceutical Council) there have been many changes in the practice environment of pharmacy technicians. The responsibilities of pharmacy technicians have changed extensively requiring an update to the standards for training to ensure that newly qualified pharmacy technicians can practice effectively in the workplace. In 2015 Rosado, John, Puaar, and Bates completed an investigation for the General Pharmaceutical Council on the initial education and training standards for pharmacy technicians and whether they were aligned with practice requirements. Various findings were published in the report among which was that due to the expanding and changing scope of practice of pharmacy technicians the standards required updating to include aspects such as accuracy checking activities (accredited checking pharmacy technicians) and other activities such as medicine reconciliation and medicine counseling to patients at discharge. Subsequently the General Pharmaceutical Council, in 2017, published updated standard for initial education and training of pharmacy technicians which took cognizance of the changing role of the pharmacy technician (General Pharmaceutical Council, 2017). Training providers may continue (during 2018) to present programs accredited against the 2010 standards but must develop new programs aligned to the 2017 standards and commence presentation of the new programs as from 2019 (General Pharmaceutical Council, 2018b).

In the USA the Pharmacy Technician Certification Board is a body which advocates for a single national standard for pharmacy technician certification (Pharmacy Technician Certification Board, 2017a). In 2013 the Pharmacy Technician Certification Board announced amendments to the requirements for certification that would be phased in by 2020. One of the suggested amendments was the requirement for completion of an accredited educational program (Pharmacy Technician Certification Board, 2013). However, in 2017, the Pharmacy Technician Certification Board suspended the implementation of the requirement for completion of an accredited training course (Pharmacy Technician Certification Board, 2017e). The Board, following consultation with stakeholders, felt that further thought, research and stakeholder consultation was required prior to implementation of the requirement for completion of an accredited course. Therefore, in the USA, there is currently no requirement for completion of an educational program prior to certification/registration. There are, however, recommendations in various stares which support the completion of relevant education and training.

Accreditation of pharmacy technician educational programs in the USA is undertaken by the American Society of Health-System Pharmacists/Accreditation Council for Pharmacy Education Pharmacy Technician Accreditation Commission (American Society of Health-System Pharmacists, 2018a). The Commission is a collaborative activity between the two organizations. The American Society of Health-System pharmacists has been accrediting training programs for pharmacy technicians since 1982 while the Accreditation Council for Pharmacy Education has been involved in accreditation of pharmacist education since 1932. A collaboration between the two organization for accreditation of Pharmacy Technician programs commenced about four to five years ago. Model curriculums (American Society of Health-System Pharmacists, 2015), accreditation standards (American Society of Health-System Pharmacists, 2018b), and guidance documents (American Society of Health-System Pharmacists, 2016a) have been published by the American Society of Health-System Pharmacists. The accreditation standards were updated in 2018 (for implementation in 2019) and the updated guidance document and model curriculum are due for publication in late 2018 (American Society of Health-System Pharmacists, 2018c). Content required in the programs includes: personal/interpersonal knowledge and skills; foundational professional knowledge and skills; processing and handling of medications and medication orders; sterile and nonsterile compounding; procurement, billing, reimbursement, and inventory management; patient- and medication-safety; technology and informatics; regulatory issues; and quality assurance (American Society of Health-System Pharmacists, 2015). Thus, although completion is not a requirement for certification a system does exist for accreditation of pharmacy technician education and training programs in the USA.

Extended Role for Pharmacy Technicians

The curriculums for education and training programs for pharmacy technicians should be directly linked to skills required in the workplace as the training must provide the pharmacy technician with the knowledge and skills they will require to function effectively in practice.

This implies that the development and updating of such programs must be ongoing as the workplace is an ever evolving space. The role fulfilled by the pharmacy technician has evolved over the past 10–15 years requiring new knowledge and skills. Areas that have developed to be included in technician scopes of practice include not only product related skills (e.g., accredited checking technicians) but also patient related skills (e.g., medicine reconciliation).

As the scope of the pharmacy technician continues to expand so will new knowledge and skills areas be required in the education and training programs. Some of the areas, around the world, which are devolving to the pharmacy technician role include supervisory roles and extended patient related roles.

In Australia possible areas for implementation of an extended role for pharmacy technicians are: clinical roles including medication reconciliation, counseling, and inpatient unit technician; accuracy checking technicians; technician led dispensaries; research, data collection, and education; and dispensing and ward stock management. In provision of pharmaceutical services to remote areas in Australia pharmacy technicians in Australia assist with: outreach services to remote areas where the pharmacy technician provides support to remote clinics in terms of stock control issues—this includes visiting the sites; medication profile maintenance; and dealing with queries about remote access to medicines (Society of Hospital Pharmacists of Australia, 2016).

In South Africa the scope of the pharmacy technician, although not yet implemented due to lagging legislation, includes supervisory capacity and the ability to work under indirect supervision with only a telephonic link to the supervising pharmacist to deal with queries.

In 2017 there was extensive debate in pharmacy circles in the UK relating to a General Pharmaceutical Council proposal to allow pharmacy technicians to supervise and sign off the training of preregistration pharmacy technicians (Torjesen, 2017). The supervision of pharmacy technician training by pharmacy technicians will be implemented as from 31 August 2018 (Cox, 2018; General Pharmaceutical Council, 2018c). Further debate in the UK involves a possible role for pharmacy technicians in the supervision of community pharmacies (Clews, 2018). Consultation relating to this matter is ongoing in 2018. Possible future areas for expansion of the general role of the pharmacy technician, in the UK, include skills which currently exist as post registration qualifications. Some of these qualifications are: accuracy checking pharmacy technician; medicines management skills program (including medicines reconciliation); clinical pharmacy/medicines management for pharmacy technicians; patient consultation skills; community pharmacy training, e.g., healthy living; national vocational qualification assessor; internal quality assessor; management; medicines information technicians training; pharmaceutical technology and quality assurance; procurement and supply; and teaching qualification.

The American Society of Health-System Pharmacists (2016b) has stated that extended roles for pharmacy technicians exist in the following areas: accuracy checking; purchasing or fiscal management; supervisory positions; assistance with medication history; medication therapy management; immunizations; quality improvement; hazardous drug handling; patient assistance programs; education and training; community outreach; drug use evaluation; adverse drug event monitoring; industry; and informatics. Generally in the USA the roles of pharmacy technicians are restricted to those activities not requiring professional judgment. The opinion is that further education and training and experience would be required for pharmacy technicians who would assume an extended role (Mattingly and Mattingly, 2018).

In Idaho, USA, legislative changes have allowed for an expanded scope for pharmacy technicians. The additional roles permitted include: accuracy checking activities; ability to accept verbal prescriptions; transfer of prescriptions; and performing remote data entry and vaccine administration (Adams, 2017).

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Certification, Credentialing, and Privileging in Clinical Pharmacy

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Introduction

Health care providers and the systems they work in are becoming increasingly accountable for the quality of the care delivered to patients. An important part of this accountability involves certification, credentialing, and privileging. While these processes traditionally involve physicians, they are starting to include pharmacists and other healthcare professionals as they take on greater patient care responsibilities, particularly in managing more complex patients and their medication regimens (Council on Credentialing in Pharmacy, 2010a; Forster et al., 2011).

There is often misunderstanding and confusion about the meaning of key terms when discussing certification, credentialing, and privileging in clinical pharmacy, as well as in the broader context of health care. The definitions for certification, credentialing, and privileging are defined in the glossary, and are approved by the Council on Credentialing in Pharmacy, a coalition of 10 United States-based, pharmacy organizations who are committed to providing leadership, guidance, public information, and coordination for credentialing programs in or relevant to pharmacy (Board of Pharmacy Specialties, In press d).

The proper use of the aforementioned terms is important because they help stakeholders, such as patients, physicians, other healthcare providers, legal/regulatory agencies, administrators, and payers, understand the readiness and authority of a healthcare professional to provide patient care services, and in the case of accreditation, the readiness of a site or program to deliver certain services. While stakeholders may misunderstand or confuse the meaning of these terms, it is a provider's professional responsibility to accurately convey their meaning to them so they can assess the knowledge and skill of a healthcare professional delivering services and better understand their scope of practice (Council on Credentialing in Pharmacy, 2009).

It is also important to understand that a credential (i.e., academic degree, license, certificate, or any number of other documents) is evidence signifying various professional qualifications, whereas credentialing and privileging are processes. Those processes will most likely include the requirement for evidence, essentially a credential, which represents a certain level of training, knowledge, and/or skill. Credentials focus on individuals while the term accreditation focuses on organizations, sites, and programs (i.e., an ASHP-accredited pharmacy residency or a hospital that is accredited by The Joint Commission.) In summary, individuals hold credentials while places or programs hold accreditations (Council on Credentialing in Pharmacy, 2010b).

Certification

Certification of individuals is internationally accepted in many industries and professions as a means to assure that the individual meets the requirements identified by the certifying agency. Certification, as opposed to other types of assessments, has a defined process to develop and validate the content outline for the certification and always includes an examination. Objective criteria and established standards to score the examinations are in place, which helps assure fairness and consistency in assessing competence to hold the certification. Because certifications are issued by bodies specifically designed to do so, they help assure impartiality and manage conflict of interest. Certifications can give confidence to stakeholders that the certification holder or certificant has been independently assessed and that there is a uniform standard being applied to award certification to an individual. Another important feature of certification is the process for maintenance of certification, which includes requirements for ongoing continuing education and/or reexamination. The maintenance of certification is important because the knowledge base of a given profession is almost always evolving as a result of new research and technological advances. It is through the maintenance of certification

process that stakeholders can have a measure of assurance that the certification holder maintains the level of competence that was initially achieved when the certification was first awarded (Institute for Credentialing Excellence, 2009).

Specialization and board certification in healthcare are inextricably linked; board certification is the process that independently evaluates whether a healthcare provider meets the eligibility criteria and demonstrates the knowledge and skill to achieve a designation in a specialty or specific health care practice area (Board of Pharmacy Specialties, In press a).

In the United States, specialty practice in medicine has been recognized for over 100 years and serves as a model for other professions. As medical practice became increasingly specialized, physicians practicing in those areas, along with various medical schools, saw a need to design a process to recognize which practice areas were specialties and to issue credentials to assure the public of a physician's qualifications to deliver specialized care. Established in 1917, the American Board of Ophthalmology was the first medical specialty board in the United States. The American Board of Otolaryngology was formed in 1924 with other medical specialty boards being formed throughout the 1930s and later (Talbert and Ellis, 2013). Today, there are 24 medical specialty boards that comprise the American Board of Medical Specialties (ABMS), whose mission is to serve the public and the medical profession by improving the quality of health care (American Board of Medical Specialties, In press).

By comparison, pharmacy in the United States did not begin to address specialization until a Task Force on Specialties in Pharmacy was formed by the American Pharmaceutical Association, now American Pharmacists Association (APhA), in 1973 (APhA Task Force, In press). While the APhA Task Force on Specialties in Pharmacy did not identify any existing pharmacy specialties, the group concluded that an official board with independent decision-making authority should be formed and granted authority to recognize pharmacy specialties based upon approved criteria. Furthermore, it was deemed that the board should have the responsibility to determine, which pharmacists are qualified to hold certification as specialists in officially recognized pharmacy specialties. To carry forth these tasks, the Board of Pharmaceutical Specialties, now the Board of Pharmacy Specialties (BPS), was created in 1976 as an autonomous division of the APhA (APhA Task Force, In press).

The criteria to recognize pharmacy specialties established by the APhA Task Force on Specialties in Pharmacy have remained largely unchanged since the founding of BPS (Board of Pharmacy Specialties, In press b).

These criteria are as follows:

- Need as a condition of requiring supply
- Demand defined as a willingness and ability to purchase the services of a Board Certified Pharmacist
- Number of practitioners and the amount of TIME spent in the practice of the specialty
- Specialized Knowledge based upon one or more of the pharmaceutical sciences and the biological, physical, behavioral, and administrative sciences which underlie them
- Specialized tasks/skills describe in detail, specialized tasks performed routinely by practitioners in the proposed specialty, which are not performed by pharmacists in general, as well as the special skills required to perform the tasks specified
- Education and/or Training describe in detail the education, postgraduate training programs, and/or experience required to acquire the specialized knowledge and skills and
- The area of specialization shall be one in which there is an adequate Transmission of Specialized Knowledge through professional, scientific, and technical literature directly related to the specialty area (Board of Pharmacy Specialties, In press b).

The mission of BPS is to improve patient care and increase awareness of the need for BPS Board Certified Pharmacists as integral members of multidisciplinary healthcare teams. BPS aims to achieve this through recognition and promotion of specialized training, knowledge, and skills in pharmacy, and through specialty board certification and recertification of pharmacists throughout the world. Board Certification through BPS has become recognized as a standard for determining which pharmacists are qualified to contribute at advanced practice levels as a result of the rigorous standards mandated by BPS board certification and recertification. As of 2017, BPS recognizes 11 pharmacy specialties and over 31,000 pharmacists in more than 26 countries hold BPS certification (Board of Pharmacy, In press). The pharmacy specialties currently recognized are: ambulatory care pharmacy, cardiology pharmacy, compounded sterile preparations pharmacy, critical care pharmacy, geriatric pharmacy, infectious diseases pharmacy, nuclear pharmacy, nutrition support pharmacy, oncology pharmacy, pediatric pharmacy, pharmacotherapy, psychiatric pharmacy, and solid organ transplantation pharmacy (Board of Pharmacy Specialties, In press c).

The Growth of Certification and Specialization

An assessment of Canadian community pharmacists by Jorgenson, Penm, MacKinnon, and Smith noted that pharmacy practice is evolving clinically on a global basis, and as the profession expands clinically, pursuit of certification is a natural outgrowth of that progression. The study concluded that the majority of community pharmacists in Canada would support a certification process to recognize pharmacist specialization. The authors also cite an example in New Zealand that once specialty practice was established, the government provided funding for services including prescribing and anticoagulation management and further noted that pharmacists in Canada are following this global trend (Jorgenson et al., 2017).

Suzuki et al. report that board certification maintains quality in the Japanese healthcare system and is also required for reimbursement. Their study concluded that board certification was more prevalent in designated specialty cancer hospitals with better adherence to adequate chemotherapy. The certifications in this report were Board-certified Pharmacists in Oncology Pharmacy and Board-certified Oncology Pharmacy Specialists (Suzuki et al., 2016).

Ignoffo et al. concluded, via a review of data and a Delphi panel process, that BPS Board Certified Oncology Pharmacists (BCOP) can provide clinical services that could help alleviate a projected shortfall in needed patient visits for cancer treatments in the United States (Anon, 2016).

Steeb et al. note that certification has advanced the case for provider recognition in the United States. They also reported that the Certified Pharmacy Technician (CPhT) enables pharmacists to grow their patient care services and that this is consistent with national goals to provide quality, cost-efficient care (Steeb et al., 2015).

In Australia, the government funds medication management reviews (MMRs) through the Society of Hospital Pharmacists of Australia (SHPA). The MMR program is a team-based model, which looks to help consumers make the best use of their medicines. To be eligible to participate in this program, pharmacists must earn board certification through a specialty recognized by BPS or through completion of a master's degree in either Clinical Pharmacy (M. Clin Pharmacy) or Pharmacy Practice (M. Pharm Practice), as well as a portfolio review conducted by the National Alliance for Pharmacy Education (NAPE) (Lawson, 2017).

The American College of Clinical Pharmacy (ACCP) has issued a position statement on the board certification of pharmacist specialists. In this statement, ACCP affirms its vision that all pharmacists who have responsibility for managing patients with complex or special drug therapy needs will hold board certification. The statement also supports board certification for pharmacists who supervise students and/or residents when they provide services to patients with complex pharmacotherapy needs, teach students about therapeutics, and deliver continuing pharmacy education that focuses on therapeutics or complex drug therapies. The college goes on to state that they believe that board certification is a valid assessment of a pharmacist's level of specialized knowledge in a designated area of practice and that attaining board certification contributes to improved patient care (American College of Clinical Pharmacists, 2011).

The integrated health system at the University of Wisconsin-Madison (UW Health) has made the decision that all pharmacists employed there in direct patient care roles obtain board certification by 2018. The impetus to reach this decision included: evolving collaborative practice models requiring greater demonstration of competence through credentialing, voluntary approaches to achieving universal certification being unlikely to succeed, health-system leadership being assumed by physicians who understand board certification, and evolving payment models and insurance contracts increasingly requiring board certification. The authors also commented that the rigor of the certification and recertification requirements were deemed valuable by the leadership of the department (Hager et al., 2017).

These observations in multiple countries further reinforce the point that certification is valuable in assuring standardization of service and quality and to help distinguish those individuals with specialized knowledge and skills. What makes board certification stand out is that the process is an independent evaluation of the knowledge and skills of an individual. It provides stakeholders a level of assurance that the individuals they are hiring, approving, or utilizing for service delivery have met a consistent standard.

The physician community is ahead of the pharmacy profession in that more than 80% of all licensed physicians in the United States hold a certification from the ABMS (Anon, 2017). On the other hand, it is estimated that between 8% and 10% of U.S. pharmacists hold a BPS board certification (Board of Pharmacy Specialties, 2017). As described earlier, it should be noted that the growth of pharmacist board certification appears to align with the growth of clinical pharmacy services, not only in the United States but in other nations as well. Fig. 1 shows the growth of BPS Board Certification. Fig. 2 shows the international adoption of BPS Board Certification by country.

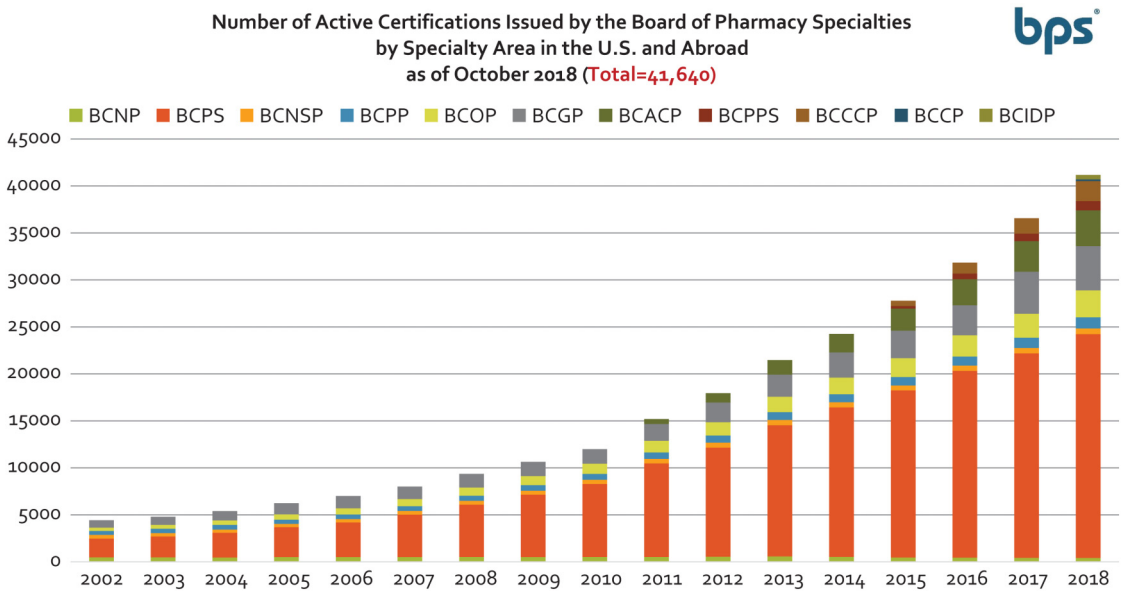

Figure 1 Growth of BPS Board Certification.

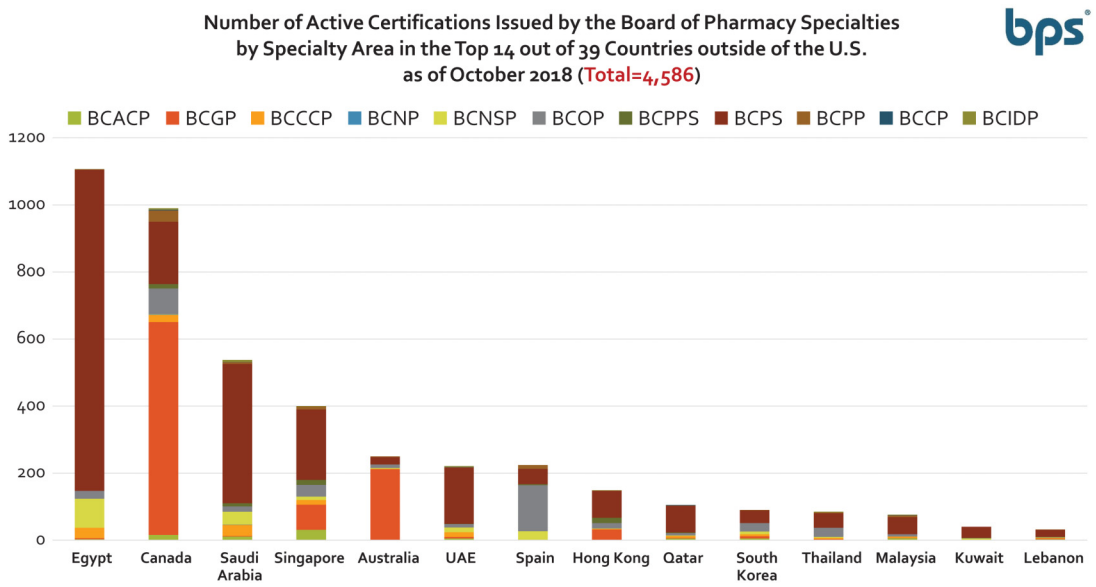

Figure 2 International adoption of BPS Board Certification.

Differences Between Certifications and Certificates

Some confusion exists over certificate programs and certifications particularly within pharmacy. The American Council for Pharmacy Education (ACPE) has renamed what were previously known as certificate programs to practice-based Continuing Pharmacy Education (CPE). ACPE states that the purpose of these programs is to instill, expand, or enhance practice competencies through the systematic achievement of specific knowledge, skills, attitudes, and performance behaviors. The content must be evidence-based and should include a live and/or home study component as well as a practice experience component. The minimum amount of credit for these activities is 15 contact hours (American Council for Pharmacy Education, 2009).

Essentially, practice-based CPE is an assessment-based certificate program. The certificate awarded upon the completion does not merely indicate that the participant was in attendance, but that they have met a predetermined competency threshold based upon the course materials. The fact that some training and educational programs may issue a document or certificate indicating successful completion of the course of study and the assessment does not make the program a certification (American Council for Pharmacy Education, 2009).

The Institute for Credentialing Excellence publishes the Standard for Assessment-Based Certificate Programs, and similar to CPE, this type of offering is defined as providing instruction or training to assist participants in gaining specific knowledge, skills, and/or competencies. Furthermore, this standard states that there is an evaluation of the learning, and a certificate is only awarded to those who meet the performance, proficiency, or passing standard for the assessment (Knapp and Kendzel, 2009).

The National Commission for Certifying Agencies (NCCA) Standards for the Accreditation of Certification Programs states in Standard 3: Education, Training, and Certification that "Appropriate separation must exist between certification and education or training functions to avoid conflicts of interest and to the protect the integrity of the certification program" (National Commission, 2004). Therefore, a major distinction between a professional or personnel certification and a practice-based CPE, assessment-based certificate program, or other certificate programs, is that certification is an independent assessment of predetermined knowledge, skills, and competencies, which requires that the certification be time-limited with a corresponding requirement for recertification (National Commission, 2004). Practice-based CPE, assessment-based certificate programs, and other certificate programs are based upon the provision of education and training, and the assessment measures whether the participant has achieved the stated learning outcomes for that particular program (American Council for Pharmacy Education, 2009; Knapp and Kendzel, 2009).

A hallmark of board certification is that the examination is not linked to a specific course of study, training program, or text. Instead, it draws on multiple references to assess whether an individual possesses the knowledge, skills, and competencies to earn the certification (National Commission, 2004). Individuals who earn board certification are often issued a certification mark or initials that designate their achievement (National Commission, 2004). One example of a widely recognized certification mark issued in pharmacy is the designation BPS Board Certified Pharmacotherapy Specialist (BCPS) (Board of Pharmacy Specialties, In press d). The initials and certification mark are important because they signify to various stakeholders, including the public, that an independent evaluation of the individual's knowledge and skill level has taken place. There is an implied trust extended by stakeholders to the certifying agency that the certifying agency knows the particular competencies that should be demonstrated in order to hold the certification and that the certified individual has the knowledge and skill to perform the related functions at a minimally competent level (Institute for Credentialing Excellence, 2009).

Table 1 Comparison of assessment-based certificate program and professional or personal certification program

Assessment-based certificate program	*Professional or personnel certification program*
Provides instruction and training (nondegree granting)	Assesses knowledge, skills, and/or competencies previously acquired
Goal is for participants to acquire specific knowledge, skills, and/or competencies	Goal is to validate the participant's competency through a conformity assessment system
Assessment is used to evaluate mastery of the intended learning outcomes; linked directly to the learning event	Assessment is best used to assure baseline competencies and to differentiate professionals; independent of a specific learning event
Assessment content may be narrower in scope	Assessment content is usually broad in scope
Awards a certificate to recognize mastery of the specific learning outcomes; it is NOT a certificate of attendance or participation, which is awarded to individuals who have attended or participated in a course or training program but did not have to demonstrate mastery of the intended learning outcomes	Awards designations to recognize achievement
To earn accreditation, complies with the ICE 1100 Standard and follows the ACAP application procedures	To earn accreditation, complies with the NCCA Standards for the Accreditation of Certification Programs and follows the NCCA application procedures

Whereas the "test" for certificate programs is based upon the course materials, certification examinations are based upon a job/practice analysis, also referred to as a role delineation study. The role delineation study is a process, which identifies the requisite knowledge and tasks performed by the individual in the delivery of distinct services. Typically, subject matter experts in the field will convene to identify the knowledge and task statements associated with the performance of a specific profession, occupation, or role being certified. The resulting knowledge and task statements are often grouped into broader performance domains and are validated by those practicing in the field based upon the criticality of the knowledge and task and the frequency with which the knowledge is used or the task performed. The results of the validated knowledge and task statements create a content outline with weightings assigned to each domain based upon the ratings derived from the frequency and criticality ratings for the knowledge and task statements. The content outline and related weightings become the "blueprint" by which a valid certification examination is developed (Institute for Credentialing Excellence, 2009) (**Table 1**).

Credentialing and Privileging

Credentialing and privileging are important for the primary purpose of protection. Most importantly, credentialing and privileging protect patients by helping assure that patients receive safe, high-quality care by individuals who have the appropriate qualifications to deliver such care. Credentialing and privileging also protect various institutions, organizations, and other health care entities that offer services because they provide a mechanism to evaluate the qualifications of practitioners working within them (McCarthy, 2006).

In the broader view of healthcare, credentialing and privileging continue to gain increased importance for multiple reasons: the increased complexity of patient care including specific procedures, greater emphasis on patient safety, and increasing legal liability. Patients also assume that the healthcare professionals they interact with are qualified to deliver services and that the institutions that employ these individuals have some type of process to verify competence (McCarthy, 2006).

In the United States, the *Darling v. Charleston Community Memorial* legal ruling propelled the credentialing and privileging processes into the mainstream of managing health care institutions. In this 1965 case, the court awarded a monetary judgment to the plaintiff by an Illinois hospital as damages for a leg amputation that came about because of the improper casting of a broken leg and medical mismanagement of a related infection. The results of this decision radically changed hospital liability law because the decision extended direct liability to the hospital as a provider of patient care and the established a duty of care on the part of the hospital. Prior to this ruling, no equivalent ruling related to hospital liability. In a 40-year span from 1965 to 2005, this ruling had been cited in over 300 state and federal cases. There were subsequent accreditation standards and various laws and regulations that grew out of this decision. It is interesting to note that part of the evidence in this case references the Illinois Department of Public Health regulations that state it is the hospital governing board's responsibility to, among other things, have clear standards for granting practice privileges including the ongoing review of clinical experience based upon patient medical records (Mitchell, 2005).

While the processes of credentialing and privileging are more common among physicians, as pharmacists assume a greater role in the delivery of health care, including patient safety, it is increasingly common to have pharmacists as part of these processes to verify competence (Jordan et al., 2016).

While the terms credential and credentialing sound very similar, they have distinct definitions and applications. A credential is documented evidence of attaining a professional qualification and is in fact often a paper document, although technology has now given rise to various digital credentials in some industries as evidence of professional qualifications. Common examples of pharmacy credentials can include a diploma, license, board certification, or residency certificate. Credentialing, as defined previously, can signify 1 of 2 processes. The first process is granting a credential, for example, when a school or college of pharmacy issues a diploma. The second credentialing definition refers to a process by which an organization or institution obtains, verifies, and

assesses an individual's qualifications to provide patient care services. Within healthcare, the more common use of the term credentialing refers to the second definition related to the verification and assessment of a provider's credentials to provide patient care (Council on Credentialing in Pharmacy, 2010a).

In summary, a credential is a document, either paper or electronic, and credentialing is a process. In the English language, credential is a noun referring to a thing (document) and credentialing is a verb referring to an action. One source of confusion is that the credentialing process used by health care organizations involves the verification of credentials. Privileging is also a process where the scope of services provided by a practitioner is authorized for delivery by that institution based upon a review of both credentials and performance (Council on Credentialing in Pharmacy, 2010a).

The best way to think about credentialing and privileging might be to examine the purpose of each. The credentialing process documents that a health care provider has attained the credentials needed to provide patient care within a particular practice setting. Privileging helps assure that the professional being considered to deliver specified services or have the "privilege" to do so at a specific organization has the defined competencies deemed necessary. The documentation required for credentialing usually supports broad-based service delivery and employment, while the documentation required for privileging can include some of the same documentation as credentialing but will also require additional and more detailed information (Council on Credentialing in Pharmacy, 2010a, 2014).

An example might be that in order to provide general services at a community pharmacy, a pharmacist would be required to hold credentials such as a diploma indicating graduation form an accredited college of pharmacy and a license or registration to practice in that jurisdiction (Council on Credentialing in Pharmacy, 2010a). The verification of these credentials could be considered credentialing. The process of reviewing documents for employment decisions is a form of credentialing. However, if that community pharmacy offers immunizations, they may decide that an additional credential is needed to immunize, such as the APhA Pharmacy-Based Immunization Delivery certificate (Pharmacist.com, In press). Documentation of that certificate would be required as well as other criteria set by the community pharmacy before the pharmacist would be granted the privilege to immunize patients in that pharmacy. However, some pharmacies may require an immunization certificate as part of the general employment requirement if immunization is part of the regular services offered.

It is important to note that institutions and health care organizations can have significant variations in their approach to credentialing and privileging. Those variations can even be greater when it comes to the credentialing and privileging of nonphysician health care providers. All pharmacists will usually participate in a credentialing process at the time of employment and as a condition on ongoing employment, although that process is often not thought of or labeled as credentialing and just referred to as the hiring process. The privileging process for pharmacists is not commonplace but is being seen with increasing frequency as pharmacists assume more direct patient care roles (Blair et al., 2007; Council on Credentialing in Pharmacy, 2010a).

Credentialing

Most health care organizations have credentialing processes in place. These processes can range from simple to elaborate and vary in degree of formality depending upon the needs of the organization. The Council on Credentialing in Pharmacy outlines 5 basic steps in a credentialing process (Council on Credentialing in Pharmacy, 2014).

1. Application
2. Verification
3. Analysis
4. Decision
5. Monitoring and Recredentialing

Application—This step involves the prospective employee completing paperwork to request formal consideration for a position. In the pharmacy profession, items on the application could include but may not be limited to:

- Education and training documentation
- Licensure information
- Proof of professional liability insurance coverage
- Signed and dated forms attesting to the accuracy of the information supplied and a release to allow the organization to verify the information provided.

Verification—When an application is received, it is reviewed and needs to be verified for accuracy. Credentials (i.e., licenses and certifications) are usually verified by contacting the primary source that issues the credential. In credentialing (as well as privileging), primary source verification of credentials is an important step to help assure that the credential being represented has in fact been earned by the individual and is not fraudulent. To verify credentials, the issuing body can be contacted in writing, via phone or facsimile or other electronic means, and their response should be recorded by the employer. In smaller organizations, the verification step may be performed by the hiring manager or supervisor; however, in other organizations, verification can be a function of the human resources department, or contracted to a Credential Verification Organization (CVO). Credential verification

organizations should be evaluated carefully by health care entities before contracting for services to assure that they have quality management processes in place that yield accurate results for the entity.

Analysis—Once the documentation is collected, it will need to be reviewed and evaluated. Some organizations use a staff committee to review credentials or even a multidisciplinary committee; in other instances, the analysis may be discussed between the hiring supervisor and the human resources department.

Decision—Once the analysis has taken place, a decision needs to be made regarding whether the candidate has met the requirements for the position.

Monitoring and Recredentialing—The monitoring process is ongoing and includes a general performance evaluation involving multiple factors such as work outputs, customer service, adherence to rules, policies, procedures, and legal/regulatory requirements. If there are performance deficiencies, a performance improvement plan may be utilized, which, in some instances, could result in limiting or restricting work activities. In extreme cases, the monitoring and recredentialing process could also lead to termination. On a more positive note, strong performance as documented through monitoring and evaluation could lead to expanded responsibilities and promotion for the employee. As part of the credentialing process, organizations should require individuals to promptly report any changes in the status of the information that they have submitted that impact their service to the organization and patients, ithat is, disciplinary action by a licensing or regulatory board, criminal activity, etc. Most organizations also have processes in place for recredentialing that can include certain in-house training, maintaining an active license or other continue professional development activities that are designated and deemed part of the ongoing credentialing process (Board of Pharmacy Specialties, 2017).

The credentialing process should be documented in a policy and procedure to assure that it is consistently applied and followed. Additionally, the credentialing process should contain a mechanism for candidates to review the information gathered, make corrections, and explain discrepancies. These processes are a matter of fairness to individuals and should be consistent with various employment laws within the jurisdiction.

Privileging

Privileging is a process where a practitioner is authorized by a health care organization to provide specific patient care services. Privileges are granted to an individual through a defined review process that is usually based upon a combination of education and practice experience. The basic process for granting and maintaining privileges is very similar to credentialing; the steps and the differences are outlined as follows (Council on Credentialing in Pharmacy, 2014):

Application—The application for clinical privileges should be initiated by the practitioner requesting permission to perform specific clinical activities. There may be a pre-application, which serves to determine if the individual meets basic eligibility criteria such as name and address, education, license status, and proof of current insurance coverage. Application for clinical privileges must include both a description of the privileges being sought and the required information and documentation that support the practitioner's ability to deliver the described patient care services. Privileging applications tend to be more in depth in the data required and very likely includes information such as a photograph, past or present challenges to licensure or registration, voluntary relinquishment of licensure or registration, voluntary or involuntary termination of health care staff membership, voluntary or involuntary limitations, restrictions or termination of clinical privileges at other institutions, as well as patient case data. Because clinical privileges tend to involve specialized services, it is very common to request information regarding board certification, residency training, or other relevant practice experience beyond the simple listing of employment. Applications for privileges will also include a number of attestations that the applicant must sign regarding items such as agreement to follow the institution's bylaws, various rules and regulations, accuracy and truthfulness of all information submitted, and a release of liability for the institution and staff involved in the peer review to make a decision on granting privileges. Most organizations have policies that establish timelines for the submission of information and the timeliness of the credentials and experience that are contained in the application (Council on Credentialing in Pharmacy, 2014; Lavalley, 2006).

Verification and Analysis—In some health care organizations, particularly health systems and hospitals, the initial application form may undergo a preliminary review to assure that it is complete. Once the application is accepted and begins to move forward, the health care organization must verify the information provided is accurate. Various accrediting bodies in the United States, such as The Joint Commission, require that much of the information undergo primary source verification. The verification step is usually conducted by a credentialing office. Once the information is filed, the application usually moves to the chair of the department in which the individual is applying for clinical privileges. It is the responsibility of the department chair to evaluate the validated application against the criteria established by the department related to the clinical privileges that are sought (Council on Credentialing in Pharmacy, 2014).

Review and Decision—The department chair will make a recommendation regarding the application to the healthcare organization's credentialing committee (usually a committee of peers) and that recommendation, along with the complete validated application, will be reviewed. The credentialing committee will interview the applicant to discuss any issues or concerns they have with the application and to further assess the readiness of the individual to provide services. The committee will then develop a written report and a recommendation, and that is submitted to the medical executive committee, which is usually comprised of the chair of each department. The medical executive committee reviews the information and makes a recommendation to the

organization's governing board for the final decision (Lavalley, 2006). The recommendation may include that direct supervision be provided by a privileged practitioner for a period of time when services may be at high risk or there are concerns regarding the individual's current competence or experience (Board of Pharmacy Specialties, 2017). Pharmacy administrators need to be aware of various laws and regulations that may define services that a pharmacist can provide both with and without supervision and to be sure that the privileging process is consistent with them. In the United States, this is largely governed on a state-by-state basis and involves not only the pharmacy practice act and regulations but can also be influenced by provisions in the medical practice act and regulations as well as any laws and regulations governing hospitals and other health care entities. This will also vary from country to country. Another example is within the European Union where there is variation among member states on the mutual recognition of professional qualifications.

Clinical privileges are usually time-limited, and reapplication is required. A 2-year duration is common. The reapplication process is very similar to the initial application and will always include performance data. Performance data can be very challenging in that objective data such as the number and types of procedures performed are relatively easy to obtain but offer little insight into outcomes. Outcomes can be highly subjective and impacted by issues such as severity of illness and comorbidities, although more institutions are looking to include performance data as a means to improve quality (Council on Credentialing in Pharmacy, 2014).

Designing a Pharmacist Credentialing and Privileging Process

Some would argue that developing a formalized pharmacist credentialing and privileging process may increase liability to the organization and the individual. Conversely, one could also argue that institutions and individuals are already exposed to liability through the normal process of delivering care and that establishing clear parameters for credentialing and privileging can help mitigate risk. Health care and pharmacy in particular are highly regulated (Council on Credentialing in Pharmacy, 2014). Credentialing, in its broadest application, is a form of self-regulation and if a profession does not monitor and regulate itself adequately, then it will most certainly face government imposed laws and regulations to address various issues. However, credentialing and privileging can only mitigate risk if both the institution and the individual agree to abide by their respective scope of responsibility and service.

As discussed earlier, the fact that pharmacy practice is evolving clinically speaks to the need for pharmacy to align their practices with the other health professionals and the systems in which they practice. The Council on Credentialing in Pharmacy states that pharmacists should be expected to participate in credentialing and privileging processes to ensure competency to provide quality care. The Council's guiding principles on post-licensure credentialing of pharmacists states that "for all practice settings, employers and payers should be encouraged to adopt and implement their own credentialing and privileging processes for pharmacists to determine and authorize the patient care responsibilities appropriate for the particular patient populations and care delivery" (Council on Credentialing in Pharmacy, 2011).

Pharmacists need to be at the forefront of designing credentialing and privileging processes for the profession because pharmacists have the subject matter expertise unique to the practice of pharmacy. A critical discussion that needs to take place within pharmacy administration is what training, skills, and credentials are needed for service delivery and if they are appropriately matched to the privileges being sought (Council on Credentialing in Pharmacy, 2014).

With that said, pharmacy leaders and pharmacists themselves need to be responsible for the delivery of patient services in a manner consistent with other professions including peer review and outcome reviews. Because the process of credentialing and privileging is not new in health care, the pharmacy profession should align with the general processes designed by the medical staff, human resources, and quality improvement departments within the organization while bringing to light the specific patient care responsibilities and unique health care contributions the pharmacist will be accountable for and is prepared to deliver (Council on Credentialing in Pharmacy, 2014).

The Joint Commission has outlined 14 steps to developing a privileging process that could serve as a useful template for pharmacy departments to consider (The Joint Commission, In press).

1. Define the scope of the care your organization is providing.
2. Review the various laws and regulations that define what a practitioner can do independently and what must be done with supervision.
3. Further review laws and regulations to determine the scope of practice. For example, does the scope or practice allow the pharmacist to order laboratory tests or administer vaccinations?
4. Based upon the above, what qualifications and credentials do you want the practitioners to possess? Advanced degree? Residency training? Board certification?
5. Establish methods/process to formally request privileges, formal application document, letter of request, etc.
6. Develop a verification process for the core credentials that are required, that is, is the license current? Are there pending or past actions taken against that practitioner's license? It is strongly suggested and may even be required by law in some areas that the verification step is primary source verification.
7. Establish a record keeping system to store information obtained through the verification step.
8. Identify any organization or department-specific requirements. Examples can include residency training, board certification, and insurance documentation.

9. Obtain a written statement from the applicant attesting that the individual has no issues that could impact his or her ability to deliver care described in the privilege requested. Areas for attestation include that the individual has no issues, past or present with his or her licensure, registration, or employment at another organization. Departments will need to consult with the human resources department within their health care organization to design this attestation in compliance with local laws and regulations.
10. Identify a pharmacy administrator, usually the director or head of service as the individual, to assess whether the information submitted in the privileging application meets the required qualifications.
11. Based upon your organization's governing structure, the pharmacy administrator should receive formal approval from another administrator(s) at the organization with a recommendation to the organization's governing body regarding the privileges requested by the individual who applied for them.
12. A formal process should be developed to notify the practitioner who applied for privileges in writing with the decision.
13. Develop a filing system to maintain evidence of the privileges granted in the practitioner's credential file.
14. Develop a system to track information that will change such as license status and board certification.

There are practical considerations and challenges that should also be considered when developing a clinical privileging process. The fact that patient services are now delivered within systems that have many care delivery sites including multiple hospitals, clinics, pharmacies, and physician office practices underscores the importance that credentialing and privileging processes need to reach all areas where care is delivered and not just focused on the traditional walls of the hospital. The expansion of health systems raises the question as to whether the process needs to be centralized or driven on a facility-by-facility basis. There are arguments that could be made for and against both approaches including workload, efficiency, and consistency. For example, if a pharmacist practices at multiple facilities, should he or she be privileged at each facility, and should each facility have variations in its privileging process? Can an argument be made for centralizing the application? If the application is centralized, is there a process to share this information across the various facilities within a system? If the privileging timelines are different between facilities, is there a mechanism to harmonize them so that practitioners could avoid reapplication annually, semiannually, or more frequently? Most privileging processes are still paper-based; is there physical space to store this information? Is there an efficient way to routinely access the files to make sure they are current?

Performance data will need to be developed that are appropriate to the scope of services delivered by the pharmacist. It is often difficult to attribute an outcome to an individual because of the fact that many health care professionals interact with and provide patient services; however, serious thought needs to be given to what will be measured. A starting point could be a discussion with the institution's quality improvement department to identify areas that the organization is looking to address such as length of stay, readmission rates, and adverse events. Often, these areas can be impacted by medication use and may be appropriate starting points for identifying the pharmacist performance data to be collected.

In developing a privileging process, it needs to be clearly stated that the responsibility to provide full and complete information and to update that information as needed falls directly upon the pharmacist seeking clinical privileges. The privileging process will not work properly unless the pharmacist accepts full accountability for transparency in reporting and in the regular updating of required information.

These are just some of the logistical issues that need to be addressed when designing a pharmacist privileging process; in most cases, the pharmacy department should align with the institution's processes but the institution also faces the same challenges and issues for physician privileging. None of these challenges and issues should be viewed as a reason not to embark on privileging but should be addressed in advance so that program functions appropriately and meets the goal of assuring quality patient care.

Conclusion

A fundamental driver in the advancement of certification, credentialing, and privileging in clinical pharmacy, particularly in the United States, has been in the increase in the complexity of patient care (Council on Credentialing in Pharmacy, 2010a). Medications are one of the society's most important weapons in the fight against both acute and chronic disease, and pharmacogenomics are also becoming an important tool in addressing genetic disorders. It is exciting to observe the advancement of clinical pharmacy services in a number of countries around the world because pharmacists have the training, knowledge, and expertise to help patients in all settings make the best use of their medications (Jorgenson et al., 2017).

With the advancement in clinical pharmacy and an increased role of the pharmacist in the provision of direct and indirect patient care services comes great responsibility and accountability. The responsibility and accountability extend to a number of stakeholders including the organizations that employ pharmacists, public, and private entities that pay for pharmacists' services, colleagues in other health care professions including but not limited to medicine and nursing and the most important stakeholder, the patient (American College of Clinical Pharmacists, 2011).

The accountability of clinical pharmacists in delivering patient care must include embracing the tenets of board certification, credentialing, and privileging. Participating in board certification, credentialing, and privileging demonstrates the willingness of the clinical pharmacist to assure all stakeholders of their education, training, skills, and ability to provide patient care and to serve as valuable members of the health care team. The role of the clinical pharmacist will not advance by simply stating to possess the

knowledge and expertise to deliver patient care; these competencies must continually be demonstrated and assessed if clinical pharmacy is going to continue to evolve (American College of Clinical Pharmacists, 2011).

While there are many intricacies and details associated with certification, credentialing, and privileging of all health care professionals including pharmacists, a foundational element of all three areas is the welfare of the public. In health care, that welfare includes patient safety, alleviation of pain and suffering, improved outcomes, and cost-effectiveness with the ultimate goal being full restoration of health. While there are other drivers such as reducing or mitigating liability, professional satisfaction, prestige, peer recognition, and reimbursement, the patient should always remain the most important reason to pursue any professional credential or designation (Council on Credentialing in Pharmacy, 2009; Council on Credentialing in Pharmacy, 2010a; Forster et al., 2011; McCarthy, 2006).

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Glossary

Certification The voluntary process by which a nongovernmental agency or an association grants recognition to an individual who has met certain predetermined qualifications specified by that organization. This formal recognition is granted to designate to the public that this individual has attained the requisite level of knowledge, skill, and/or experience in a well-defined, often specialized, area of the total discipline. Certification usually requires initial assessment and periodic reassessments of the individual's knowledge, skills, and/or experience (Council on Credentialing in Pharmacy, 2006).

Credentialing (1) The process of granting a credential (a designation that indicates qualifications in a subject or an area). (2) The process by which an organization or institution obtains, verifies, and assesses qualifications to provide patient care services (Council on Credentialing in Pharmacy, 2006).

Privileging The process by which a healthcare organization having reviewed an individual healthcare provider's credentials and performance and found them satisfactory authorizes that individual to perform a specific scope of patient care services within that organization (Council on Credentialing in Pharmacy, 2006).

Accreditation The process by which an association, organization, or government entity grants public recognition to an organization, site, or program that meets certain established qualifications or standards as determined through initial and periodic evaluations (Council on Credentialing in Pharmacy, 2006).

Practice-based CPE activity [Previously named Certificate programs in Pharmacy] These CPE activities are primarily constructed to instill, expand, or enhance practice competencies through systematic achievement of specified knowledge, skills, attitudes, and performance behaviors (American College of Clinical Pharmacists, 2011).

Role Delineation Study Any of several methods used singly or in combination to identify the performance domains and associated tasks, knowledge, and/or skills relating to the purpose of the credential and providing the basis for validation (Institute for Credentialing Excellence, 2009).

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Clinical Pharmacy Professional Standards in European Union

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Introduction

In the context of this entry/chapter, the term standards encompasses two of the many shades of meaning listed in the Oxford English Dictionary, namely (Oxford English Dictionary, 2018):

- A rule, principle, or means of judgment or estimation; a criterion, measure.
- A definite level of excellence, attainment, wealth, or the like, or a definite degree of any quality, viewed as a prescribed object of endeavor or as the measure of what is adequate for some purpose;

The first of the two, which derives from earlier references to standard measures such as those of weight and length, is a description which tells the reader what it is.

The second is clearly related to the idea of quality and of a desired level of quality.

In both, it is clear that comparison is facilitated by a standard and that bringing two elements to the same standard could be referred to as standardization.

In health-care practice, standards are usually introduced for at least one of three reasons:

- To describe the activities, roles, and responsibilities of a professional
- To describe what is specified by a level of quality
- To aid the measurement and monitoring of performance

Since providing health care is a complex activity of which pharmacy services comprise an important part, it is not surprising that there are many standards created by, and applied to, pharmacy and pharmacists. Individual pharmacists, pharmacy department and teams, hospitals and clinics, health service authorities and regulators, representative bodies, and international associations have all been authors of standards that meet their particular aims and objectives. Since individuals, teams, and departments operate within larger health service organizations and sectors, it is important that their standards align with the relevant standards of the health service and of the professional regulatory body. These larger organizations and sectors are subject to local or national regulations which, in turn, often lead to the creation of standards and frameworks.

Although many standards have been used to define the provision of pharmacy services and to monitor the quality of those services, the standards that apply to clinical pharmacy and to clinical pharmacy in Europe especially have been relatively few in number. Therefore, some context must be provided to make this understandable.

Context

Clinical pharmacy was first described in the hospital setting and the term was used to distinguish it from the other activities carried out by pharmacists, such as compounding, dispensing, and medicines information. It represented a ward-focused activity, and one that involved consultation with doctors and nurses. This change in the pharmacist's roles and responsibilities was most readily accepted in the United States, the United Kingdom, Australia, and Canada and gradually gained momentum from the late 1960s onwards. Initially, individual pharmacists and hospital pharmacies began to provide clinical pharmacy and subsequently, formal support and leadership came from pharmacy associations (American College of Clinical Pharmacy was established in 1979; United Kingdom Clinical Pharmacists Association was established in 1981). Subsequently, with the recognition of the role, the clinical pharmacist's job description was established and clinical pharmacy was spread to more hospitals.

In hospital practice, a group of activities can be readily classified as clinical pharmacy while in community practice, some service development can be classed as clinical, but pharmacists usually have to perform multiple roles and to be flexible so that the practice can respond to varying service demands and needs. In addition, in community practice, other terms, such as cognitive services, have also been used to distinguish them from dispensing and medication provision.

Across Europe, clinical pharmacy has developed at varying speeds and in different ways; in Italy (Lombardi et al., 2018), Austria (Rose et al., 2018), Germany (Rose et al., 2018), and the Netherlands (Bosma et al., 2008; Rose et al., 2018), there is little clinical pharmacy, whereas in Spain (Saavedra-Mitjans et al., 2018), France (Allenet et al., 2006), Portugal (Falcão et al., 2014), and Belgium (De Rijdt and Desplenter, 2016; Somers et al., 2018), there is significantly more, while in Denmark (Neilsen et al., 2013) and Sweden (Sjölander et al., 2017) development continues. National programs for the implementation of clinical pharmacy are rarely found; most development has been within hospital groups or individual hospitals. However, even today, there is also a considerable variation within countries, as a recent study of Switzerland shows (Rose et al., 2018).

In the United States and the United Kingdom, the intention had been for pharmacists to provide patient-focused care in collaboration with prescribers and nurses, but in some countries, this was not possible, and instead population-focused or institution-focused services, such as Therapeutic Drug Monitoring and Medicines Information, came to be referred to as clinical services since they support rational prescribing and formulary development. This distinction between the patient and population focused services continues to this day and is reflected in practice with some countries, such as Austria, Germany, and the Netherlands (Rose et al., 2018), providing more population-focused services. Countries with more of a patient focus employ more clinical pharmacists and this can be seen in the data gathered in the European Association of Hospital Pharmacists surveys (European Association of Hospital Pharmacy, Survey Results, 2016).

There are also other factors that ensured that clinical pharmacy developed first in hospitals: As large health-care institutions, hospitals must adopt structured procedures to function efficiently and some, because they are University Teaching Hospitals, have the added impetus of providing specialist clinical care for a regional or nationally, of providing education and of conducting clinical trials and research—in each of these instances, the greater complexity of healthcare requires more highly qualified specialists to deliver the care required (Gillespie et al., 2009). This has resulted in the development of advanced services such as the Integrated Medicines Management Service in Northern Ireland (Scullin et al., 2007), the Lund Integrated Medicines Management in Sweden (Hellstrom et al., 2001), and the team-based model in Ireland (Byrne et al., 2017).

The result of this varied and sometimes divergent pattern of development has been that within Europe in 2018, the most significant clinical pharmacy standards, in terms of their widespread application and the most accessible in terms of their publication, are to be found in the United Kingdom (Department of Health, 2013; Royal Pharmaceutical Society, 2017). In other countries, hospital groups and individual hospitals have their own service descriptions, and these are neither regional nor national standards. At the European level, the most relevant document for the development of clinical pharmacy in the next few years is not a set of standards, but a description of hospital pharmacy, published by the European Association of Hospital Pharmacists (The European Statements of Hospital Pharmacy, 2014).

Current Standards

Although the Northern Ireland Clinical Pharmacy Services Standards (NI 2013) (Department of Health, 2013) and the Royal Pharmaceutical Society Standards for Hospital Pharmacy Services (RPS 2017) (Royal Pharmaceutical Society, 2017) documents were published only 4 years apart, they differ considerably in both their scope and structure (**Table 1**) and their content (**Table 2**).

Notably, both documents come from pharmacy bodies/groups, even though the RPS drafting group comprised lay people and other health-care professionals as well as pharmacists. Furthermore, both documents encompass the individual and the system approaches and both organize their standards under the headings of Acute or Care services and General Support or System services with most of the individual activities being contained in the Acute or Care sections. Most notably, the RPS document begins with standards that relate to Care and this highlights the primacy of the patient and of clinical pharmacy practice in the United Kingdom.

The standards themselves are general statements of what should be done but while the NI document is primarily pharmacist task-oriented, the RPS document is more process- and outcome-oriented for pharmacist, pharmacy teams, and patients. Consequently, the Acute Services section of the NI standards is a clear description of the tasks that a clinical pharmacist and the pharmacy team should perform, and the inclusion of an audit document template shows the intent of the Health and Social Care Trusts of Northern Ireland to standardize and monitor the quality of the Clinical Pharmacy Services that they provide. The RPS document indicates the context of providing hospital pharmacy services in the United Kingdom—a strenuous and comprehensive attempt to ensure that patients are empowered, or at least informed about their treatment. Both documents reflect the importance in Northern Ireland and the United Kingdom of patient safety and of utilizing pharmacists to provide care through pharmacist led clinics and through prescribing. However, both also set out in considerable detail the multidisciplinary nature of much of the pharmacists' work and of the importance of teamwork and of communication. Some activities, such as those concerned with safety, whether medication errors or pharmacovigilance responsibilities, are grouped under Acute Services in the NI document whereas the RPS distributes these activities across both the Care and Systems Domains. Some of the activities referred to are more frequently discussed in the United Kingdom and Northern Ireland than elsewhere in Europe, such as the reuse of patient's own medicines and the self-administration of medicines, while others, such as the pharmacoeconomic evaluation of medicines and financial management, are common to all European countries.

The NI document serves an operational need of the health service, whereas the RPS document sets out a framework for the profession, which it is intended, will be used as the basis for the development of operating documents by pharmacists and others in any care setting within the NHS.

Table 1 Comparison of the Northern Ireland and Royal Pharmaceutical Society Standards documents

Northern Ireland Clinical Pharmacy Standards (Department of Health, 2013)	*RPS professional standards for hospital pharmacy services (Royal Pharmaceutical Society, 2017)*
Published by; type of body	
Pharmacy Service of the Health and Social Care Trusts of Northern Ireland; Health Service Regional Authorities	Royal Pharmacy Pharmaceutical Society; Professional representative body
Authors, contributors; composition process	
Heads of pharmacy service of each of the five Health and Social Care Trusts; not specified	Steering Group, multidisciplinary and lay representatives ($n = 27$) supported by RPS team and External Reference group; RPS standards development process, accredited by NICE – Literature review → draft prepared by Steering Group in consultation with External Reference group → published for consultation → revised draft developed and reviewed by Steering Group in consultation with External Reference group → consensus reached → standards published.
Aims and objectives	
"The principal objective of this document is to improve the clinical pharmacy contribution to patient care through the development of a structured, systematic approach to clinical pharmacy practice."	"To provide professional standards that are supportive, enabling, and professionally challenging is a key function of a leadership body." "The professional standards describe quality pharmacy services (what good looks like)." "The standards provide a broad framework that will support pharmacists and their teams to continually improve services, shape future services and roles, and deliver high quality patient care across all settings and sectors."
Intended audience	
Hospital setting is implied with pharmacist working in a multidisciplinary team in a "hospital area" for which the pharmacy staffing level and structure (pharmacists and technicians) are specified.	Chief Pharmacists, Directors of Pharmacy, pharmacy teams, Commissioners/ purchasers of pharmacy services, regulators, insurers, Governments, legislators, and patients.
How they should be used	
Standards "need to be supported by local standard operating procedures specific to individual trusts."	Applicable to all settings. For Chief Pharmacists and Directors of Pharmacy to consider accountability. For benchmarking an existing service(s). For continuous quality improvement and innovation of new services.
Structure	
Standards grouped in two sections; Acute (services)—11 standards; General Support (services)—12 standards	Standards are grouped into domains and defined by dimensions and statements.
Standards are divided into two sets of components: basic standard requirements and advanced requirements	The domains are labeled one, two, and three but not named; one is about care; two is about medicines governance and safety; and three is about leadership, systems, and workforce.
Potential value and purpose of each standard are set out in a section entitled "Why it is important"	Domain one contains three standards with eight dimensions. Domain two contains two standards and nine dimensions Domain three contains three standards and nine dimensions
Each standard is supported by and audit template that arranged as—indicators; audit results; comments on action to be taken and verification of completion.	The standards are supported by a handbook.
Examples of standard operating procedures are set out in an appendix and the time taken to complete specific clinical tasks in different specialties is set out in another appendix.	Examples of practice and case studies are hosted in the RPS website.
A glossary is provided.	A glossary is provided.

In France in 2010, the Société Française de Pharmacie Clinique (La Société Française de Pharmacie Clinique, 2010) published an update of its framework describing the scope of practice of hospital pharmacists in seven chapters, including one on clinical pharmacy (**Table 3**). This chapter sets out three themes of practice: dispensing; role of the clinical pharmacist in therapeutics and in the optimization of the use of medicines including sterile medicinal products; involvement of pharmacy in the education, concerning therapeutics, of the patient. The four standards (critère) that are listed for the clinical pharmacist include those of

Table 2 Detailed comparison of the Northern Ireland and Royal Pharmaceutical Society Standards

Northern Ireland (Department of Health, 2013)		*Royal Pharmaceutical Society (Royal Pharmaceutical Society, 2017)*	
Acute		*Domain One*	
Standard	*Basic requirements*	*Standard*	*Element*
1. Medicine History Interview and Medicines Reconciliation	An accurate medicine history is obtained on admission to hospital.	1: Putting patients first Pharmacy services enable patients to be fully involved in their own care and to make shared decisions about their treatment and their medicines.	1.1 Patient focused services The principle of "no decision about me, without me" underpins the design and delivery of pharmacy services.
2. Medicine Therapy Monitoring (Pharmaceutical Care)	Pharmacists provide medicine therapy monitoring routinely to all patients. Where this is not possible, criteria shall exist to identify patients, who would benefit most from medicine therapy monitoring.		1.2 Information about medicines. Patients have access to information and support in order to make shared decisions about the use of medicines or the implications of choosing not to take them.
3. Prescription Monitoring and Review	Patients' prescription charts are monitored and reviewed in conjunction with the patient's medical notes and relevant medical laboratory results by a pharmacist at regular intervals.		1.3 Support with effective medicines use. Systems are in place to identify patients who may need support, or to allow patients to request support with medicines choice and use.
4. Prevention, detection, assessment, and management of adverse drug reactions	Pharmacists play an important role in the prevention, detection, assessment, management, and reporting ADRs. Emphasis should be on the prevention of ADRs and on the prevention of re-exposure in patients who have already experienced an ADR.	2: Episode of Care Patients' medicine requirements are regularly assessed and responded to in order to keep patients safe and to optimize their outcomes from medicines.	
5. Prevention, Assessment and Management of Drug Interactions	Pharmacists monitor for potential and existing drug interactions when monitoring and reviewing patient's medicine therapy.		2.1 At pre-admission, on admission or at first contact Patients' medicines are reviewed to ensure an accurate medication history, for clinical appropriateness and to identify patients in need of further pharmacy support.
6. Therapeutic Drug Monitoring	Pharmacists to optimize therapy for medicines where there is a known, close relationship between serum concentration and therapeutic effect and adverse effect use TDM.		2.2 Care of the patient Patients have their medicines reviewed by pharmacy team members who play an active role in the clinical management of patients. Patients can access the pharmacy expertise that they need to ensure that their medicines are clinically appropriate, and their outcomes from medicines are optimized.
7. Prevention, identification, management, and reporting of medication incidents	Pharmacists contribute to the prevention, identification, management, and reporting of medication incidents.		2.3 Patients' outcomes Patients' goals and outcomes from, and experiences of treatment with, medicines are documented, monitored, and optimized.
8. Multidisciplinary Working	Where appropriate the pharmacist shall attend ward rounds and clinical meetings as a member of the health-care team.	3: Integrated Transfer of Care Health and social care practitioners receive and share relevant information about the patient and their medicines when a patient transfers from one care setting to another.	

(*Continued*)

Table 2 Detailed comparison of the Northern Ireland and Royal Pharmaceutical Society Standards (*cont.*)

Northern Ireland (Department of Health, 2013)		*Royal Pharmaceutical Society (Royal Pharmaceutical Society, 2017)*	
Acute		*Domain One*	
Standard	*Basic requirements*	*Standard*	*Element*
9. Provision of Medicines Information Advice by Pharmacists	Pharmacists have a responsibility to provide appropriate, evidence-based timely information and advice on medicine-related matters to meet the requirements of health-care providers and patients and/ or their carers.		3.1 Patient needs Patients are given information about their medicines and have their expressed needs for information met.
10. Discharge	The pharmacist ensures that all medicines prescribed at discharge are clinically accurate and appropriate. The patient is dispensed a supply of their prescribed medicines and is provided with accurate, up-to-date information about their medicines. Accurate and up-to-date information of a patient's medicines at discharge is safely and effectively communicated to primary care health-care professionals.		3.2 Professional responsibilities Accurate and complete information about the patient's medicines is transferred to the health or social care professional(s) taking over care of the patient at the time of transfer. Arrangements are in place to ensure a safe supply of medicines for the patient and ongoing support where necessary.
11. Patient Medicine Education	Medicine education services shall be provided to patients or their carers where appropriate. If this is not possible categories of patients where maximal benefit is likely should be identified.		

General support	*Domain Two*
Standard	*Standard*
12. Continuing professional development	4. Medicines Governance
13. Resources	5. Efficient Supply of Medicines

General support	*Domain Three*
Standard	*Standard*
14. Staffing levels and structure	6.Leadership
15. Documentation	7. Systems Governance and Financial Management
16. Quality of clinical pharmacy services	8. Workforce
17. Health promotion	
18. Pharmacoeconomic evaluation of the use of medicines	
19. Pharmacist led clinics	
20. Supplementary and independent prescribing	
21. Communication	
22. Self-administration of medicines	
23. Reuse of patient's own medicines	

ADRs, Adverse drug reactions; *TDM*, therapeutic drug monitoring.

Table 3 French Society of Clinical Pharmacy, Standard of Hospital Pharmacy (La Société Française de Pharmacie Clinique, 2010)

Domain: Clinical Pharmacy and Therapeutic Patient Management	
Theme	*Standard*
Reference 5.1 Drug dispensing and traceability of health products	
	Criterion 5.1.1 Identify prescribers authorized to prescribe in the health facility
	Criterion 5.1.2 Analyze and validate prescriptions
	Criterion 5.1.3 Prepare and deliver drug doses
	Criterion 5.1.4 Inform the patient about their therapies and the proper use
	Criterion 5.1.5 Achieving traceability of health products managed by the PUI subject to specific regulations
Reference 5.2 Roles of the clinical pharmacist in the therapeutics and optimization of drug use and sterile medical devices	
	Criterion 5.2.1 To control therapeutic strategies and implement recommendations in the form of protocols
	Criterion 5.2.2 Know and understand patient data including clinical, biological and therapeutic
	Criterion 5.2.3 Know how to optimize drug therapies and sterile medical devices and integrate with équipes médicales et paramédicales
	Criterion 5.2.4 Propose protocols on the proper use of health products
Reference 5.3 Pharmaceutical involvement in therapeutic patient education (TPE)	
	Criterion 5.3.1 Acquire training in TPE
	Criterion 5.3.2 Be part of professionals involved in the TPE including drug therapies
	Criterion 5.3.3 Participate in the implementation of TPE programs

ensuring that the guidelines and protocols about the use of medicines are followed, as well as knowing and understanding the relevant data found in the patient's hospital charts and records. Some other aspects particularly relevant to clinical practice, such as risk management, are classed as systems-related roles. Similar to the NI Clinical Pharmacy Services Standards, the framework includes an explanation of the standard and suggestions for its implementation and evaluation. The authors and contributors and the methods used to prepare the document are clearly described.

Commentary on Practice in Europe

Many years ago, pharmacy was described as an incomplete profession (Denzin and Mettlin, 1968). In fact, all health-care professions are forced and seek to change as health care, technology, and society exert pressure on traditional practices and relationships (Henman, 2008). In pharmacy, these pressures are perhaps more acute. Hospital pharmacy has sought to define itself repeatedly over the last 40 years and since clinical pharmacy is most closely associated with hospital practice, that process of change has affected clinical pharmacy. As time has gone on, other ideas, such as pharmaceutical care (Hepler and Strand, 1990) and medicines optimization (National Institute for Health and Care Excellence, 2015), have been introduced and used in a number of ways in different European countries. This has changed the context and led to standards concerning clinical pharmacy being replaced or subsumed within other policy documents.

The International Pharmacy Federation (FIP) first published a description of hospital pharmacy in 2008 known as the Basel Statements but it was not until 2014 that the final version was approved and published (International Pharmacy Federation, 2015). The FIP statements do not mention clinical pharmacy, but instead, refer to "Influences on Prescribing" to group together some of the clinical activities of a hospital pharmacist (**Table 4**). In some European countries, the reception of the FIP Statements was one of muted approvals, and the representative body, the European Association of Hospital Pharmacists, set about creating a document to reflect its members' views (European Association of Hospital Pharmacy, 2018). This document entitles one section "Clinical Pharmacy Services" and it contains eight statements.

Comparison of the EAHP and FIP statements suggests that pharmacists globally are reluctant to use terms like clinical, whereas in Europe, this reluctance has been overcome. It can be argued that the differences between the two documents are structural and organizational, but equally, the EAHP statements on Clinical Pharmacy Services are patient-centered, whereas the first two of the FIP statements are about establishing formulary and participation in a drugs and therapeutics committee. Both documents clearly show not only the breadth of the scope of hospital pharmacy practice but also its highly structured and team-based nature. Although both documents are entitled, "statements," and set out to delineate the roles and responsibilities of hospital pharmacists, they are phrased as exhortations to pharmacists, and can be read as an agenda, a manifesto, which is undoubtedly one way in which they should be used.

EAHP have further developed their strategy regarding clinical pharmacy in three important initiatives:

- Support for the implementation of the statements is provided by the Statement Implementation Learning Collaborative Centres and a self-assessment tool (European Association of Hospital Pharmacy, 2018).
- They have adapted their annual hospital survey pharmacy to concentrate on selected aspects on a rotating basis, and so in the 2015–16 survey, clinical pharmacy was one of the themes (European Association of Hospital Pharmacy, Survey Results, 2016).

Table 4 Comparison of FIP (International Pharmacy Federation, 2015) and EAHP Hospital Pharmacy statements (European Association of Hospital Pharmacy, 2018)

FIP basel statements, n = *65*	*EAHP statements,* n = *44*
Headings Overarching and Governance Statements Theme 1: Procurement Theme 2: Influences on Prescribing Theme 3: Preparation and Delivery Theme 4: Administration Theme 5: Monitoring of medicines use Theme 6: Human Resources, training, and development	Theme/Section Headings 1. Introductory Statements and Governance 2. Selection, Procurement, and Distribution 3. Production and Compounding 4. Clinical Pharmacy Services 5. Patient Safety and Quality Assurance 6. Education and Research
Theme 2: Influences on prescribing statements	*4. Clinical pharmacy services statements*
24. Hospitals should utilize a medicine formulary system (local, regional, and/or national) linked to standard treatment guidelines, protocols, and treatment pathways based on the best available evidence. 25. Hospital pharmacists should be key members of pharmacy and therapeutics committees to oversee all medicines management policies and procedures, including those related to off-label use and investigational medicines. 26. Hospital pharmacists should have a key role in educating prescribers at all levels of training on the access to and evidence for responsible use of medicines, including the required monitoring parameters and subsequent prescribing adjustments. 27. Hospital pharmacists should be an integral part of the multidisciplinary team responsible for therapeutic decision-making in all patient care areas. 28. Hospital pharmacists should promote seamless care by contributing to the transfer of information about medicines whenever patients move between and within health care settings. 29. Appropriately trained and credentialed hospital pharmacists should participate in collaborative prescribing.	4.1 Hospital pharmacists should be involved in all patient care settings to prospectively influence collaborative, multidisciplinary therapeutic decision-making: they should play a full part in decision-making including advising, implementing, and monitoring medication changes in full partnership with patients, carers, and other health-care professionals. 4.2 All prescriptions should be reviewed and validated as soon as possible by a hospital pharmacist. Whenever the situation allows, this review should take place prior to the supply and administration of medicines. 4.3 Hospital pharmacists should have access to the patient's health record. Their clinical interventions should be documented in the health record and analyzed to inform quality improvement interventions. 4.4 All the medicines should be entered on the patient's medical record and reconciled by the hospital pharmacist on admission. Hospital pharmacists should assess the appropriateness of all patients' medicines, including herbal and dietary supplements. 4.5 Hospital pharmacists should promote seamless care by contributing to transfer of information about medicines whenever patients move between and within healthcare settings. 4.6 Hospital pharmacists, as an integral part of all patient care teams, should ensure that patients are offered information about their clinical management options, and especially about the use of their medicines, in terms they understand. 4.7 Hospital pharmacists should inform, educate, and advise patients, carers, and other health care professionals when medicines are used outside of their marketing authorization. 4.8 Clinical pharmacy services should continuously evolve to optimize patients' outcomes.

- In addition, EAHP has developed and published a competency document to support their proposal for a Common Training Framework in Europe (European Association of Hospital Pharmacy, 2018)—and one of this document's domains is, "Patient care and clinical competencies."

Both of these initiatives will support the development of clinical pharmacy in Europe and as each hospital, each region, and each country pursues its own strategies to improve the care of patients in hospitals, standards will be developed and utilized.

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Clinical Pharmacy Professional Standards in Low- and Middle-Income Countries

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Introduction

Clinical pharmacy is usually understood as referring to those services rendered by pharmacists which are directly involved with patient care. However, there is also a view that clinical services are those provided at the bedside, as opposed to in any other setting. Such a view would exclude services rendered in pharmacies as opposed to hospitals or other in-patient settings, such as long-term stay facilities or frail care facilities. That interpretation would seem overly restrictive. Another view holds that clinical services are those that are nondistributive in nature, sometimes referred to as cognitive services. However, while the practice of pharmacy cannot be equated only with the filling of prescriptions issued by an authorized prescriber, it is clear that the concept of pharmaceutical care would incorporate the provision of medicines, the distributive portion of what should be a comprehensive pharmaceutical service aimed at achieving desired patient outcomes. A final point of some debate is whether clinical pharmacy services can be delivered at the population as opposed to individual patient level. Many pharmacists are involved in medicines selection, in the development of clinical practice guidelines and in such fields as pharmacovigilance, pharmacoeconomics, and pharmacoepidemiology. Just as clinical epidemiology evolved as a clinical service offered at the population level, so public health pharmacy relies on the same set of clinical pharmacy skills that are employed in direct patient care.

Clinical Pharmacy in Low- and Middle-Income Countries

Although there are few hard data to support this claim, the extent of advanced clinical pharmacy services in many low- and middle-income countries (LMICs) is constrained by the shortage of skilled human resources. The 2017 International Pharmaceutical Federation (FIP) report entitled "Pharmacy at a glance" showed that the median pharmacist density, expressed as the number of pharmacists per 10,000 population based on a sample of 74 countries, was 5.09 (International Pharmaceutical Federation, 2017). However, the median density in high-income countries (7.61 per 10,000 population) was 12.6 times than that in low income countries (0.60 per 10,000 population). Across the 58 countries that provided data, 75% of actively practicing pharmacists worked in community pharmacies, 13% in hospital pharmacies and 12% elsewhere. The median density of hospital pharmacists was only 1.05 per 10,000 population, but was seven times higher in South-east Asian countries (2.74) than in Africa (0.40).

In 2018, the FIP published a report on pharmacy workforce, covering the period from 2006 to 2016 (International Pharmaceutical Federation, 2018). Over that time period, though mean global pharmacist density had increased from 6.63 to 7.36 per 10,000 population, that growth had not been equally spread across countries and regions. More than half of the total absolute global growth in pharmacist capacity had occurred in the World Health Organization's Eastern Mediterranean and European regions. Not surprisingly, growth in pharmacist capacity was lowest in low-income countries, and highest in high-income countries. The mean absolute change in capacity was only 0.24% in the African region, over the decade.

It is therefore reasonable to expect that the delivery of clinical pharmacy services would be limited in areas with an absolute lack of training pharmacy workforce, and especially of pharmacists with advanced clinical training.

Pharmacy Credentialing and Specialization

Statistical reports like those developed by FIP focus on the whole of the pharmacy workforce, which refers to the total of all registered pharmacist practitioners, pharmaceutical scientists, pharmacy technicians, and other pharmacy support workforce cadres, as well as preservice students/trainees, working in a diversity of settings with a diversity of scope of practice. While it is possible to differentiate between registered pharmacists and other cadres, it is more difficult to identify those within the pharmacist group who have specialized clinical training or formalized specialty status. Many countries still offer a Bachelor of

Pharmacy degree (usually of 4 years' duration) as the entry point into the professional register, perhaps preceded by completion of a preregistration "internship" and sometimes a preregistration examination. The gradual spread of the more clinically oriented PharmD degree or a clinically oriented Master of Pharmacy entry-level qualification has been seen to a greater extent in better resourced countries.

There are global attempts, though, to expand the number of clinically-trained pharmacists and pharmacy specialists, notably through the efforts of the Board of Pharmacy Specialties (https://www.bpsweb.org/). The BPS was established by the American Pharmacists Association (APhA) in 1976 and its mission is "to improve patient care and increase awareness of the need for BPS Board Certified Pharmacists as integral members of multidisciplinary healthcare teams through recognition and promotion of specialized training, knowledge, and skills in pharmacy and specialty board certification and recertification of pharmacists throughout the world". Importantly, the certification examination used by the BPS is now offered in sites outside of the USA, such as in Egypt and Saudi Arabia. The 2017 BPS Annual Report noted that while only 10% of US pharmacists were BPS-certified, there were over 4000 pharmacists in other countries that held this certification (Board of Pharmacy Specialties, 2017). At that point, there were probably about 2.8 million pharmacists registered to practise around the globe.

Professional Standards

Professional standards of practice can be issued by a wide variety of bodies. Legally enforceable standards may be issued by the body which is entrusted with registering pharmacists to practise. These structures are variably referred to as Pharmacy Councils, Boards, Orders or Chambers. What marks them apart from voluntary professional associations and societies is that they are created by statute and given regulatory powers, as well as the powers to discipline those who are registered. However, professional and learned societies may also be the source of professional standard, to which those who voluntarily belong to such groupings are expected to adhere. Such documents may be aspirational in nature, rather than prescriptive.

At a global level, the International Pharmaceutical Federation (FIP) issues periodic Statements of Policy (https://www.fip.org/statements) that may cover clinical pharmacy professional activities. Recent examples include the FIP Statement on "The role of pharmacists in reducing harm associated with drugs of abuse" (2018), on "Control of Antimicrobial Resistance" (2017), on "Strategic development of medicines information for the benefit of patients and users of medicines" (2017) and on "The Effective Utilization of Pharmacists in Improving Maternal, Newborn and Child Health" (2013). A particularly apposite example is the FIP Statement on "Collaborative Pharmacy Practice" (2010). FIP also issues Statements of Professional Standards, such as on "The Role of the Pharmacist in Encouraging Adherence to Long-term Treatments" (2003). FIP has also produced an over-arching document on "Codes of Ethics for Pharmacists" (2014). These Statements are, by their very nature, globally applicable, but aspirational and not legally enforceable.

In 2011, the FIP issued a set of Good Pharmacy Practice (GPP) standards jointly with the World Health Organization (WHO) (International Pharmaceutical Federation, 2011). The document states that "GPP is the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care". Importantly, the GPP standards stated that "it is essential that there be an established national framework of quality standards and guidelines."

An example of such a set of quality standards, developed and implemented as legally enforceable requirements, is the Good Pharmacy Practice standards issued by the South African Pharmacy Council and regularly updated (South African Pharmacy Council, 2010). **Table 1** shows some of the standards that are applicable to clinical services in this upper middle-income country. As the South African Pharmacy Council is a statutory body, with disciplinary powers, it has the legal ability to ensure compliance with the GPP standards and uses them in its inspectorate function.

Although many of the South African GPP standards are specific to the distributive functions of pharmacists, and provide the basic details of what is expected in terms of infrastructure and equipment, they also cover a range of nondistributive functions, as shown in the table. However, there is one glaring omission, and that relates to the stipulation of enforceable staffing norms for different types of pharmacies, at different levels of care.

FIP's Hospital Pharmacy Section has developed an aspirational set of statements that are intended to guide the development of hospital pharmacy practice is all settings. The updated 2016 version of the Basel Statements on the Future of Hospital Pharmacy form the basis for local efforts (Vermeulen et al., 2016). There is good evidence of how these Statements have been used to assess and then to advance hospital pharmacy practice is LMICs (Penm et al., 2014, 2015a, 2016). In addition, validated tools for assessing such services have been developed (Penm et al., 2012, 2015b). **Table 2** shows some of the updated Basel Statements that have particular relevance to clinical pharmacy practice, as numbered by the Hospital Pharmacy Section. Basel Statement #2 expressly calls for the development of both global and hospital practice standards.

With specific reference to hospital-based clinical pharmacy, the most widely cited national standards are probably those developed by the American Society of Health-System Pharmacists (ASHP; https://www.ashp.org/Pharmacy-Practice/Policy-Positions-and-Guidelines). The ASHP differentiates between policy positions ("short pronouncements on one aspect of practice"), statements ("express basic philosophy"), guidelines ("offer programmatic advice"), therapeutic position statements ("concise responses to specific therapeutic issues") and therapeutic guidelines ("thorough, evidence-based recommendations on drug use"). However, the ASHP emphasizes that the "use of ASHP's guidance documents by members and other practitioners is strictly voluntary". They state that "their content should be assessed and adapted based on independent judgment to meet the needs of local health-system settings". They can, therefore be used, with appropriate judgment and adaptation, in LMICs.

Table 1 Examples of South African Good Pharmacy Practice standards (2010)

GPP Statement	*Text*
1.2.13.1	Every pharmacy must have at least one type of area for the furnishing of information and advice. In cases where a pharmacy only has a semi-private area(s) at each point where dispensing of medicine to the patient or the patient's agent/caregiver occurs, there must in addition be access to another separate private room/area where communication can take place between a pharmacist and a patient or the patient's agent/caregiver in private.
2.8.2	Pharmacists and other persons registered with Council must (within their scope of practice) give advice and information to patients on how to use medicines safely and effectively to maximize therapeutic outcomes.
2.11.2	Ward pharmacy is a patient-orientated, decentralized service where the pharmacist becomes an integral and indispensable part of the professional health team of the hospital/institution: 1. Ward pharmacists must utilize their knowledge and skills of pharmaceutical sciences and product awareness to promote safety, efficacy and economy in the use of medicines; 2. ward pharmacists must offer advice to clinicians and nurses on appropriate medication to ensure that medicines are used correctly and in the appropriate therapeutic context
2.13	A pharmacy can offer services relating to screening and testing a patient's biochemical and physiological parameters. Pharmacists who are competent to do so may provide such screening and monitoring services.
2.14	Although the pharmacist's involvement with immunization varies with each practice setting, the pharmacist can be actively involved in the following activities: 1. educating the public and other health care professionals about immunization; 2. advocating pediatric immunization; 3. providing immunization for international travel; 4. screening patients who are at risk of preventable infectious diseases by occupation, life-style or an underlying disease state; 5. administering immunization agents; 6. recording immunization data; and 7. using the immunization database to generate reminder letters for booster doses.

Table 2 Examples of the FIP Hospital Pharmacy Section Basel Statements (2016)

Basel Statement	*Text*
2	At a global level, evidence-based hospital pharmacy practice standards should be developed. These should assist national efforts to define standards for the extent and scope of hospital pharmacy services and should include corresponding human resource and training requirements.
30	Hospital pharmacists should assume responsibility for storage, preparation, dispensing, and distribution of all medicines, including investigational medicines.
36	Hospital pharmacists should support the development of policies regarding the use of medicines brought into the hospital by patients, including the evaluation of appropriateness of complementary and alternative medicines.
41	Hospital pharmacists should ensure that clinically relevant allergies, drug interactions, contraindications, past adverse events, and other relevant medication history details are accurately recorded in a standard location in patient records and evaluated prior to medicine use.
54	Pharmacists' clinically relevant activities should be documented, collected, and analyzed to improve the quality and safety of medicine use and patient outcomes. Activities that significantly impact individual patient care should be documented in the patient record.
65	Postgraduate clinical courses should be developed to prepare hospital pharmacists for collaborative prescribing of medicines, including instruction in legal and professional accountability.

However, there is no publicly accessible indication of the extent to which this has occurred in any resource-constrained environments.

Many other national and regional structures in high-income countries have produced similar documents. An example are the European Association of Hospital Pharmacy Statements issued in 2014, for which a self-assessment tool has been developed (http://sat.eahp.eu/en/home) (Anon, 2014). The European Statements on Hospital Pharmacy are intended to be implemented in the countries from which the Association draws its membership, which are predominantly high-income countries. However, the membership does incorporate a number of transitional economies, such as those from the former East bloc (Bulgaria, Croatia, the Czech Republic, Estonia, The Former Yugoslav Republic of Macedonia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, and Slovenia) and Turkey. The implementation plan for the European Statements therefore has to take into account the needs of such settings, and their very different resource bases. The Association has appointed Statement Implementation Learning Collaborative Centres (SILCC), which include hospitals in various countries which are willing to train pharmacists, and has also undertaken to provide national member associations with small grants to help hospital pharmacists take advantage of such training opportunities.

Conclusion

Although there are global professional standards for the provision of clinical pharmacy services, these are not always translated into applicable and relevant documents that can be applied or even enforced at local levels, particularly in LMICs. However, these are not aimed at clinical pharmacy in its full depth and range, but are mostly specific to hospital pharmacy practice. Clinical pharmacy cannot be simply equated to hospital pharmacy. The severe lack of skilled pharmacy workforce makes the provision of acceptable, professional clinical pharmacy services in resource-constrained settings extremely difficult. However, there are aspirational and at times legally enforceable standards in such settings, as well as global support for their development.

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Clinical Pharmacy Professional Standards in United States of America and Canada

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Background

Professional standards set specific expectations of a profession or discipline and the members of that profession/discipline. Such standards are commonly used to guide professional development, competence, attitude, behavior, ethics, and performance. In the case of a health profession or discipline, professional standards are often applied to create goals and expectations for students, postgraduates in training, and licensed and/or credentialed members of the profession/discipline.

Although rooted in the standards of pharmacy and other health professions, clinical pharmacy's standards are largely based on the definition of clinical pharmacy. The first contemporary definitions of clinical pharmacy emerged in the late 1960s. In 1967, Paul F. Parker described clinical pharmacy as "a concept or philosophy emphasizing the safe and appropriate use of drugs in patients. It is achieved only by interacting responsibly for drugs with all of the health disciplines who are in any way concerned with drugs" (Parker, 1967). Shortly thereafter, the American Association of Colleges of Pharmacy Committee on Curriculum defined clinical pharmacy as "that area within the pharmacy curriculum which deals with patient care with emphasis on drug therapy. Clinical pharmacy seeks to develop a patient-oriented attitude" (Lemberger, 1968). Gloria Francke commented further on clinical pharmacy in a 1969 article, noting, "The practice of clinical pharmacy . . . utilizes [the pharmacist's] professional judgment based on his theoretical knowledge while working with the members of the health-care team to foster safe and appropriate use of drugs in patients" (Francke, 1969).

The founding documents of the American College of Clinical Pharmacy (ACCP) defined clinical pharmacy in 1979 as "a health science discipline that embodies the application, by pharmacists, of the scientific principles of pharmacology, toxicology, pharmacokinetics, and therapeutics to the care of patients." In the preface to the 2003 Encyclopedia of Clinical Pharmacy, Dipiro noted, "Clinical pharmacy incorporates the patient-oriented practices of pharmaceutical care as well as drug policy management, research, [and] education" (DiPiro, 2003). ACCP subsequently published the most comprehensive definition to date, including a description of clinical pharmacy as:

> " . . . a health discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; it blends a caring orientation with specialized therapeutic knowledge, experience, and judgment for the purpose of ensuring optimal patient outcomes. As a discipline, clinical pharmacy also has an obligation to contribute to the generation of new knowledge that advances health and quality of life" (ACCP, 2008).

Taken together, these definitions have been influential in the development of the US clinical pharmacy standards.

Table 1 ACCP Standards of practice for clinical pharmacists

I.	Qualifications
II.	Process of care
III.	Documentation
IV.	Collaborative, team-based practice and privileging
V.	Professional development and maintenance of competence
VI.	Professionalism and ethics
VII.	Research and scholarship
VIII.	Other responsibilities

Clinical Pharmacy Standards in the United States

ACCP published in 2014 the first set of comprehensive standards for clinical pharmacists (ACCP, 2014). The purpose of the standards is to define for the pharmacy profession, other health professionals, policy makers, payers, and the public what should be expected of clinical pharmacists (Table 1). In addition, they are intended to provide guidance to those engaged in developing and assessing clinical pharmacy educational curricula and training programs. Finally, the standards are designed to "set the bar" as clinical pharmacy practice, research, and education continue to grow and evolve around the world.

The Standards and Their Applications

Qualifications

Clinical pharmacists provide comprehensive medication management (CMM) (PCPCC, 2012) and related care for patients in all health care settings. They are licensed pharmacists with specialized advanced education and training who possess the clinical competencies necessary to practice in team-based, direct patient care environments (ACCP, 2008; Mitchell et al., 2012). Accredited residency training or equivalent post-licensure experience is required for entry into direct patient care practice. Board certification is also required once the clinical pharmacist meets the eligibility criteria specified by the Board of Pharmacy Specialties (BPS) (ACCP, 2013).

Process of Care

Patient care is coordinated among providers and across systems of care as patients transition in and out of various settings. The clinical pharmacist's process of care comprises the following components (Fig. 1).

- Assessment of the patient
- Evaluation of medication therapy
- Development and implementation of a plan of care
- Follow-up evaluation and medication monitoring (ACCP, 2014)

Documentation

Clinical pharmacists document directly in the patient's medical record medication-related assessments and plans of care to optimize patient outcomes. Documentation should be compliant with the accepted standards for documentation (and billing, where needed) within the health system, health care facility, outpatient practice, or pharmacy in which one works. Where applicable, existing institutional/organizational guidelines or requirements must be considered as they relate to the use of electronic health records (EHRs), health information technology and exchange systems, and e-prescribing.

The components of the encounter are essential to include in the documentation, which may be communicated in the form of a traditional SOAP (subjective data, objective data, assessment, and plan) note or other framework consistent with the standards of documentation within the practice setting. These include the medication history, the active problem list with an assessment of each problem, and the plan of care to optimize medication therapy and improve patient outcomes (ACCP, 2014).

Collaborative, Team-Based Practice, and Privileging

Clinical pharmacists work with other health professionals as members of the health care team to provide high-quality, coordinated, patient-centered care (Doherty and Crowley, 2013). They establish written collaborative drug therapy management agreements (CDTM) with individual physicians, medical groups, or health systems and/or hold formally granted clinical privileges from the medical staff or credentialing system of the organization in which they practice (ACCP, 2013). These privileging processes, together with the applicable state pharmacy practice act, confer certain authorities, responsibilities, and accountabilities to the clinical

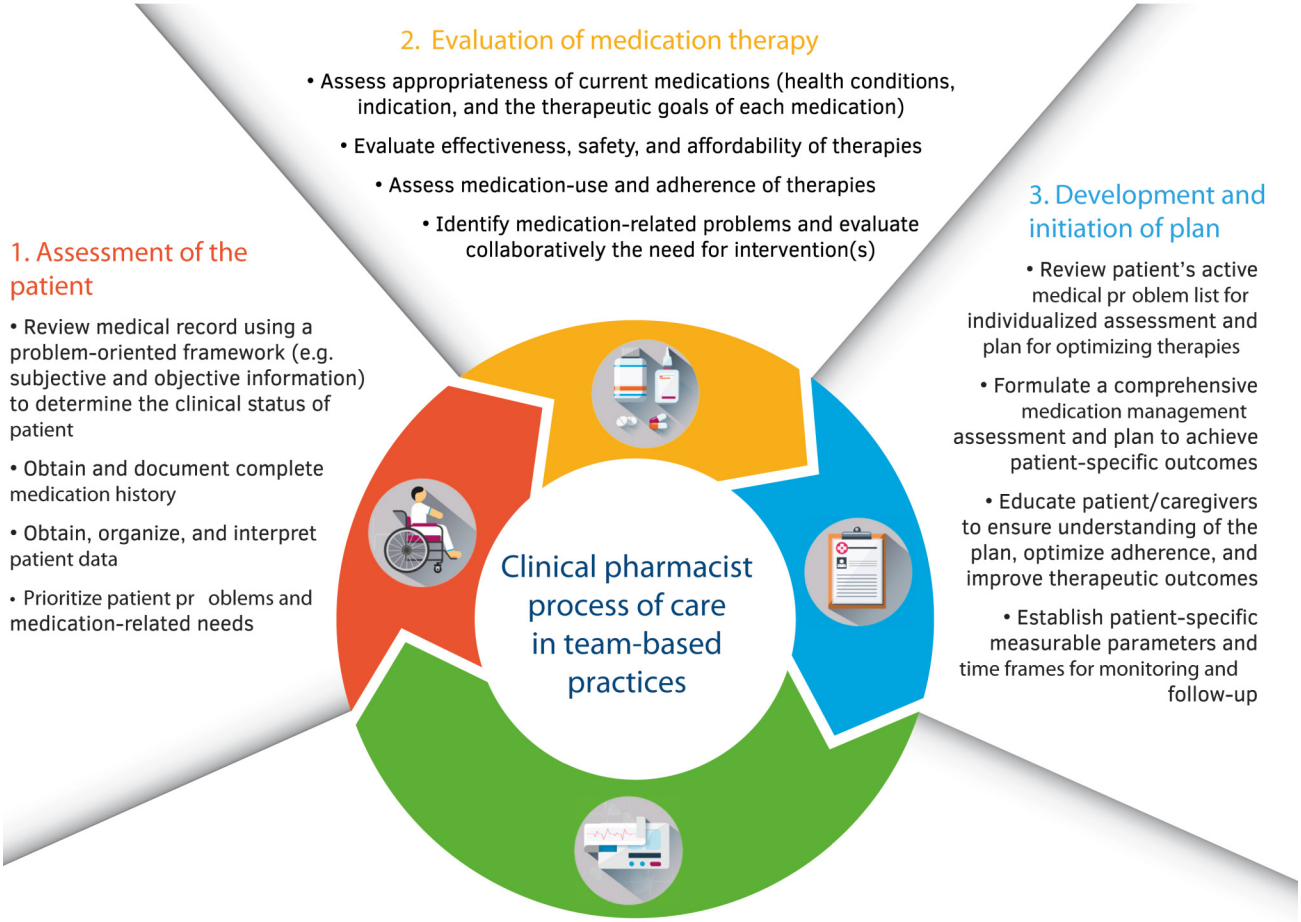

Figure 1 Clinical pharmacist process of care in team-based practices.

pharmacist as a member of the health care team and contribute to the enhanced efficiency and effectiveness of team-based care (ACCP, 2014).

Professional Development and Maintenance of Competence

Clinical pharmacists maintain competence in clinical problem-solving, judgment, and decision-making, communication and education, medical information evaluation and management, management of patient populations, and a broad range of therapeutic knowledge domains (Burke et al., 2008; Saseen et al., 2017). Clinical pharmacists maintain competency through:

- Certification and maintenance of certification in the appropriate specialty relevant to their practice, including those recognized by the BPS or other nationally recognized multiprofessional certifications;
- Consistent participation in continuing professional development (CPD) activities that enhance direct patient care practice abilities; and
- Maintenance of active licensure, including required continuing pharmacy education activities, through the appropriate state board(s) of pharmacy (ACCP, 2014).

Clinical pharmacists also pursue professional and career development by participating in activities that enhance research and scholarship, teaching, leadership, and/or management (ACCP, 2014).

Professionalism and Ethics

Clinical pharmacists have a covenantal, "fiducial" relationship with their patients. This relationship relies on the trust placed in the clinical pharmacist by the patient and the commitment of the clinical pharmacist to act in the best interest of individual patients and patient populations, within the context of legal and ethical parameters. Clinical pharmacists exhibit the traits of professionalism: responsibility, commitment to excellence, respect for others, honesty and integrity, and care and compassion (Roth and Zlatic, 2009). They subscribe to the pharmacy profession's code of ethics and adhere to all pharmacist-related legal and ethical standards (ACCP, 2014).

Research and Scholarship

Clinical pharmacists support and participate in research and scholarship to advance human health and health care by developing research questions; conducting or participating in clinical, translational, and health services research; contributing to the evolving literature in evidence-based pharmacotherapy; and/or disseminating and applying research findings that impact the quality of patient care (ACCP, 2014).

Other Responsibilities

Clinical pharmacists serve as direct patient care providers, but they may also serve as educators, researchers, clinical preceptors/mentors, administrators, managers, policy developers, and consultants. As the clinical pharmacy discipline grows, it must continue to familiarize more patients, families, caregivers, other health professionals, payers/insurers, health care administrators, students, and trainees with the full range of clinical pharmacists' responsibilities (ACCP, 2014).

Relevant Standards in Canada

Although Canada has not developed standards for clinical pharmacists, per se, they have issued several guiding documents that should inform clinical pharmacists and clinical pharmacy practice in Canada (**Table 2**). The National Association of Pharmacy

Table 2 Documents that set forth clinical pharmacy-related outcomes and indicators in Canada

Document	*Outcomes/indicators*
NAPRA/ANORP Model Standards of Practice (2009) [a]	• Expertise in medications and medication use • Collaboration • Safety and quality • Professionalism and ethics
AFPC[b] Educational Outcomes (2017)	• Care provider • Communicator • Collaborator • Leader–Manager • Health advocate • Scholar • Professional
CSHP[c] Key Performance Indicators for Inpatient Clinical Pharmacy Services (2015)	• Medication reconciliation on admission • Development of a pharmaceutical care plan • Resolution of drug therapy problems • Participation in interprofessional patient care rounds • Patient education during the hospital stay • Patient education at discharge • Medication reconciliation at discharge • Bundled patient care interventions
CPhA[d] Blueprint for Pharmacy (2015)	• Initiation of prescription drug therapy • Ordering and interpretation of laboratory tests • Medication review and assessment

[a]National Association of Pharmacy Regulatory Authorities and the Association des nationale organismes de réglementation de la pharmacie.
[b]Association of Faculties of Pharmacy of Canada.
[c]Canadian Society of Hospital Pharmacists.
[d]Canadian Pharmacists Association.

Regulatory Authorities (NAPRA) and the Association des nationale organismes de réglementation de la pharmacie (ANORP) have published the Model Standards of Practice (MSOP) for Canadian Pharmacists (NAPRA/ANORP, 2009). The MSOP are minimum standards of practice all pharmacists must meet. They are categorized into four domains:

- Expertise in medications and medication use
- Collaboration
- Safety and quality
- Professionalism and ethics

The MSOP include components that relate to emerging scope of practice activities but do not provide explicit standards of practice for clinical pharmacists.

The Association of Faculties of Pharmacy of Canada (AFPC) have recently updated the educational outcomes for first professional degree programs in pharmacy (AFPE, 2017). Identifying patient care as the core activity of the discipline of pharmacy prompted AFPE to make revisions in its most recent version of desired educational outcomes. These outcomes are intended to prepare graduates to fulfill a variety of roles beyond those to enter pharmacy practice in general, including those that are more clinically-focused. The AFPE educational outcomes are defined in terms of seven roles with associated key competencies:

- Care provider
- Communicator
- Collaborator
- Leader–Manager
- Health advocate
- Scholar
- Professional

The Canadian Society of Hospital Pharmacists (CSHP) has established, using an evidence-based, consensus-building process, eight key performance indicators for clinical pharmacy services provided to inpatients (Fernandes et al., 2015):

- Medication reconciliation on admission
- Development of a pharmaceutical care plan
- Resolution of drug therapy problems
- Participation in interprofessional patient care rounds
- Patient education during the hospital stay
- Patient education at discharge
- Medication reconciliation at discharge
- Bundled patient care interventions (provision of all seven of the foregoing services)

These performance indicators, particularly the "bundled intervention" indicator, are consistent with the ACCP standards' "process of care" component. However, the indicators are restricted to inpatient practice only.

The Canadian Pharmacists Association released in 2015 an update of progress in achieving its "Blueprint for Pharmacy" (CPhA, 2015), a long-term, multi-stakeholder effort designed to facilitate changes in Canadian pharmacy practice. Although the blueprint does not set standards of practice for clinical pharmacists, it provides a means of documenting the advancement across individual Canadian provinces of specific clinical services, including the initiation of prescription drug therapy, ordering and interpretation of laboratory tests, and medication review and assessment.

Extensions of the Standards

In addition to clinical pharmacy standards of practice, the discipline is shaped by other practice-related documents and resources that align with the standards. The ACCP standards have served as the foundation for development of clinical pharmacist competencies, evaluation, process of care, and scope of practice.

Clinical Pharmacist Competencies

The six ACCP core clinical pharmacist competencies apply to practitioners engaged in CMM in team-based, direct patient care environments. They are analogous to the competency expectations for practicing physicians (ACCP, 2013). Therefore, they align with the competencies embraced by the Accreditation Council for Graduate Medical Education (**Table 3**) (ACGME, 2017). Although the competencies of clinical pharmacists are similar to those of physician providers, clinical pharmacist competencies more aptly reflect a focus on pharmacotherapy and achieving optimal medication-related outcomes. These competencies are intended to ensure that a practitioner can provide CMM as outlined in the ACCP Standards of Practice (ACCP, 2014). The core competency domains are direct patient care; pharmacotherapy knowledge; systems-based care and population health; communication; professionalism; and continuing professional development. **Table 4** provides a detailed description of each domain. Clinical pharmacists may need to

Table 3 Comparison of physician and clinical pharmacist competencies in the United States (Saseen et al., 2017)

ACGME physician competencies	*ACCP clinical pharmacist competencies*
1. Patient care and procedural skills	1. Direct patient care
2. Medical knowledge	2. Pharmacotherapy knowledge
3. Systems-based practice	3. Systems-based care and population health
4. Interpersonal and communication skills	4. Communication
5. Professionalism	5. Professionalism
6. Practice-based learning and improvement	6. Continuing professional development

Table 4 Description of clinical pharmacist competencies.[a] (Saseen et al., 2017)

Competency domain	*Elements of the competency*[b]
Direct patient care	• Assess patients, including identifying and prioritizing patient problems and medication-related needs. • Evaluate drug therapy for appropriateness, effectiveness, safety, adherence, and affordability. • Develop/initiate therapeutic plans and address medication-related problems. • Follow up on and monitor the outcomes of therapeutic plans. • Collaborate with other members of the health care team to achieve optimal patient outcomes across the continuum of care. • Apply knowledge of the roles and responsibilities of other health care team members to patient care.
Pharmacotherapy knowledge	• Demonstrate and apply in-depth knowledge of pharmacology, pharmacotherapy, pathophysiology, and the clinical signs, symptoms, and natural history of diseases/disorders. • Locate, evaluate, and assimilate scientific/clinical evidence and other relevant information from the biomedical, clinical, epidemiological, and social-behavioral literature. • Use scientific/clinical evidence as the basis for therapeutic decision-making. • Possess the knowledge and experience commensurate with certification in one or more BPS specialties. • Enhance and maintain pharmacotherapy knowledge, including recertification or other appropriate methods of self-assessment and learning.
Systems-based care and population health	• Use health care delivery systems and health informatics to optimize the care of individual patients and patient populations. • Participate in identifying systems-based errors and implementing solutions. • Resolve medication-related problems to improve patient/population health and quality metrics. • Apply knowledge of pharmacoeconomics and risk-benefit analysis to patient-specific and/or population-based care. • Participate in developing processes to improve care transitions. • Design quality improvement processes to improve medication use.

Communication	• Communicate effectively with:
	  ◦ Patients, caregivers, families, and laypersons of diverse backgrounds.
	  ◦ Other health professionals and stakeholders.
	• Provide clear and concise consultations to other health professionals.
	• Develop professional written communications appropriate to the audience.
	• Use verbal communications tailored to varied clinical and patient-specific environments.
	• Communicate with appropriate levels of assertiveness, confidence, empathy, and respect.

Professionalism	• Uphold the highest standards of integrity and honesty. • Commit to a fiducial relationship with patients, always working in their best interests. • Serve as a credible role model/leader for students, trainees, and colleagues by exhibiting the values and behaviors of a professional. • Advance clinical pharmacy through professional stewardship, training of future clinical pharmacists, and active engagement in professional societies.
Continuing professional development	• Commit to excellence and lifelong learning. • Demonstrate skills of self-awareness, self-assessment, and self-development. • Continually identify and implement strategies for personal improvement through professional development. • Provide professional education to students, trainees, or other health professionals. • Maintain BPS certification to ensure that therapeutic knowledge is up-to-date.

[a]These competencies are necessary to provide CMM in team-based, direct patient care environments. Other competencies will be acquired as the clinical pharmacist progresses through his/her career and engages in additional professional activities.

[b]These elements help describe each competency but are not intended to be all-inclusive. Other related elements may apply, depending on the clinical pharmacist's practice setting and activities.

master additional areas of competence as they progress through their careers (e.g., leadership, research, or professional education). Therefore, it is not intended that the core competencies set forth all competencies that clinical pharmacists may acquire over time or that is needed to succeed in specific professional pursuits (Saseen et al., 2017).

Template for the Evaluation of the Clinical Pharmacist

The template serves as a tool to measure, evaluate, and document a clinical pharmacist's performance in any practice setting. It highlights the six core competency domains likely to be part of every clinical pharmacist's job description as listed in **Table 3**. For each domain, several tasks and examples of performance measures—including observations or reviews of clinical decisions or documentation based on encounters with patients, caregivers, families, laypersons, or other health professionals—can be found built into the template. For some tasks, a wide variety of assessments can be used to evaluate performance (Lee et al., 2017).

Those responsible for evaluating clinical pharmacists can modify the template and choose the type of assessment that best fits their institution and department. Clinical pharmacists may be evaluated by their supervisor, their peers, or other members of the health care team (e.g., physicians). Depending on the institution, the clinical pharmacist's peers may be appointed to a best practices, continuous quality improvement, or peer review committee (Haines et al., 2010). Each institution or organization will set its own criteria for success according to the clinical pharmacist's experience level, how long he or she has practiced within the department, and other factors. Finally, cut-points, as well as actions to take if the clinical pharmacist fails to meet the criteria for success, should be determined (Lee et al., 2017).

Although best practices for clinical pharmacists are highlighted in the template, each institution or organization can select the evaluable items within the domains that apply to the clinician's practice setting and the tasks most appropriate for the scope of clinical services provided. Similarly, some clinical pharmacists may also be responsible for conducting research, leading/managing others, or teaching. For these clinical pharmacists, other items (e.g., "optional tasks") may be added to the appropriate domains of the template (Lee et al., 2017).

Scope of Practice for Clinical Pharmacists

The first clinical pharmacist scope of practice document was released in 2016 (ACCP, 2016b). Although an individual professional's scope of practice is technically limited to that which state/provincial law or regulation allows based on specific education, experience, and demonstrated competency, this document provides additional information to facilitate a clearer understanding of clinical pharmacy practice by the public, health professionals, and policy-makers. It includes the following sections:

- Professional practice
- Education
- Accountability
- Responsibility

Comprehensive Medication Management in Team-Based Care

CMM is the foundational direct patient care practice of clinical pharmacists, provided in collaboration with other health care providers, to optimize each patient's medication experience and clinical outcomes. ACCP has published a guide that provides information about the practice, how it is structured and delivered, who is qualified to deliver it, and which patients it is likely to benefit most (ACCP, 2016a). This reference is intended for use by those employing or contemplating the incorporation of clinical pharmacists into team-based practice, designing and assessing clinical pharmacy education and training programs, and policy-makers seeking greater understanding of the practice of clinical pharmacists (ACCP, 2016a).

A variety of educational and training outcomes, objectives, and competencies have been articulated for pharmacists and/or clinical pharmacists, including, but not limited to the AACP CAPE Educational Outcomes (Medina et al., 2013); AACP Core Entrustable Professional Activities (EPAs) for New Pharmacy Graduates (Haines et al., 2017); and ASHP Residency Competency Areas, Goals, and Objectives (CAGOs) (ASHP, 2016). However, unlike the profession of medicine, there is limited alignment between pharmacy's professional degree outcomes, EPAs, residency CAGOs, and clinical pharmacist competencies. While great effort has been made by some to identify and articulate in detail the components that shape the discipline of clinical pharmacy, opportunities to more clearly align this work exist. The complementary nature of the clinical pharmacist standards of practice, competencies, and evaluation template, and the CMM guide, serves as an example of how such alignment can be developed.

The Future: Standards-Driven Professional Development

Establishing standards is an effective method for developing and advancing a discipline. The evolution of clinical pharmacy as the universally accepted core professional activity of the pharmacy profession remains in-progress. However, as the clinical pharmacy discipline continues to grow and mature across the globe, it is anticipated that clinical pharmacy standards will influence future national/international pharmacy practice guidelines or blueprints; standards for professional degree education; postgraduate

training competencies, goals, and objectives; credentialing and clinical privileging; research expectations; guidance for maintenance of competence; and codes of ethics and professionalism.

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Competency Standards for Clinical Pharmacists

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Introduction: Global Perspective

The United Nations (UN) Sustainable Development Goals (SDGs) are a universal call for action to, among others, ensure good health and well-being (SDG 3), which can be directly related to pharmacists, to their professional development and clinical expertise. One of the SDG 3 aims is to achieve universal health coverage, and provide access to safe and affordable medicines and vaccines for all (UN, 2015; WHO, 2015). Pharmacists have an important role, through the provision of medicine expertise, to support the achievement of this particular goal.

In the World Health Organization (WHO)—Global strategy on human resources for health: workforce 2030—published in 2016: the first objective 1 states "optimize performance, quality and impact of the health workforce (. . .)." WHO suggest as one of the policy options from countries to consider, is the adoption of transformative strategies toward scaling-up education supported by competency-based learning. There is a need for a coordinated approach linking human resources for health planning and education, to encourage inter-professional education and collaborative practice. Preparing healthcare professionals to work together as a team to effectively intervene on social determinants of health and expertise in public health is essential for better health outcomes (WHO, 2016). With a global shortage of healthcare workers undermining the delivery system in many countries, the critical effort to scale up training and education health workers demands vision, knowledge sharing, and tools to avoid common difficulties and to consider each training opportunity in the broader context of strengthening human resources for health (WHO, 2006, 2013; FIP, 2016a).

The International Pharmaceutical Federation (FIP), in supporting the implementation of the recommendations from the UN and WHO, has developed a roadmap for a needs-based pharmaceutical workforce transformation (FIP, 2017; Anderson et al., 2010, 2012). A globally shared vision was achieved—during the global conference on pharmacy and pharmaceutical education—so that pharmacists can accept responsibility and accountability for improving global health. The global conference aimed to address the education and developmental needs to create a competent pharmaceutical workforce, which included initial education and training for pharmacists and pharmaceutical scientists (FIP, 2017). One of the key outcomes of the conference is the Pharmaceutical Workforce Development Goals (PWDGs) that were created to activate and provide purpose to the other documents published (FIP, 2016b, 2016c, 2016d). The 13 PWDGs describe workforce development through education and the relevant one for this chapter is PWDG #5—Competency development, with the rational of the use of evidence-based developmental frameworks to support professional career development (FIP, 2016b).

As medications are getting more expensive, medication outcomes are less than desirable, and overall quality of healthcare is not at the standard desired. Healthcare needs to identify professionals to take the lead in improving the different parameters. Since pharmacy is the profession in all countries focused on medications, it is important to train and employ pharmacists that apply their knowledge, skills, and values toward direct patient care. Hence, clinical competent pharmacists improve health outcomes, minimize the risk associated with medicines use and ensure patient safety (Bond and Raehl, 2007; Jacknin et al., 2014). As an important professional within any healthcare system, it is essential to be competent and highly skilled, equipped with the knowledge and skills relevant for the health needs of the population (Austin, 2013; FIP, 2012b).

Competence and competencies are terms, which are increasingly accepted at a global level in healthcare and are being directly linked to professional roles. Competency-based approaches put professional practice at the core of education and practitioner development programs (Bates et al., 2004). Competency frameworks have become increasingly common due to the need for transparency in the training, development, and accreditation of healthcare professionals (Bates and Bruno, 2008). Published research demonstrates that when competency frameworks are used alongside standards of practice, it facilitates pharmacists' performance, promotes fitness to practice, supports the identification of knowledge gaps and learning needs, and promotes continuing professional development (CPD) —as they can form the foundation for educational and assessment tools, when designed according to educational outcomes (Mills et al., 2008; Coombes et al., 2010; Rutter et al., 2012; Stojkov et al., 2014; Meštrović et al., 2012).

Since competency is a complex construct, the authors have attempted to clarify concepts and to provide examples of the multifaceted information, by focusing on the following key questions:

What is competency?

What are the characteristics of competency?

How to develop competency standards or frameworks?

How to operationalize it?

Is there one that can be used as a guide?

What is the need for competency standards in clinical pharmacy practice?

How have other countries approached it?

The references, and examples provided will help the reader to navigate through this intricate topic and have the necessary resources and tools to further pursue a clinical pharmacy, or to design and implement competency standards or frameworks for clinical pharmacy.

For the purposes of this chapter, competency framework is defined as: a complete collection of competencies that are thought to be essential to performance; competencies: as the knowledge, skills, behaviors, and attitudes that an individual accumulates, develops, and acquires through education, training, and work experience; and competency: as a single item of knowledge, skill, behavior, and attitude.

What is Competency?

The concept of competence has been evolving from a concept representing knowledge to a more complex model, which includes expertise and the application of the knowledge, behavior, and skills to be able to perform in the workplace (Miller, 1990). There are diverse definitions of competency, theoretical views and ultimate objectives of defining competencies. Govaerts (2008) proposes that "*competency is the (individual) ability to make deliberate choices from a repertoire of behaviours for handling situations and tasks in specific contexts of professional practice, by using and integrating knowledge, skills, judgment, attitudes and personal values, in accordance with professional role and responsibilities*." The author adds that it should be contingent on task behavior, outcomes and the justification of the choice made, with reflection on the performance given (Govaerts, 2008).

In healthcare, a professional's competence is an evident expectation, but in reality, evidence shows that the level of professional competence is not always what it should be. The competencies expected to ensure skillful performance, in a certain work environment need to be clearly identified in order to ensure a proper assessment of competence. Healthcare professionals, patients, and society systematically redefine the quality of care expected to be delivered and make increased demands on "competencies" (McRobbie et al., 2001; Wass et al., 2001).

There is always some confusion attached to the term "competency" which poses challenges in reaching a consensus and creates the need to clarify what constitutes competence. However, there is no doubt that knowledge, skills, attitudes, and values are intrinsic to competence and competency development. Confusion will remain if there is no agreement on the motives for using the concept, whether it is competency versus a goal, an objective, or even an outcome. It should not be a list containing a summary stating what needs to be learned or checklists. It is important to reach an agreement on what is meant by competence and, more importantly, how it can be measured leading to a better understanding of professional practice (Bruno et al., 2010).

The advancement of medical knowledge in recent years has pushed education toward a competency-based approach, not only in pharmacy but also in medicine education as well. Documents and training modules in medical education frequently refer to concepts of competency (Ward et al., 2001). Competency-based approaches, then, put professional practice at the core of education and competence development programs, preparing students for the profession.

The use of the term "competency-based criteria" emphasizes the importance of competencies and diverts attention away from other critical factors. Criteria processes have drifted toward a primary focus on competencies. Many sophisticated criteria processes now assess only competencies. However, a thorough assessment of performance must at least take account of how well a practitioner completes work-relevant activities. For many organizations, improved selection criteria will be achieved if greater attention is given to using selection exercises and processes that are better matched to the job and by investing more time and effort into the training of assessors. Appropriate selection criteria are crucial for a good competency framework (Whiddett and Hollyforde, 2003).

Despite rapid changes in the work environment and advances in technology, it is possible to define with exact terms professional competence concerning attributes, such as knowledge, skills, and attitudes, which must be acquired. Healthcare providers should be able to adapt to changes by taking on new roles within their field as lifelong learners (FIP, 2014).

What are the Characteristics of Competency?

Confusion will remain if it is not agreed on the motives for using the concept and the number of definitions of competency will continue to grow. It should not be a list containing a summary stating what needs to be learned. It is important to reach an agreement on what it is meant by competence and, more importantly, how can it be measured (Whitcomb, 2002).

A contemporary definition of competence includes knowledge, skills-based and behavioral attributes and professional values. Competency is "a single item of knowledge, skill, behavior, and attitude" and relates to specific capabilities from these domains: competence is the full repertoire of competencies; performance is what the individual does rather than what they can potentially do; and effectiveness is the "bottom line"—the effect of the performance on the recipient (**Table 1**). This definition leads to the concept of behavioral competencies: a typical behavior observed when effective performers apply motives, traits, skills, etc. to a relevant task (Whiddett and Hollyforde, 2003).

Miller's pyramid describes competence as the ability to "do the job" and is a key area to be assessed in clinical practice, although this only applies when it is the combination of task orientated competence and the behaviorally related competencies that are required to deliver quality care (**Fig. 1**).

Competencies are not simply a list of characteristics such as motives, traits, or skills—for example, the ability to clearly communicate or prefer rewards to be based on results. Competencies provide examples of what would be seen when people use these characteristics effectively. Competencies help to assess how people combine and use knowledge, abilities, motives, etc., when tackling job tasks, rather than simply measuring knowledge, abilities, or motives in isolation.

Looking holistically, all the concepts directly contribute toward the development within an individual of effective and sustained performance (Mills et al., 2005; Obiols et al., 2007). Competence per se is about the overarching capacity of a person to perform. Competence can be a complex construct but it should provide a practical and realistic framework for individual practitioner development. There is a growing suggestion that a competency-based approach is sensible and sustainable for pharmaceutical workforce development (FIP, 2016a, 2016b).

It is an attractive concept as it can be measured and evaluated—not always easily—but it can be done. We are more than the sum of our competencies, but being competent is definitely on the route-march toward effective performance (Armitage and Raza, 2008). Simply knowing what should be done in certain circumstances does not translate into greater competence. To be a competent

Table 1 Key differences between competency and competence

	Competency	*Competence*
Focus	The person	The job/role
Outline	Behaviors observed in effective people	Related tasks in the job/roles
Performance indicators	Behavioral statements	Outputs from the job, task, or role

(Modified from Whiddett, S., Hollyforde, S., 2003. A Practical Guide to Competencies—How to Enhance Individual and Organisational Performance, second ed. Chartered Institute of Personnel and Development, New York.)

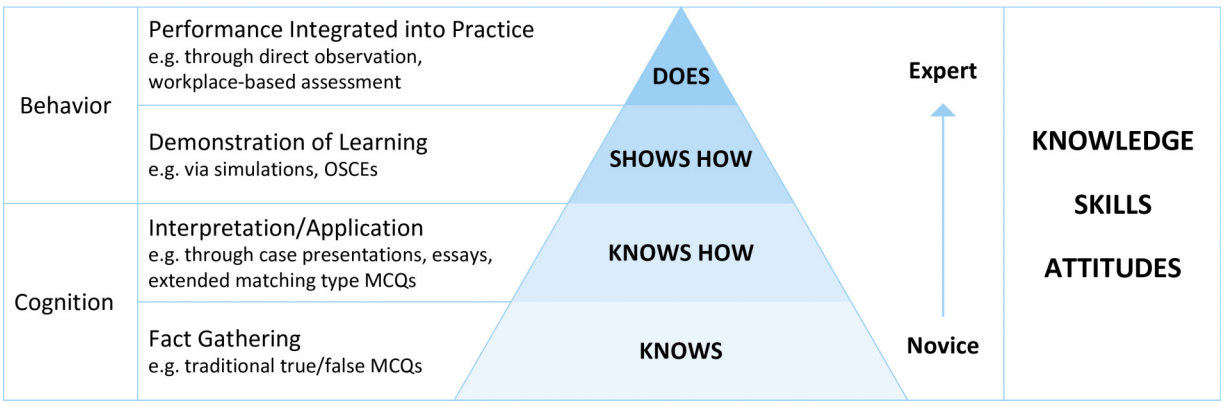

Figure 1 Miller's pyramid for assessing clinical competence. (*Modified from Miller, G.E., 1990. The assessment of clinical skills/competence/performance. J. Acad. Med. 65, 563–567.*)

practitioner, regardless of the profession, experience and reflection on the practice performed is required. The opposite side of competence is ineffectiveness (Bates and Bruno, 2008).

How to Develop Competency Standards or Frameworks?

The purposes of competency frameworks are diverse. Some look for descriptions of a hierarchy based on diverse competency thresholds, whereas others are more determining in nature and aim to promote pharmacists' competencies over time (Bates et al., 2004; Meadows et al., 2004; Mills et al., 2005, 2008; Obiols et al., 2007; Coombes et al., 2010). According to Whiddett and Hollyforde, a competency framework is a collection of competencies fundamental for valuable performance. These types of frameworks are normally used in training and development and as a means by which to measure fitness for purpose. The behavioral indicators are the basis for the framework. The closely related behaviors are organized into competencies and similar competencies are grouped into clusters.

A "competency framework" is the term given to the complete compilation of clusters, competencies (with or without levels), and behavioral indicators. Large, complex, and detailed frameworks are explicit about what is required for all applications and all roles. However, such frameworks run the risk of being impractical because they have to describe behavior in great detail and often cannot cater for minor variations between similar jobs. This detail also means that such frameworks can quickly become out of date (Whiddett and Hollyforde, 2003). Competency frameworks should be designed to help enhance individual performance. They should not compensate for poor practice. The behaviors within a competency framework should be the behaviors necessary for effective performance.

Miller's pyramid of competence is a simple conceptual model, which outlines the goal of valid development of competence by testing what the practitioner actually "does" in the working environment (**Fig. 1**). Traditionally, learning assessments have focused on what a practitioner "knows" or "knows how." However, the real challenge lies in the assessment of performance when completing tasks, i.e., competence in practice and how the practitioner performs in real situations (Miller, 1990).

The current impetus for developing competency frameworks in pharmacy is being driven by the different pharmaceutical sectors, often by using external consultants, and with limited scope for integration. The risk is that competencies that should be regarded as generic attributes may be described differently, leading to confusion and fragmentation. Any failure to ensure the appropriate generalization of competencies across the pharmaceutical advanced areas and sectors also has the potential to limit individual development.

To facilitate the development of the practitioner, workplace-based assessment is of importance, which should be conducted by a mentor or supervisor with appropriate tools. The role of a mentor or supervisor is to support the practitioner's development in the workplace without being connected with the assessment tools or directly managing their performance. The mentor can identify the appropriate level of his mentee regarding the overall performance, provide feedback on how development is progressing and also be a role model. There should be a mentoring program for the mentor or supervisor providing the mentorship, in order to become fully effective developmental organizational structure (Coombes et al., 2010).

Competency frameworks can be used to support a range of different professional activities. Normally, they are used to assist with training and development, by helping individuals and managers define gaps in skills and knowledge against accepted standards of practice, and to help identify specific training and development needs (RPS, 2013, 2014; PSA, 2016).

How to Operationalize it?

To be able to operationalize any competency framework in practice, a set of tools has to be developed in concurrence with the framework itself. These tools provide formative assessments, which inform educational planning, identify areas for development, and monitor performance. The developed framework needs to have an assessment grid, in which the practitioner and the observational practitioner can match the criteria against the practice. As mentioned before, other tools can be used to support the overall evaluation, such as mini-peer assessment tools (mini-PAT), a mini-clinical evaluation exercises (mini-CEX), multiple choice questions (MCQs), objective structured clinical examinations (OSCEs), and case based discussions (CbD) (CoDEG, 2007; QH, 2009). A portfolio based on a competency framework and associated assessment tools can be used to demonstrate a practitioner's capability at work, providing a platform for further development (RPS, 2014; PSA, 2016).

For a competency framework to be effective it must be usable and fit for its intended purpose. It should be clear and easy to understand, be relevant, take into account expected future changes, contain behavioral indicators that do not overlap, contain behaviors that are necessary and appropriate, and be fair.

Items for an effective competency framework

For a competency framework to be effective it must be usable and fit for its intended purpose. To be fit it should at least conform to certain quality standards, such as:

Clear and easy to understand;

Relevant to all people who will be affected by the framework;

Takes account of expected changes (versatility);
Has discrete elements (e.g., behavioral indicators do not overlap);
Elements should be of the same type;
Behaviors should be necessary and appropriate;
Fair to all affected by its use.

These standards provide a good base for evaluating and testing a framework, during and after it is finished. The language used in the framework has to be relevant to all of those who will be using it, whether the framework is generic or specific. The basic building-blocks of competencies are behaviors; all aspects therefore should be behavior-based (Whiddett and Hollyforde, 2003).

(*Modified from Whiddett, S., Hollyforde, S., 2003. A Practical Guide to Competencies—How to Enhance Individual and Organisational Performance, second ed. Chartered Institute of Personnel and Development, New York.*)

Therefore, a global competency framework has an important role in the international setting. Aiding in the creation of practitioner developmental frameworks and associated evaluation tools, should be able to meet the needs of any country. It supports pharmacist development and leads to better overall workforce performance, and thus better patient care outcomes.

Is There One That Can Be Used as a Guide?

The FIP Global Competency Framework (GbCF) for services provided by pharmacy workforce was developed based on documents that were closely related to education development frameworks for pharmacists. The GbCF regards the foundation of initial education and training and its intention is to act as a mapping tool or guidance. In the document, competencies are described using behavioral terminology, and should not be viewed as a functional "task list." The competencies that are based on behaviors are useful for developmental purposes, which are the primary intention of the GbCF. Due to the nature of the ever-evolving healthcare, it will continue to be developed as the profession changes (FIP, 2012a).

The GbCF v1 was developed through a robust research process with a literature search, content analysis consensus groups and global surveys (Bruno, 2011). Documents focused on educational development frameworks for pharmacists were used, originated from Australia, Canada, New Zealand, Thailand, United Kingdom, United States, and Zambia. Common behaviors within the different frameworks were identified, resulting in a comprehensive table of competencies categorized into four domains: Pharmaceutical Public Health, Pharmaceutical Care, Organization and Management, and Professional/Personal (**Fig. 2**). Clinical competencies can be found in two of the framework domains, in the Pharmaceutical Public Health Competencies domain (includes behaviors such as, "*advise on health promotion and disease prevention and control, and healthy lifestyle*", and all the behaviors included in the medicines information competency) and in the Pharmaceutical Care Competencies domain (includes behaviors such as, "*ensure appropriate medicines, route, time, dose, documentation, action, form and response for individual patients*" among several others).

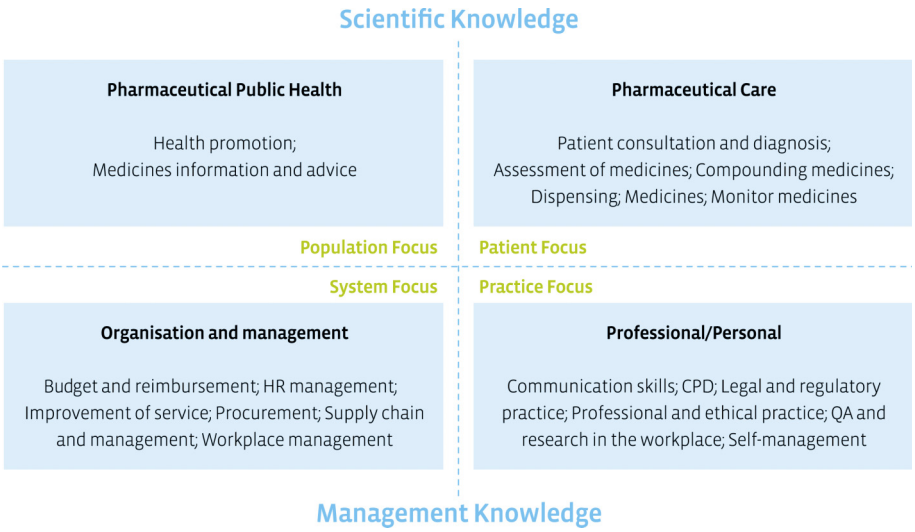

Figure 2 Domains and illustrative competencies from the GbCF v1 for pharmaceutical services. (*Reproduced with permission from International Pharmaceutical Federation (FIP) Education Initiatives (FIPEd), 2012b. A Global Competency Framework for Services Provided by Pharmacy Workforce. FIP, The Hague, Netherlands. Available from: http://www.fip.org/files/fip/PharmacyEducation/GbCF/GbCF_v1_online_A4.pdf (Accessed 31 March 2018).*)

Fig. 2 illustrates—as a visual concept—the GbCF division into clusters and competencies, allowing the reader to comprehend the focus of each cluster as well as what type of knowledge is needed to achieve the competencies included in the clusters or domains (FIP, 2012a). The intention behind is to facilitate adaption into the needs of the countries or local settings that use the framework as a starting point. The European Association of Hospital Pharmacists has used the concept to provide an overview of the Common Training Framework (EAHP, 2017).

The framework was specifically designed to provide global guidance on the practice-based expectations of foundational pharmacy practice. Evidence suggests that even though some country-specific variations occur in pharmacy practice, there exists a set of practice-related competencies that are globally applicable for foundation practice development (PSI, 2013; FIP, 2016a). Published evidence from the field of medicine also has shown transnational applicability of the Canadian CanMEDS Physician Competency Framework to medical practice in Netherlands, Denmark, and Australia (Ringsted et al., 2006; Scheele et al., 2008; DHMA, 2014; RANZCP, 2012).

Since the GbCF development, it has been successfully used to design pre-service education and training curriculum in a number of countries (FIP, 2013; Udoh et al., 2018). It has also been used to develop country-specific foundational pharmacy frameworks in Ireland, the Pacific Island Countries, Croatia, Singapore, and Serbia (PSI, 2013; Mucalo et al., 2016; Brown et al., 2012; Stojkov et al., 2016; FIP, 2016a). There are recent developments in several other countries, but not yet published—Kuwait, Montenegro, Oman, Jordan, Turkey, Indonesia, Philippines, and Vietnam (to name a few). In the United States, there exists the 2013 Center for the Advancement of Pharmacy Education (CAPE) Education Outcomes that exist to assist faculty in guiding curricular development and the follow-up assessment of these outcomes (Medina et al., 2013). For Europe, there exists the European Pharmacy Competences Framework (EPCF). This provides competency profiles for community, hospital, and industrial pharmacists (Atkinson et al., 2016).

What is the Need for Competency Standards in Clinical Pharmacy Practice?

Clinical pharmacy has been defined by the American College of Clinical Pharmacy as the "discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, and disease prevention" (ACCP, 2018). While there are no universal specific activities that clinical pharmacists undertake on a routine basis, there are general functions that are incorporated into their daily functions based upon work area. In the inpatient (acute care) setting, pharmacists are responsible for ensuring an accurate medication list at intake, and that the patient is taking optimal medications throughout their admission. These recommended therapies which the patient is receiving needs to be based upon clinical evidence, cost-effectiveness, and appropriateness for their disease state and laboratory parameters (i.e., renal function).

Upon discharge, the clinical pharmacists ensure that their prescriptions are appropriate when they transition to the next level of service without issues. On the outpatient (ambulatory care) side, pharmacists are playing increasing roles in the management of patients. While the historical role has been medication dispensing, it is much more than that now. These services extend from counseling patients on their medications, administering immunizations, conducting baseline physical assessment skills, undertaking medication therapy management, and initiating, modifying, and discontinuing medications on a patient (i.e., prescribing).

Due to the need of the patient and the positive impact of these services, clinical pharmacy is becoming an essential service. The result of this is that there is a need to have training and education in all schools of pharmacy as well as practitioners providing these services in all healthcare settings. Even if schools of pharmacy trained students appropriately in this discipline, there is still a need for practicing pharmacists to continually update their skills because new medications are introduced regularly and research is being conducted and published frequently, which can alter treatment goals and recommendations. The methods vary that individuals utilize to stay current.

Some countries do not have a requirement for ongoing education that is tied to re-licensure. Other countries require a minimum number of educational hours to be documented, whereas some require the upkeep of a learning portfolio that documents all activities undertaken throughout the year. While it is ideal that a practicing pharmacist takes it upon themselves to be a lifelong learner outside of the requirement of the regulatory authority, this does not happen for all. There is also the responsibility of the employer to have assurances that their pharmacists are competent.

How Have Other Countries Approached it?

Australia

In 2016, Australia developed a national competency standards framework for pharmacists in Australia. These describe the skills, attitudes, and other attributes to practice as a pharmacist. This has five domains listed: 1. Professionalism and ethics; 2. Communication and collaboration; 3. Medicines management and patient care; 4. Leadership and management; and 5. Education and research. Domains 1, 2, and some standards from domain 4 are universally applicable to all pharmacists. While many of these directly relate to clinical pharmacy practice, deliver primary and preventative healthcare and promote and contribute to optimal use of medicines are the most directly connected (PSA, 2016).

Canada

Canada published in 2014 the professional competencies to enter practice. There are nine that have been identified. These include ethical, legal, and professional responsibilities; patient care; product distribution; practice setting; health promotion; knowledge and research application; communication and education; intra- and inter-professional collaboration; and quality and safety. While all of these could be linked to clinical pharmacy, the patient care domain is most closely identified based upon daily responsibilities. This is described as "pharmacists, in partnership with the patient and in collaboration with other health professionals, meet the patient's health and drug-related needs to achieve patient's health goals" (NAPRA, 2014).

Ireland

The competency framework developed the Pharmaceutical Society of Ireland, aims to inform the educational standards, curriculum development, and learning outcomes for undergraduate students. It will also support the implementation of CPD that will aid pharmacists to enhance their practice. The framework was based on the FIP GbCF, one of the first countries to use it as a mapping tool through a number of sequential steps, to tailor to the Irish pharmacy setting. The core competency framework contains the following domains: professional practice, personal skills, supply of medicines, safe and rational use of medicines, public health, and organization and management skills. For Ireland, the framework will provide a useful benchmark for patients, other healthcare professionals, policy-makers and others of the key skills, knowledge, attitudes, and behaviors associated with and expected of pharmacists (PSI, 2013).

New Zealand

In the case of New Zealand, the Pharmaceutical Council of New Zealand, published the 2015 version of the standards that builds on past efforts, with several competencies re-grouped into domains of responsibility as well as new competencies have been added to ensure that standards remain relevant and applicable to evolving roles. It is important to revisit the competency standards and frameworks to make sure they are still relevant and valid for their purpose. Competence standards can also demonstrate to the public and other healthcare professionals the medication expertise that pharmacists bring to patient care, and the role they play in ensuring the safe and responsible use of medicines. The domains in the standards are divided into mandatory and optional. In the mandatory domains, it includes professionalism in pharmacy and communication and collaboration; as optional domains, there are health and medicines management, public healthcare, supply and administration of medicines, and leadership and organizational management (PCNZ, 2015).

United Kingdom

In the United Kingdom, through the Royal Pharmaceutical Society, has a series of competency frameworks. One that is used for the start of practice is called the Foundation Pharmacy Framework, as it focuses on the building blocks needed to start developing competencies (RPS, 2014). The next one in the series is for advanced pharmacy (RPS, 2013). This is to represent all sectors of practice and can form the basis of the professional portfolio. Six key areas have been identified to evaluate advanced stages of practice: expert professional practice; collaborative working relationships; leadership; management; education, training, and development; and research and evaluation (RPS, 2013). The Royal Pharmaceutical Society has also developed a competency framework for prescribers (RPS, 2016). This organizes the framework into two sections: the consultation and prescribing governance. The consultation, having six competencies, is focused on assessing the patient, consider the options, reach a shared decision, prescribe, provide information, and monitor and review, while the prescribing governance, having four competencies, is divided into prescribe safely, prescribe professionally, improve prescribing practice, prescribe as part of a team (RPS, 2016). While this area is not usually identified as a need for pharmacists since so few practices in this setting, pharmacists in the United Kingdom have been granted authority to do so. However, this framework is broader than just pharmacists as it is to be used for all prescribers.

United States

The Joint Commission, a healthcare accrediting body in the United States, requires an institution to ensure that the employee is competent to undertake the function in which they are employed. They specifically state that documentation should exist "in the personnel file that the employee's clinical knowledge, experience, and capabilities are appropriate for assigned duties per the requirements of the minimum data set for competency" (JC, 2017). To complete this function fully, one must determine what the needed competencies a clinical pharmacist should have for their job responsibility, a plan in place to accomplish them, and a method for documenting achievement. For example, some of the routine activities of the clinical pharmacist are anticoagulation management, antimicrobial stewardship, pharmacokinetic dosing, cardiopulmonary resuscitation, and medication counseling. Mastery of these functions and ongoing education to ensure this skill needs to be included in the personnel file for each employee that is engaged.

Recently, the American College of Clinical Pharmacy updated its competencies of a clinical pharmacist. These are provided to ensure that "clinical pharmacists possess the knowledge, skills, attitudes, and behaviors" in order to provide clinical pharmacy in the

patient care setting. They provided six different competency domains in which one should document their expertise: direct patient care, pharmacotherapy knowledge, systems-based care and population health, communication, professionalism, and CPD. These competency domains are consistent with those expected by physicians within the United States, as recommended by the Accreditation Council for Graduate Medical Education (Saseen et al., 2017).

Implement overview—US case studies

While it is important to discuss and describe which competencies are necessary as a clinical pharmacist, it is critical to implement a process to accomplish it within an organization. The following are highlights of three case studies that have implemented different programs for competency achievement and documentation within their institution. These are three case studies, all within hospitals in the United States, to demonstrate different methods to achieve it.

- *Ohio State University Wexner Medical Center:* All pharmacists that are involved in direct patient care, both in the acute and ambulatory care setting, are required to be credentialed and privileged for those roles. This process is managed by a pharmacy leader, but the rules governing the medical staff are followed and it is overseen by the hospital's credentialing department. They developed core privileges that would cover all clinical pharmacist activities, no matter the location. Peer review occurs to ensure that the pharmacist functions appropriately and maintains required competencies (Jordan et al., 2016).
- *Johns Hopkins Hospital:* They desired to enter into collaborative practice agreements (drug therapy management agreements) with their clinical pharmacists and their respective physician groups. These clinical pharmacists that desire this privilege must obtain them through the respective medical department in which they function. The protocols, which guide these activities and are subsequently reviewed by the Pharmacy and Therapeutics Committee, and their competencies are documented and evaluated by the medical departments (Jordan et al., 2016).
- *University of Wisconsin Health:* This organization undertook a departmental approach to require certification for all pharmacists in direct patient care roles. The certification required, for most individuals, were those awarded by the Board of Pharmacy Specialties. The department, because of this requirement, will pay for the expense for the individual to take the exam. The expectation is to be completed by 2018 for all pharmacists in direct patient care to obtain this credential to demonstrate their competency to provide this role (Hager et al., 2017).

Conclusion

Since pharmacy is a clinical profession, it needs to demonstrate to both society and other healthcare providers that it is competent to manage a patient's medication therapies. This begins with identifying what competencies one wants to require of a clinical pharmacist, and then develop a process to document and maintain competency.

To achieve a high-quality infrastructure for pharmacy, the educational system should be mapped to the required competencies of pharmacists to provide the relevant pharmaceutical services for meeting the health needs in any given country context. While no one national model may be appropriate for all systems, there are significant global health drivers that suggest that a competency-based approach is sensible and sustainable for the pharmaceutical workforce development.

To conclude, the global changing healthcare milieus with ageing populations have resulted in increased prevalence of chronic diseases and associated comorbidities. This mandates complex care services. The availability of a competent pharmaceutical workforce, capable of providing complex evidence-based medicines expertise and pharmaceutical care services is fundamental.

Glossary

Clinical pharmacy: Discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, and disease prevention.

Source: American College of Clinical Pharmacy (ACCP), 2018. Definition of Clinical Pharmacy. Available from: https://www.accp.com/stunet/compass/definition.aspx.

Competency: A single item of knowledge, skill, behavior, and attitude.

Source: Bruno, A., 2011. The Feasibility, Development and Validation of a Global Competency Framework for Pharmacy Education (Thesis for Doctor of Philosophy). University College London (UCL), School of Pharmacy, London.

Competency framework: A complete collection of competencies that are thought to be essential to performance.

Source: International Pharmaceutical Federation (FIP) Education Initiatives (FIP*Ed*), 2012a. A Global Competency Framework for Services Provided by Pharmacy Workforce. FIP, The Hague, Netherlands. Available from: http://www.fip.org/files/fip/PharmacyEducation/GbCF/GbCF_v1_online_A4.pdf.

Competencies: Knowledge, skills, behaviors, and attitudes that an individual accumulates, develops, and acquires through education, training, and work experience.

Source: International Pharmaceutical Federation (FIP) Education Initiatives (FIP*Ed*), 2012a. A Global Competency Framework for Services Provided by Pharmacy Workforce. FIP, The Hague, Netherlands. Available from: http://www.fip.org/files/fip/PharmacyEducation/GbCF/GbCF_v1_online_A4.pdf.

Continuing professional development (CPD): The responsibility of individual pharmacists for systematic maintenance, development, and broadening of knowledge, skills, and attitudes, to ensure continuing competence as a professional throughout their careers.

Source: International Pharmaceutical Federation (FIP) Education Initiatives (FIP*Ed*), 2012a. A Global Competency Framework for Services Provided by Pharmacy Workforce. FIP, The Hague, Netherlands. Available from: http://www.fip.org/files/fip/PharmacyEducation/GbCF/GbCF_v1_online_A4.pdf.

Performance: An effective and persistent observable behavior. What an individual actually does as opposed to what they can do.

Source: International Pharmaceutical Federation (FIP) Education Initiatives (FIP*Ed*), 2012a. A Global Competency Framework for Services Provided by Pharmacy Workforce. FIP, The Hague, Netherlands. Available from: http://www.fip.org/files/fip/PharmacyEducation/GbCF/GbCF_v1_online_A4.pdf.

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Continuing Professional Development for Clinical Pharmacists

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Introduction

As defined by the International Pharmacy Federation and the World Health Organization, Good Pharmacy Practice is "the practice of pharmacy that responds to the needs of the people who use the pharmacists' services to provide optimal, evidence-based care" (International Pharmaceutical Federation, 2018). Essential to the provision of Good Pharmacy Practice is the ability of the pharmacist to optimally provide evidence-based care to his or her patients (Davidoff et al., 1995). Professional degree programs, including pre-service educational and training programs, prepare students to enter professional practice but are not sufficient for equipping pharmacists for a lifetime of practice given the rapidly changing nature of healthcare (Institute of Medicine, 2010a). The constant evolution of science, technology, and medicine requires that pharmacists continue to not only maintain the knowledge and skills learned during pre-service education and training but also build upon this foundation through the acquisition of new knowledge, skills, attitudes, and values following entry into practice. For example, knowledge pertaining to newly released medications and updated disease-state management guidelines must be learned as healthcare continues to evolve. Similarly, new skills needed to optimize care must be learned and mastered. Attitudes and values, including a commitment to change, that are appropriate to evolving roles and responsibilities of pharmacists must be demonstrated (Pereles et al., 1997; Mazmanian et al., 1997; Mazmanian and Mazmanian, 1999; Wakefield et al., 2003; Wakefield, 2004). Education must be lifelong as continued learning is essential for individual pharmacists to maintain the competence for practice in a rapidly changing and advancing healthcare environment (Institute of Medicine, 2010a).

Options for ensuring that practitioners maintain competence can include a wide variety of methods ranging from periodic re-examination of practicing pharmacists to mandatory completion of continuing education (CE) activities. To circumvent the need for pharmacists to partake in periodic re-examinations or other forms of direct assessment of competence or performance, many countries instead require pharmacists to engage in lifelong learning through participation in a minimum number of hours of CE activities in the hopes of ensuring competence for practice is maintained (Tran et al., 2014). An expanded and more holistic approach to lifelong learning has, however, now been adopted by some countries such as Canada, the United Kingdom, Australia, and New Zealand (Pharmacy Board of Australia, 2015; Pharmacy Council of New Zealand, 2010; Canadian Pharmacists Association, 2018; General Pharmaceutical Council, 2017). The Continuing Professional Development (CPD) model aims to ensure that participation in CE activities and other forms of structured or unstructured learning is ultimately translated into enhanced competence and application of the learning in practice. CPD has been defined as "a self-directed, ongoing, systematic and outcomes-focused approach to lifelong learning that is applied into practice" (Accreditation Council for Pharmacy Education, 2015). CPD provides a framework or model through which pharmacists can approach their lifelong learning. The CPD process is intended to ensure that pharmacists maintain competency to practice and that learning is based on actual needs or professional development goals (Rouse, 2004a).

Important aspects of the CPD model include:

The process is **self-directed** in that it is driven by the individual pharmacist;
The process is an ongoing **cycle** proceeding through stages of self-reflection, planning, learning, evaluation, and application;
The learning is **outcomes-focused** addressing the needs and goals of the individual pharmacist;

The learning outcomes are **applied** to the individual pharmacist's practice to achieve performance and practice improvements; and

All elements of the CPD process are **documented** to provide a written record of the pharmacist's professional development and support future learning (Accreditation Council for Pharmacy Education, 2015).

With CPD, the pharmacist is responsible for identifying and addressing their own professional development needs and goals through a self-assessment process. The CPD process is centered firmly on the needs of the individual practitioner and encourages a systematic and intentional approach for maintaining competence (Rouse, 2004a). The educational needs of each pharmacist will be unique depending on his or her current knowledge, skills, and abilities in relationship to the individual's practice environment, roles, and responsibilities. Self-reflection forms the foundation and starting point from which the CPD process is built, as development of personalized learning goals stems from the identification of the specific learning needs of the pharmacist. In this regard, the CPD process assists the pharmacist in ensuring he or she maintains the necessary knowledge, skills, attitudes, and values to competently practice pharmacy within the individual's specific practice setting throughout his or her career. Self-assessment should identify both strengths and limitations in addressing the needs of the healthcare system in which they practice.

Findings from the self-assessment process referred to above are used to identify competency gaps that are the basis of the pharmacist's learning needs or goals (hereinafter, just referred to as needs). Once learning needs have been identified, the next step is for the pharmacist to create and implement a personalized learning plan. To close the "learning loop," the pharmacist should evaluate whether the educational plan sufficiently addressed his or her learning needs. The learner must identify any barriers or challenges and evaluate the reasons for any shortfalls in achieving objectives, as this should serve to inform future learning plans and strategies. Documentation is an essential component of the CPD process. A portfolio system (either written or electronic) is often used to document the pharmacist's progress through different stages of the CPD cycle, including the application and impact of learning. Once the CPD cycle has been fully implemented and routinely practiced by the pharmacist, ideally he or she will progress through the CPD cycle seamlessly.

The CPD Cycle

Fig. 1 graphically depicts the stages of the CPD cycle (Accreditation Council for Pharmacy Education, 2014a). The different stages of the cycle are described in detail in the following sections. The "infinity" CPD cycle depicted in Fig. 1 with five sequential stages and "Record & Review" integral to all stages of learning was offered by the Accreditation Council for Pharmacy Education (ACPE) in the USA. It has been adopted in several countries but it differs from earlier depictions of the cycle, which typically only include the four sequential stages of the learning cycle, along with recording (the portfolio). The "infinity" cycle was designed to stress the importance of application of learning in the CPD model.

Reflect

Reflection is the starting point for self-directed learning and the CPD process (Accreditation Council for Pharmacy Education, 2014b). Reflection is the process of identifying the pharmacist's individualized learning needs and areas for improvement (Walsh, 2006). Consideration should be given to the pharmacist's current practice setting as he or she reflects on his or her current competence in the context of the typical healthcare needs of the patient population under his or her care, the goals of the healthcare organization, and his or her roles and responsibilities in the organization. Educational needs, including the need for either additional knowledge or new skills, required to enhance patient care, implement a new service, and expand the pharmacist's role as a member of the healthcare team should be identified. It is essential for pharmacists to be as specific as possible when identifying areas for improvement. Efforts to identify educational needs should involve a comprehensive analysis of the pharmacist's workplace environment. In this regard, input from peers and supervisors can prove valuable to the reflection process.

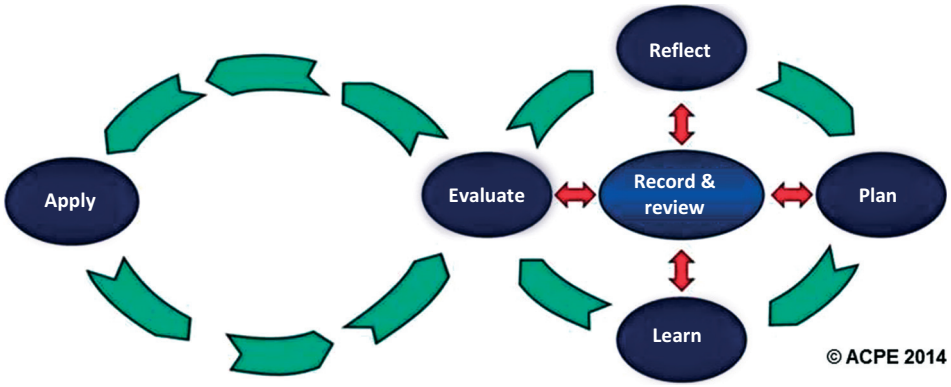

Figure 1 A CPD cycle (from ACPE).

The pharmacist should reflect on his or herself, his or her work, the workplace, and the patient population for which they provide care. Questions to consider during reflection can include:

- What are the needs of the patient population that I serve? With what disease states or medical conditions do patients commonly present in my practice?
- What do I currently know and am able to do that helps me address these needs/conditions?
- What additionally do I need to know or be able to do to address these needs/conditions?
- What are the current responsibilities of my job?
- What competencies do I need to have to be able to fulfill these responsibilities?
- Are there any areas in which I am not fully competent to fulfill my job responsibilities?
- What types of questions do I commonly receive from patients or other healthcare workers?
- What are the needs/goals of the healthcare organization in which I work?
- What are my current strengths for addressing these needs/goals?
- What are areas/opportunities for improvement or introduction of new services that would assist in addressing these needs/goals?
- Are there any areas in which patient care (access, quality, satisfaction, etc.) can be improved?
- What barriers (e.g., technical, logistical, organizational) currently impede my ability to effectively address my job responsibilities? What can I do to overcome these barriers?
- What are my personal career goals?
- What is my natural learning style? What learning methods work best for me? Are there learning methods that I must use to develop needed competencies, but which do not come naturally to me?

Several professional organizations have compiled lists of competencies that may be useful for pharmacists who are engaging in the reflection process. For example, **Table 1** describes pharmacist roles and responsibilities as outlined in the Joint FIP/WHO Guidelines on Good Pharmacy Practice (International Pharmaceutical Federation, 2011).

Alternatively, **Table 2** provides another option for self-assessment as it outlines the entrustable professional activities drafted by the American Association of Colleges of Pharmacy (American Association of Colleges of Pharmacy, 2017). EPAs outline tasks that pharmacists should be able to perform independently after graduation from a pharmacy degree program. A practicing pharmacist can periodically conduct a self-assessment of his or her ongoing ability to complete the activity described for those competencies relevant to his or her roles and responsibilities within the healthcare system.

Pharmacists providing high-level patient care services may find **Table 3** useful. **Table 3** provides the Core Clinical Competencies identified by the American College of Clinical Pharmacy for pharmacists providing comprehensive medical management services as a member of a healthcare team (Saseen et al., 2017).

Ideally, each pharmacist should be able to identify and list three to five learning needs and opportunities that he or she will work to address over both the short (e.g., within one year) and long-term (e.g., three to five years).

Reflection exercises can occur in both scheduled and unscheduled settings and timeframes (**Box 1**). An example of a scheduled reflection "*on practice*" would include an annual performance evaluation during which the individual reflects on his or her practice and job responsibilities and performance in the context of the needs of the organization. In such situations the competencies described above may prove useful to the pharmacist's self-assessment process. Inclusion of reflection exercises in the annual review and goal-setting process is one mechanism through which employers can support the CPD process and address needs and goals of individual employees as well as the larger organization.

Table 1 Pharmacists roles

Role	*Competency*
Prepare, obtain, store, secure, distribute, administer, dispense, and dispose of medical products	I can prepare extemporaneous medicine preparations and medical products
	I can obtain, store, and secure medicine preparations and medical products
	I can distribute medicine preparations and medical products
	I can administer medicines, vaccines, and other injectable medications
	I can dispense medical products
	I can dispose of medicine preparations and medical products
Provide effective medication therapy management	I can assess a patient's health status and needs
	I can manage a patient's medication therapy
	I can monitor a patient's progress and outcomes
	I can provide information about medicines and health-related issues
Maintain and improve professional performance	I plan and implement continuing professional development strategies to improve current and future performance
Contribute to improve effectiveness of the healthcare system and public health	I disseminate evaluated information about medicines and various aspects of self-care
	I engage in preventive care activities and services
	I comply with national professional obligations, guidelines, and legislations
	I advocate and support national policies that promote improved health outcomes

Table 2 Entrustable professional activities

Domain	*Assessment*
Patient Care Provider	I can collect information to identify a patient's medication-related problems and health-related needs (e.g., I can obtain a medication history from a patient).
	I can analyze information to determine the effects of medication therapy, identify medication-related problems, and prioritize health-related needs.
	I can establish patient-centered goals and create a care plan for a patient, caregiver(s), and other health professionals that is evidence-based and cost-effective.
	I can implement a care plan in collaboration with the patient, caregivers, and other health professionals.
	I can follow-up and monitor a care plan.
Interprofessional Team Member	I can collaborate as a member of an interprofessional team.
Population Health Promoter	I can identify patients at risk for prevalent diseases in a population.
	I can minimize adverse drug events and medication errors.
	I can maximize the appropriate use of medications in a population.
	I can ensure that patients have been immunized against vaccine-preventable diseases.
Information Master	I can educate patients and healthcare professionals regarding the appropriate use of medications.
	I can use evidence-based information to advance patient care.
Practice Manager	I can oversee the pharmacy operations for an assigned work shift.
	I can fulfill a medication order.
Self-Developer	I can create a written plan for continuous professional development

Table 3 Core clinical competencies

Competency domain	*Elements of competency*
Direct Patient Care	I can assess patients, including identifying and prioritizing patient problems and medication-related needs.
	I can evaluate drug therapy for appropriateness, effectiveness, safety, adherence, and affordability.
	I can develop/initiate therapeutic plans and address medication-related problems.
	I can follow up on and monitor the outcomes of therapeutic plans.
	I can collaborate with other members of the healthcare team to achieve optimal patient outcomes across the continuum of care.
	I can apply knowledge of the roles and responsibilities of other healthcare team members to patient care.
Pharmacotherapy Knowledge	I can demonstrate and apply in-depth knowledge of pharmacology, pharmacotherapy, pathophysiology, and the clinical signs, symptoms, and natural history of diseases and/or disorders.
	I can locate, evaluate, interpret, and assimilate scientific/clinical evidence and other relevant information from the biomedical, clinical, epidemiological, and social-behavioral literature.
	I can use scientific/clinical evidence as the basis for therapeutic decision-making.
	I possess the knowledge and experience commensurate with certification in one or more Board of Pharmacy Specialties.
	I maintain and enhance pharmacotherapy knowledge, including recertification or other appropriate methods of self-assessment learning.
Systems-based care and population health	I can use healthcare delivery systems and health informatics to optimize the care of individual patients and patient populations.
	I can participate in identifying systems-based errors and implementing solutions.
	I can resolve medication-related problems to improve patient/population health and quality metrics.
	I can apply knowledge of pharmacoeconomics and risk-benefit analysis to patient-specific and/or population-based care.
	I can participate in developing processes to improve transitions of care.
	I can design quality improvement processes to improve medication use.
Communication	I can communicate effectively with: (1) patients, caregivers, families, and laypersons of diverse backgrounds; and (2) other health professionals and stakeholders.
	I can provide clear and concise consultations to other health professionals.
	I can develop professional written communications that are appropriate to the audience.
	I can use verbal communications tailored to varied clinical and patient-specific environments.
	I can communicate with appropriate levels of assertiveness, confidence, empathy, and respect.
Professionalism	I uphold the highest standards of integrity and honesty.
	I commit to a fiducial relationship with patients, always working in their best interests.
	I serve as a credible role model/leader for students, trainees, and colleagues by exhibiting the values and behaviors of a professional.
	I advance clinical pharmacy through professional stewardship, training of future clinical pharmacists, and active engagement in professional societies.
Continuing professional development	I commit to excellence and lifelong learning.
	I demonstrate skills of self-awareness, self-assessment, and self-development.
	I identify and implement strategies for personal improvement through continuing professional development.
	I provide professional education to students, trainees, or other health professionals.
	I maintain Board of Pharmacy Specialties certification to ensure that therapeutic knowledge is up-to-date.

Box 1 Examples of Reflection

Reflection on Practice

During an annual review, a pharmacist and his supervisor discuss the organization's goals. The pharmacist notes areas of practice which may assist in achieving the organization's goals. The pharmacist and supervisor identify an individual practice-based goal for the pharmacist which is in line with the organization's goals.

Reflection in Practice

A pharmacist receives a prescription for a medication that he or she is unfamiliar with. On reflection, the pharmacist realizes the need to improve his or her knowledge regarding the new medication.

Unscheduled reflections occur "*in practice*" during daily work experiences when the pharmacist may encounter learning needs and opportunities that currently limit the pharmacist's ability to fully address his or her job responsibilities. Such reflection exercises may not be habitual at first, but with repeated practice, the incorporation of unscheduled reflection exercises can become part of the pharmacist's unconscious daily routine. Support mechanisms, such as a daily email triggers, can help facilitate such in-practice reflection exercises.

Documentation of the CPD cycle begins with findings from the reflection process. Fig. 2 provides one example of a form that may be used to capture findings from a more formalized, scheduled reflection process. Ideally, the form employed would be easy to use and capture sufficient documentation to fully facilitate the CPD process (Accreditation Council for Pharmacy Education, 2014c).

In summary, three simple overarching questions are needed for reflection:

- What? Reflection questions should be asked and answered that describe the pharmacist's situation and environment factually and objectively.
- So What? Reflection questions should be asked and answered that describe the situation subjectively; i.e., what does it mean for the pharmacist and others with whom he or she interacts?
- What Next? Reflection questions should be asked and answered to determine what the pharmacist will do in the future to address the "What" and "So What."

The "Reflect" stage serves to identify broad learning needs and professional development goals that are refined during the "Plan" stage of the cycle. Reflection is not used to determine the pharmacist's level of competence per se, although self-assessment of competence against a validated competency framework can be useful to assist with setting learning and professional development goals.

Reflect: What do you need to learn? What are your professional strengths and opportunities for development?
List work-related situations from the past learning month/year in which you felt confident or competent:
What knowledge, skills, attitudes, and values contributed to the successes above?
List work-related situations from the past learning month/year with which you need to feel more comfortable or satisfied:
What knowledge, skills, attitudes, or values would you want to develop or improve to better manage similar situations in the future?
What areas of improvement does your supervisor recommend from your performance evaluation?
What knowledge, skills, attitudes, or values do you need to work on or acquire for the coming year?

Figure 2 Sample reflection documentation form.

Plan

During the "Plan" stage, pharmacists formulate a personal learning plan to achieve the goals identified through reflection. Learning goals are summarized as objectives or statements of what the pharmacist intends to accomplish with regard to the learning need. These objectives may be centered on implementing new services, achieving identified organizational patient care benchmarks, expanding the pharmacist's role or responsibilities, improving patient care, etc. (Rouse, 2004b). Care should be taken to ensure the learning goals are written as SMART objectives. In this regard the objectives should be:

Specific—Objectives should describe the pharmacist's intended results in a clear, detailed statement. The objective should specifically describe the intended outcome. Pharmacists should capture specifically what they are trying to achieve. The objective should be sufficiently detailed to describe the intended outcomes and what the pharmacist intends to achieve. Lack of specificity makes it difficult to monitor progress with learning and evaluate achievement of the objective either by the learner or others, such as a supervisor.

Measurable—Objectives should be written in a manner that permits the pharmacist and others to determine whether the intended outcome has been achieved. When writing objectives, pharmacists are encouraged to consider how they will know that the learning need has been met. Considerations should be given toward indicators that can be used to track progress toward achievement of the objective.

Achievable—Pharmacists should be careful not to develop objectives that are over-ambitious and unachievable. The scope of learning and the timeframe must be realistic and appropriate given the learner's other responsibilities and commitments. While pharmacists are encouraged to develop objectives that may be a "stretch" to achieve with sufficient effort and adequate time, the objective should be achievable. Unrealistic objectives set up a pharmacist for failure and may decrease the pharmacist's motivation for addressing the current and future learning needs.

Relevant—The objective should be aligned with the pharmacist's roles and responsibilities as well as the learning needs identified during reflection. Opportunities should exist to quickly apply the learning in practice to ensure that the learning is sustained and reinforced.

Timed—A realistic deadline should be established by which time the objective should be achieved, taking into consideration the scope of the learning, availability of learning resources, other commitments and responsibilities, etc.

Table 4 Categories and examples of CPD activities (Accreditation Council for Pharmacy Education, 2015)

Category	*Examples*
Continuing Education	Formalized CE activities
Academic/Professional Study	Participation in conferences, workshops, and retreats
	Undertaking academic coursework or postgraduate education
	Completion of a certification course (e.g., advanced cardiac life support)
	Completion of an independent study (e.g., directed study with defined objectives, outcomes, assessment)
	Reading and reflecting on healthcare articles and literature
	Leading or participating in journal clubs
Scholarly Activities	Conducting research in one's professional field
	Preparing or writing grant proposals
	Presenting and/or publishing scholarly works
	Serving as a content reviewer for publications, dissertations, or other scholarly works
	Test-item writing (e.g., high stakes examinations, peer-reviewed self-assessment activities, or researching, drafting, and defending questions)
Teaching and Precepting	Developing, presenting, and/or authoring educational content (e.g., academic course, seminar/webinar, publication)
	Teaching and precepting students, residents, or other healthcare professionals
	Peer coaching or mentoring programs (e.g., mentor or mentee)
Workplace Activities	Engaging in point-of-care learning, i.e., self-directed learning on topics relevant to clinical practice
	In-service training
	Job shadowing (e.g., observing an experienced professional for a defined period of time with assessment of impact on one's professional role)
	Preparing for or participating in external review, accreditation, or certification process
	Implementing performance improvement projects (e.g., current practice assessment, implement PI changes, evaluate impact/change)
	Consultation with peers and healthcare experts to address a practice problem or learning need or goal
	Serving on committees (e.g., self-study, institutional review boards, pharmacy and therapeutics, medication safety, medication therapy management)
Professional/Community Service	Serving on a committee, workgroup, or holding office in a professional association
	Training for or involvement in advocacy
	Volunteer experiences or special interest groups, e.g., emergency preparedness
	Developing inter-professional and/or outreach initiatives for health professionals and students

Box 2 Planning Examples

Immediate

Following identification of the need to be better informed regarding a recently released medication, the pharmacist searched available information sources to research the mechanism of action, pharmacokinetics, adverse effects, and uses of the new medication.

Long term

A pharmacist wishes to establish a pharmacist operated clinic to enhance patient adherence and improve the management of patients with hypertension. The pharmacist plans to research the knowledge and skills that will be required to operate the clinic as well as the regulations and management issues that will need to be addressed.

Educational Need Identified	Goal or SMART Learning Objective	Resources or Planned Activities	Timeframe for Completion

Figure 3 Sample documentation of the learning plan.

SMART learning objectives help learners to measure progress and outcomes, keep focused when no-one else is directing the learning, and ensure that the learning has application to the "real world."

Within the learning plan, pharmacists are encouraged to prioritize the learning objectives to ensure more urgent objectives are addressed in a more timely fashion. Similarly, the timeframe for completion should be considered when developing the learning plan, and a clear timeline should be developed including short, medium, and long-term goals.

Once the pharmacist has identified his or her learning objectives, learning activities and other resources should be identified to assist the pharmacist in achieving the learning objectives. CPD, unlike traditional CE, incorporates everything that pharmacists learn. In this regard, learning plans can incorporate both structured (i.e., formalized courses, traditional CE activities, etc.) and unstructured learning activities and include activities both within and outside of the workplace environment, as noted in Table 4.

The pharmacist should consider his or her preferred learning style and environment. Does the individual learn best through reading material or listening to a speaker? Does the pharmacist prefer online or live, in-person activities. Will hands-on training activities be required to attain a new skill? Resources needed to achieve the learning objectives should also be identified. The learning plan should be reviewed against the learning objectives to ensure it adequately addresses all the pharmacist's identified competency needs (knowledge, skills, attitudes, and values) (Box 2).

Pharmacists should ensure that the learning plan is carefully documented. Fig. 3 provides an example of the types of information that should be captured in a pharmacist's personal learning plan. Periodic re-evaluation of the plan is also needed to ensure the learning plan remains timely and relevant and to monitor progress toward achievement of the learning objectives. The learning plan should be modified and updated as needed.

Learn

During the "Learn" stage pharmacists put the "Plan" stage into action. Learning occurs with implementation of the learning plan. Learning plans may incorporate a variety of learning opportunities and methods including formal, structured activities as well as informal and work-based activities (Box 3). The pharmacist should make use of all available and appropriate resources to support and enhance the learning. An essential requirement is to ensure that the activities chosen assist the pharmacist to meet the identified objectives and ultimately the learning need rather than merely fulfilling regulatory requirements. Documentation of participation in the learning activities should be captured and maintained in the pharmacist's written portfolio. Fig. 4 provides an example of the types of information that should be captured when documenting learning.

Box 3 Learning Examples

Immediate

The pharmacist reviewed the medicine in question and was able to educate the patient about the medication.

Long term

The pharmacist participated in a training program during which he developed and achieved the needed knowledge, skills, and credentials to operate a pharmacist-run hypertension clinic.

Learn: Learning Activity Completion Tracker			
Learning Activity	Date Completed/ Time Engaged in Learning	What I learned	Learning Objectives Addressed

Figure 4 Sample learning documentation.

Apply

During the "Apply" stage, pharmacists utilize the new competencies developed during the "Learn" stage to implement performance and practice improvements. The need to apply new knowledge and skills provides a purpose for pharmacists to participate in the learning activity. Additionally, application of learning serves to reinforce and sustain the learning. Adult learners, including practicing pharmacists, place greater importance on learning for which a purpose has been identified, as compared to learning for learning's sake (Kaufman, 2003; Rouse et al., 2018). The immediate use of knowledge and skills developed during the CPD process provides pharmacists with a sense of accomplishment and demonstrates the benefits of participation in the learning activities (Rouse, 2004a). Witnessing the impact of one's learning can improve the self-image of the pharmacist and be a motivator for continued learning and professional development (Baume, 2001).

Incorporation of the "Apply" stage within the CPD cycle emphasizes the need for integrating learning with practice. This is a key difference between the CPD model and more traditional approaches to lifelong learning. Learning must have a purpose and pharmacists must be willing and committed to embrace and implement the needed practice changes identified during the reflection stage.

Evaluate

Evaluation occurs in two distinct phases. The first phase includes the evaluation of the learning plan and learning activities. During this phase, following completion of the planned learning activities, the pharmacist evaluates the effectiveness of the plan toward achieving the outcomes described in the learning objectives. The learning plan itself should be evaluated as to whether the plan was appropriate for addressing the learning need; for example, was the timeline realistic and the scope of learning appropriate? The correlation between the activities in which the pharmacist engaged, the resources used, and the needs outlined in the plan should be evaluated. Pharmacists should assess if the learning methods and resources used were appropriate and what was the impact on the individual's competence and confidence. The pharmacist should consider whether the learning objectives have been sufficiently achieved and what documentation there is to support this assessment. If a structured competency-based assessment or self-assessment was previously undertaken, it would be valuable to repeat the assessment to measure and document the improvement. For objectives that have not been adequately addressed, the next steps need to be identified, including the possible identification of additional learning activities. Additionally, if any challenges or obstacles were encountered, how can things be done differently in the future? Alternatively, if the learning objectives were fully achieved, the pharmacist may complete this cycle and begin a new process of reflection to identify other learning opportunities.

The second phase of evaluation is to determine the impact of the learning after the "Apply" stage. An essential element of the CPD model is the evaluation of the link between participation in educational activities and the plan's intended outcomes and impact (**Box 4**). In other words, did completion of the learning plan lead to the intended outcomes? If the outcome was to improve patient care, has an improvement been measured and documented? Did the pharmacist's participation in the learning activities lead to measurable changes in performance? Have the pharmacist's role/responsibilities been expanded? Were any organizational changes or improvements implemented? How has patient care been impacted? **Figs. 5 and 6** provide examples of forms that may be used to facilitate the evaluation process.

The learning plan should be formally reviewed on an annual basis at a minimum but may be reviewed more frequently on an ad hoc or unscheduled basis due to changing needs within the pharmacist's practice or organization. The evaluation process should include an analysis of the pharmacist's progress toward achieving the identified learning objectives. Changes in the pharmacist's practice that may require changes to the objectives and plan should be identified and incorporated within the plan. Review of the

Box 4 Evaluation and Application Examples

Immediate

After reviewing the new medicine, the pharmacist was able to fully educate the patient on the medicine. The pharmacist will be prepared should another patient have a similar question.

Long term

The pharmacist initiates the pharmacist-run hypertension clinic. Using a quality-assurance process, the pharmacist routinely evaluates and documents the effectiveness of the clinic and the impact on patient-outcomes and healthcare costs.

Evaluation and reflection
What did you learn? Were your learning needs fully met? Partially met? Not met? What challenges or barriers to learning did you experience? How may they be overcome in the future? What new learning needs were identified as a result of this experience?

Figure 5 Evaluation documentation.

Outcomes
Identify which outcomes apply to this activity: How will you change practice based on this learning? (Set specific goals.) What additional information will you pursue? When and how will you pursue it?

Figure 6 Outcomes evaluation.

pharmacist's learning plan by supervisors or another entity can provide valuable insight, providing feedback on the validity of the individual's plan, and assisting individuals having difficulty fully completing the CPD cycle.

Record and Review—Learning Portfolios

Documentation of each component of the cycle—both learning and application of learning—is integral and essential to the CPD process. Personal learning portfolios are one mechanism that has been used to document the CPD cycle. The learning portfolio is "a structured collection comprising labelled evidence and critical reflection on that evidence, produced as a part of the process of learning to show evidence of that learning" (Baume, 2001). Learning portfolios provide a means to demonstrate involvement in educational activities and other components of the CPD cycle. Ideally, the learning portfolio demonstrates the individual's progression through the CPD cycle from reflection through evaluation and application. The learning portfolio provides a means to document learning and achievement of competency. Ultimately, the portfolio may provide a basis for review by employers or regulators of the individual's efforts to maintain competence.

As depicted by the bidirectional arrows in Fig. 1, recording and reviewing should be a dynamic process that supports the learner's CPD; what is recorded in the portfolio can subsequently be reviewed to further inform and guide the learner. If the portfolio is only a static repository of information and activities, it will have limited benefit. Documentation can enhance personal accountability of the pharmacist and can provide evidence of the pharmacist's efforts and achievements to maintain or enhance competence to relevant stakeholders; e.g., employers, regulators, and credentialing bodies.

To adequately document an individual's progression, learning portfolios should include evidence of learning such as learning artifacts and reflections. Learning artifacts are items that can provide documentation of the individual's learning experiences such as educational materials, projects, presentations, photographs, videos, etc. Increasingly, digital badges, symbols indicating completion of a course or attainment of a skill, are being incorporated within the learning portfolio. Reflections are a type of artifact in which individuals reflect on the learning experience. To be truly "reflective" when writing a reflection, the learner should do more than provide a simple recounting of the experience. Rather, reflections address the importance and context of the educational experience in which the learner was engaged. While documenting all components of the CPD cycle, the learner should strive to take their level of reflection as deep as possible, moving from the conscious to the subconscious level. The three key questions discussed under Reflect—What? So What? What Next?—can assist in this regard. New learning should be articulated in the context of the individual's practice.

Regardless of the actual process used, the learning portfolio should be personal to the individual learner. The process must be user friendly, readily accessible and easy to maintain to enhance usability by the individual learner (Accreditation Council for Pharmacy Education, 2015). Use of the portfolio should be ongoing and provide a comprehensive record of the pharmacist's identified educational needs, planning of and participation in learning activities, enhancement of competency and performance, application of learning, and, where applicable, implementation of practice improvements and impact on patient care. In several countries, electronic portfolios and smart phone applications have been developed, while in other countries paper-based systems are used (National Association of Boards of Pharmacy, 2018).

If maintenance of a portfolio is just perceived as "busy work" or too complicated and time-consuming to complete, it can become a barrier to learning instead of a tool that supports learning; this must be avoided at all costs. Requirements for maintaining a learning portfolio in practice will vary and will depend on the licensure or credentialing process maintained in the country or practice setting in which the individual practices. If portfolios are evaluated by third parties, such as regulators, they should be in a standardized format and have pre-defined evaluation criteria. Documentation of the CPD process has become useful for regulatory purposes, and maintaining a structured CPD portfolio, along with other elements of the CPD model, is mandatory in several countries (Tran et al., 2014; Pharmaceutical Society of Ireland, 2010).

As the scope of practice of pharmacists continues to expand and as payment models transition from product-based to service-based to performance/outcomes-based, there will be a growing expectation by stakeholders, such as employers and credentialing bodies, for pharmacists to provide evidence of their qualifications, experience, and performance; evidence that can ideally be provided in the form of a personal portfolio (Council on Credentialing in Pharmacy, 2014).

Closing Identified Gaps

Regulation of the pharmacy profession in many countries includes the assurance of quality of pharmacy schools and other educational and training programs (International Pharmaceutical Federation, 2014a; Fathelrahman et al., 2018). In this regard, pharmacy schools must meet rigorous standards to demonstrate that graduates are competent for entry into practice. Once in practice, however, pharmacists are not required in all countries to demonstrate ongoing, contemporary competence to practice. With constantly evolving technologies, increasingly complex medications and other therapeutic agents, new knowledge and treatment protocols based on accumulated evidence and research, changing societal needs and expectations, the competencies developed by pharmacists during their pre-service education and training are not sufficient for a life of practice. For many or most pharmacists in practice, the knowledge, skills, attitudes, and values needed for contemporary, patient-centered practice were not addressed in their pharmacy school curricula. For many, there was minimal coverage of the clinical, social, behavioral, and administrative sciences, and no experiential training until after graduation. New competencies—especially those to provide comprehensive clinical services—must be developed; existing competencies must be enhanced. This is a major education and training gap, which must be addressed through effective lifelong learning models that meaningfully engage learners and achieve the needed outcomes and impact.

Mandatory participation in CE activities was introduced in many countries as a means to ensure the maintenance of practitioner competence, and it remains the most common model in pharmacy and other health professions (Tran et al., 2014; Pharmaceutical Society of Ireland, 2010; Young and Willie, 1984). Research suggests, however, that participation in mandatory CE activities does not adequately impact practitioner performance (Vaughn et al., 2006). On the other hand, there is growing evidence of the effectiveness of the CPD model (McConnell et al., 2012; McConnell et al., 2010; Dopp et al., 2010). In order to re-engineer the profession to a clinical profession, new models for practitioners' lifelong learning are called for (American College of Clinical Pharmacy, 2000; Institute of Medicine, 2010b).

Participation in the CPD process encourages pharmacists to continually analyze competence and address any deficiencies noted. Gaps between what currently exists and what is desired or needed (by patients, an organization, society) can be identified at the individual level, a local/organizational level, or even at a national or profession-wide level. Identification of learning needs and other gaps that need to be addressed, therefore, should occur at all these levels. Fig. 7 illustrates how the needs-based education model can

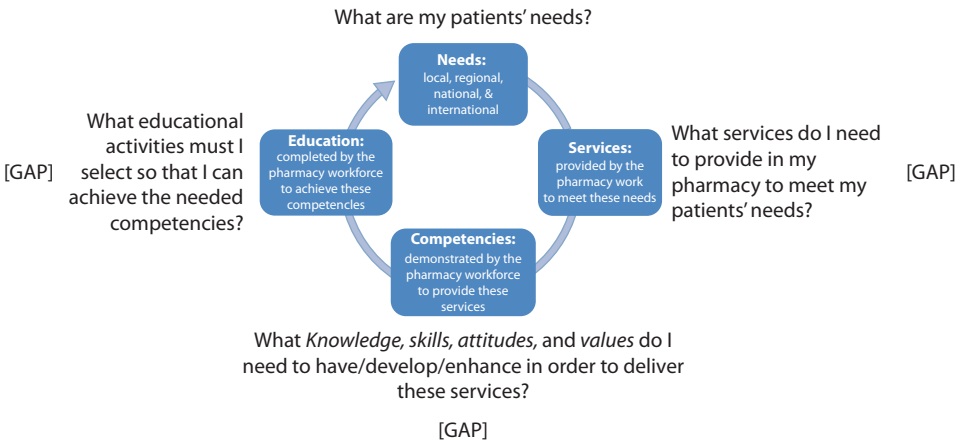

Figure 7 Personalized needs-based education.

Box 5 An Example of CE/CPD Requirements

Health professionals registered with the Health Professions Council of Namibia must complete 30 CE units annually, of which at least 5 CE units should be for ethics, human rights, and medical law (Health Professions Councils of Namibia, 2011b). Individuals who do not successfully complete 30 CE units are considered noncompliant. The consequences of noncompliance include the following: registration in a category that requires supervision; required participation in a remedial CE and training activity; completion of an examination; suspension from practice for a period of time; or another recommended action.

apply to an individual learner, with the initial focus being on the needs of the patient (International Pharmaceutical Federation, 2014a). The model helps to identify the gaps that may exist:

- A needed service is not being provided, or not at the needed level.
- All the competencies needed to provide a service have not been developed or enhanced to the needed level.
- The education or training needed to develop the competencies does not exist or has not been completed.

CPD Versus CE

CPD encompasses both traditional CE and training activities and unstructured self-directed learning activities; CPD does not eliminate the need for and value of participation in structured CE activities. CE and other formal training activities must be of high quality to produce the desired outcomes. Use of a formalized accreditation process provides quality assurance oversight to CE and training activities.

In various countries, requirements for completion of CE and/or CPD activities are often tied to maintenance of licensure (Tran et al., 2014; International Pharmaceutical Federation, 2014b). Many countries require completion of a certain number of CE hours on an annual or biannual basis for pharmaceutical professionals to be eligible to maintain licensure. Alternatively, countries that use a CPD approach to maintain licensure may require pharmaceutical professionals to accrue a certain number of CPD "points" or complete a certain number of learning cycles, complete periodic competency-based self-assessments, and maintain a personal learning portfolio or logbook (**Box 5**).

Additional Competency Assessments

In addition to focusing on scientific and clinical knowledge and skill competencies, pharmacy practitioners must also focus on maintenance of personal and professional development skills such as problem-solving, decision-making, communication, leadership, professionalism, and teamwork. Pharmacists are faced with scenarios requiring problem solving on a daily basis and must be able to successfully navigate the decision-making process to ensure the optimal solution is enacted (Martin et al., 2016). Similarly, pharmacists must be able to lead and function as a member of the healthcare team. The CPD process should ensure that pharmacists are incorporating not only knowledge and skills-based assessment, but assessment of personal and professional development skill needs as well. Identification of critical needs in these areas is essential to ensure continued competence of the pharmacy practitioner.

Challenges and Opportunities

Pharmacists engaging in CPD must identify and overcome challenges to the effective implementation of a CPD process. Of utmost importance is that the pharmacist fully embraces the CPD concept and process. Without the needed commitment to the philosophy and process, the model will break down and the effectiveness of the CPD process will be diminished. Adoption of the process and incorporation of the elements of the CPD cycle into the pharmacist's daily routine is essential but not intuitive (Haines, 2018; Motycka et al., 2010). In this regard, workloads must be amenable, and adequate time must be identified and made available for the pharmacist to engage in CPD. Adequate time and practice are essential to assist pharmacists with the CPD process (Redwood et al., 2010). Similarly, resources needed for professional development, including access to needed learning activities and funding, must be available as needed. Pharmacists employed in workplaces that support and advance the CPD process will likely incorporate the CPD process more readily and effectively. Pharmacists must become advocates for CPD within the workplace if the model has not yet been incorporated.

Meaningful support by employers will play a major role in advancing the CPD model; this is logical because in many ways the return on investment from an effective CPD model should be most evident for employers/organizations (Jeffrey et al., 2017). At the same time, however, providers of educational activities, the bodies responsible for quality assurance and accreditation of CE and CPD, and regulators (the main drivers to date in advancing the CPD model in early adopter countries) all have a role to play if the CPD model will be successfully introduced and implemented. At present the degree to which CPD has been incorporated in the regulatory system of countries worldwide varies extensively with some countries not having implemented a CPD process while

others have fully embraced it (Driesen et al., 2007). Early adopters of a regulatory model based on CPD concepts and components included the United Kingdom, some provinces in Canada, and New Zealand (Tran et al., 2014). Ghana, Kenya, Namibia, and South Africa are examples of other countries that have incorporated CPD concepts to some extent or another (Ghana Pharmacy Council, 2018; Republic of Kenya Ministry of Health Pharmacy and Poisons Board, 2013; South African Pharmacy Council, 2018; Health Professions Council of Namibia, 2011a). As identified by the Institute of Medicine (USA), more research is needed to provide evidence of what educational and regulatory strategies and models are most effective in pharmacy and other health professions (Institute of Medicine, 2010b). A regulatory model based fully on CPD principles (e.g., Ontario, Canada, and Ireland) is likely to be more complicated to administer and sustain, require more resources and expertise, and be more expensive, hence these models are still in the minority. Pharmacists' CE preferences have been studied, as have barriers to CE and CPD, including time constraints, lack of motivation and interest, lack of an accreditation system, and cost; however, having a better understanding of what intrinsically motivates a pharmacist to fully engage in meaningful CPD appears to be a key issue (Donyai et al., 2011; Austin et al., 2005; Driesen et al., 2005; Namara et al., 2009; Power et al., 2008; Ten Cate et al., 2004; Deci and Ryan, 2002).

Conclusion

The rapidly changing nature of healthcare demands that pharmacists engage in lifelong learning to maintain and enhance competency to practice. Maintenance of competency requires pharmacists to do more than complete a minimal number of hours of required CE. In this regard, pharmacists must move beyond the minimal regulatory requirements. To optimize practice and effect practice change, learning must have a purpose, a clear link to the educational needs of the individual, and strong alignment with organizational goals and priorities and societal needs. Participation in CPD requires effort, discipline, and commitment to change but, with continued implementation, benefits to individual pharmacists, patients and employers/organizations should be realized. Ideally the pharmacist's workplace would embrace and support the pharmacist's needs and the CPD process, recognizing the return on investment that can be achieved.

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Evaluating and Developing Clinical Skills

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In this chapter, evaluation and development of clinical skills are being explained. The chapter also explains define, develop, and implement pharmacists' clinical roles in the health-care systems. In different countries all over the World, there is different dynamic of clinical pharmacists' skills development, determined by local context in pharmacy education and practice (International Pharmaceutical Federation (FIP), 2015). The level of clinical knowledge and skills should be defined in all countries, both at the graduate level, as well as on the specialization and subspecialization level (Lee et al., 2017).

Generational issues connected with the clinical skills and knowledge are occurring in many educational systems, as many biomedicine undergraduate programs are now increasing clinically oriented, comparing to the past years. Therefore, the differences in the clinical approach to the patients are visible among practitioners (Boysen et al., 2016).

Interesting theories are appearing recently, stating that not just clinical, but all pharmacists have clinical knowledge and skills, therefore they all are clinical pharmacists. American College of Clinical Pharmacy defines that clinical pharmacists "work directly with physicians, other health professionals, and patients to ensure that medications prescribed for patients contribute to the best possible health outcomes."

Introduction to the Clinical Skills in Pharmacy

Pharmacist in hospitals and community pharmacies are offering patient care in structured processes, starting with data collection and assessment, using their knowledge and experience to create individual plans for their patients' needs. As in the same time, effectiveness of treatment and patient safety should be achieved, this approach require careful judgments and decision-making process. Also, risk and priority management need to apply to all clinical decisions, and this requires clinical skills of pharmacists to be developed to the desired level (Kehrer et al., 2013).

Educational Requirements

Schools of pharmacy are required and encouraged to implement curricula changes and improvements to provide students with a real opportunity to achieve clinical skills and reasoning. In many parts of the World, this change is not fully implemented, and this is due to various reasons and circumstances (Health Foundation, 2012). But, many universities have taken integrated approach to this

important change. They are successful in this process and are now setting new standards for pharmacy education and development of clinical competencies (Marriott et al., 2008).

This approach requires implementation of the experiential component of curriculum, to allow students to test their understanding and reasoning in real clinical cases, under supervision of their mentors and preceptors in practice. More attention is focused on the assessment of the clinical skills, measuring performance and quality of services in practice, including components of clinical competence such as knowledge, skills, attitudes, and values (Urteaga et al., 2015).

Definition of the Clinical Skills

The term "clinical" in the literature is offering to consider few important aspects of pharmacy practice:

- Seeing the real patients in clinical setting
- Providing the services similar to nurses and medical doctors, touching the patients
- Prescribing and deprescribing medicines
- Medicine therapy management and rational pharmacotherapy
- Providing injections and taking blood samples for the screening procedures
- Individualization of therapeutical approach and management
- Consultation and communication

New generation of medicine experts is very skilled in clinical data interpretation and prescribing, but often lack communication skills and empathy, as well as understanding the context of the practice scope of pharmacists in the health-care systems (Dalton and Byrne, 2017).

Clinical Skills Content and Development

To be able to develop clinical skills, practitioners will need problem-based education with interactive content. That dynamic process should include reasoning and discussions among learners, led by clinical experts, ideally coming from practice. Work on realistic situations will increase level of empathy and understanding, making decision process more straightforward and clear. In this educational methodology, students (or adult learners) will have to solve a number of cases to gain self-confidence.

One of the biggest barriers in developing clinical skills is the impression that pharmacists should not take any important decisions connected with pharmacotherapy without involvement of medical doctor. This kind of thinking is just a preconception, lacking pragmatic reasoning based on clinical guidelines. It was proved in pilot programs in some countries (UK), when pharmacists were working in collaboration with general practitioners in the same consultation room with the patients. Medical doctors could have recognized the benefits of pharmacists' contribution in many ways (Sims and Campbell, 2017).

As the concept of pharmaceutical care and clinical pharmacy is not older than 25 years, we still have practitioners in practice who were never educated in those disciplines, not in their undergraduate programs, but maybe also not in their continuing education activities. Therefore, they have different approach to the patient care than their young colleagues who are just entering the practice. But the controversy lies in the fact that they need to mentor and supervise younger colleagues and students, being aware that their level of clinical competence is not sufficient for their task. Some of those disciplines are pharmacogenetics, pharmacovigilance, individualization of therapy, etc. (Kimberly, 2013).

There are many educational activities offered to enhance and develop the clinical skills of pharmacist during their life-long learning, including short courses, on-line activities, clinical summer schools, or certification courses in certain clinical areas of practice.

Tools and Principles to be Used in Clinical Decisions

To develop clinical skills and reasoning, it is essential to use evidence-based sources, existing guidelines and protocols relevant to the specific country or region. There are some tools and principles to help pharmacists in this process to be structured and safe for the patients, yet at the same time efficient and aligned with the sources used by medical doctors and other health-care professionals (Frieden, 2017).

Using Drug-Related Problems Classifications

First step to conduct pharmaceutical care is to be aware that in all cases, patients' therapy should be effective and safe. Therefore, pharmacist who developed clinical skills should start planning structured counseling with patients in two parallel directions: "Is the medicine effective?" and "Do you face any problems related to the medicine use?" With collected answers, drug-related problems should be tracked related, to the possible causes. To have successful cause analyses, DRP classifications have been introduced from various sources.

A drug-related problem (DRP) exists when a patient experiences or is likely to experience a new disease or symptoms that have a real or potential association with the pharmacotherapy that the patient is taking. The classification of drug-related problems has, for the primary purpose, emphasized the role of the pharmacist in caring for the patient, focusing on the patient's needs and outcomes of treatment. This approach brought a new vocabulary in the description of the process of pharmacy care and created the need for

these problems to be documented, processed, and interpreted, and to take interventions in which problems would be prevented or rehabilitated in the safest way for the patient.

Pharmacist needs to demonstrate all these skills in clinical pharmacy procedures and use the classification according to their scope of practice.

One example of DRP classification is Pharmaceutical Care Network of Europe (PCNE), one that is now used widely in research, teaching, and pharmacy practice. Primary domains are Problems, Cause, Intervention, Implementation, Outcome, with details subdomains, as follows (Table 1):

Table 1 PCNE Drug-Related Problem classification, version Classification V 8.01

Primary domain	*Code V8.01*	*Problem*
1. Treatment effectiveness	**P1.1**	No effect of drug treatment
There is a (potential) problem with the (lack of) effect of the pharmacotherapy	**P1.2**	Effect of drug treatment not optimal
	P1.3	Untreated symptoms or indication
2. Treatment safety	**P2.1**	Adverse drug event (possibly) occurring
Patient suffers, or could suffer, from an adverse drug event		
3. Others	**P3.1**	Problem with cost-effectiveness of the treatment
	P3.2	Unnecessary drug-treatment
	P3.3	Unclear problem/complaint
	P3.4	Compromised quality of the medicine

	Primary domain	*Code V8.01*	*Cause*
Prescribing	**1. Drug selection**	**C1.1**	Inappropriate drug according to relevant guidelines/formulary
	The cause of the (potential) DRP is related to the selection of the drug	**C1.2**	Inappropriate drug (within guidelines but otherwise contra-indicated)
		C1.3	No indication for drug
		C1.4	Inappropriate combination of drugs or drugs and herbal medication
		C1.5	Inappropriate duplication of therapeutic group or active ingredient
		C1.6	No drug treatment in spite of existing indication
		C1.7	Too many drugs prescribed for indication
	2. Drug form	**C2.1**	Inappropriate drug form (for this patient)
	The cause of the DRP is related to the drug form		
	3. Dose selection	**C3.1**	Drug dose too low
	The cause of the DRP is related to the selection of the dose or dosage	**C3.2**	Drug dose too high
		C3.3	Dosage regimen not frequent enough
		C3.4	Dosage regimen too frequent
		C3.5	Dose timing instructions wrong, unclear or missing
	4. Treatment duration	**C4.1**	Duration of treatment too short
	The cause of the DRP is related to the duration of treatment	**C4.2**	Duration of treatment too long
Dispensing	**5. Dispensing**	**C5.1**	Prescribed drug not available
	The cause of the DRP is related to the logistics of the prescribing and dispensing process	**C5.2**	Necessary information not provided
		C5.3	Wrong drug, strength or dosage advised (OTC)
		C5.4	Wrong drug or strength dispensed
Use	**6. Drug use process**	**C6.1**	Inappropriate timing of administration and/or dosing interval
	To the way the patient gets the Drug administered by a health professional or carer, despite proper dosage on the label instructions	**C6.2**	Drug underadministered
		C6.3	Drug overadministered
		C6.4	Drug not administered at all
		C6.5	Wrong drug administered
		C6.6	Drug administered via wrong route
	7. Patient related	**C7.1**	Patient uses/takes less drug than prescribed or does not take it at all
	To the patient and his behavior (intentional or non-intentional)	**C7.2**	Patient uses/takes more drug than prescribed
		C7.3	Patient abuses drug (unregulated overuse)
		C7.4	Patient uses unnecessary drug
		C7.5	Patient takes food that interacts
		C7.6	Patient stores drug inappropriately
		C7.7	Inappropriate timing or dosing intervals
		C7.8	Patient administers/uses the drug in a wrong way
		C7.9	Patient unable to use drug/form as directed
	8. Other	**C8.1**	No or inappropriate outcome monitoring (incl. TDM)
		C8.2	Other cause; specify
		C8.3	No obvious cause

(*Continued*)

Table 1 PCNE Drug-Related Problem classification, version Classification V 8.01 (*cont.*)

Primary domain	*Code V8.01*	*Intervention*
No intervention	**I0.1**	No intervention
1. At prescriber level	**I1.1**	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed to prescriber
	I1.4	Intervention discussed with prescriber
2. At patient level	**I2.1**	Patient (drug) counseling
	I2.2	Written information provided (only)
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
3. At drug level	**I3.1**	Drug changed to . . . .
	I3.2	Dosage changed to . . . .
	I3.3	Formulation changed to . . .
	I3.4	Instructions for use changed to . . .
	I3.5	Drug stopped
	I3.6	New drug started
4. Other intervention or activity	**I4.1**	Other intervention (specify)
	I4.2	Side effect reported to authorities
Primary domain	*Code V8.01*	*Implementation*
1. Intervention accepted	**A1.1**	Intervention accepted and fully implemented
(by prescriber or patient)	**A1.2**	Intervention accepted, partially implemented
	A1.3	Intervention accepted, but not implemented
	A1.4	Intervention accepted, implementation unknown
2. Intervention not accepted	**A2.1**	Intervention not accepted: not feasible
(by prescriber or patient)	**A2.2**	Intervention not accepted: no agreement
	A2.3	Intervention not accepted: other reason (specify)
	A2.4	Intervention not accepted: unknown reason
3. Other (no information on acceptance)	**A3.1**	Intervention proposed, acceptance unknown
	A3.2	
Primary domain	*Code V8.01*	*Outcome of intervention*
0. Not known	**O0.1**	Problem status unknown
1. Solved	**O1.1**	Problem totally solved
2. Partially solved	**O2.1**	Problem partially solved
3. Not solved	**O3.1**	Problem not solved, lack of cooperation of patient
	O3.2	Problem not solved, lack of cooperation of prescriber
	O3.3	Problem not solved, intervention not effective
	O3.4	No need or possibility to solve problem

Version 8.02 *is ready and available, incorporating some validation results of V7.0, and correcting some minor issues in V8.0 and V 8.01. Please note that Version V 8 is not compatible with earlier versions, due to some fundamental changes. The version 8.02 is being validated by an international group of experts.*

Creating PICO Questions—Clinical Significance and Interpretation

Once the pharmacist collects the data from the patient and/or patient medication record and notice some problems or inconsistencies in pharmacotherapy, it is important to develop the sense of reasoning and interpretation in ever clinical case individually. This skill also needs to be evaluated and developed for clinical pharmacy practice, as in the profession, there are still generational and other barriers which needs to be overcome. IT literacy, knowledge of English language, skill of interpretation of data are all skills important for clinical pharmacists For all those cases, pharmacists will first find evidence in reliable sources (such as publications, books, handbooks, guidelines, applications, databases, and regulatory documents). In any case, pharmacists should know how to identify the PICO question.

Without a well-focused question, it can be very difficult and time consuming to identify appropriate resources and search for relevant evidence. Practitioners of Evidence-Based Practice (EBP) often use a specialized framework, called **PICO**, to form the question and facilitate the literature search. **PICO** stands for:

- Patient Problem (or Population)
- Intervention

Table 2 PICO question structure

	Think about:
Patient Problem (or Population)	What are the patient's demographics such as age, gender, and ethnicity? Or what is the or problem type?
Intervention	What type of intervention is being considered? For example, is this a medication of some type, or exercise, or rest? What problem in pharmacotherapy is it all about?
Comparison or Control (if applicable)	Is there a comparison treatment or method to be considered? The comparison may be with another medication, OTC, another form of treatment such as exercise, or no treatment at all.
Outcome (should be measured)	What would be the desired effect you would like to see? What effects are not wanted? Are there any side effects involved with this form of testing or treatment?

Table 3 PICO elements change according to question type (domain)

Question type	*Patient problem or population*	*Intervention or exposure*	*Comparison or control*	*Outcome/Measures*
Therapy (Treatment)	Patient's disease or condition.	A therapeutic measure, e.g., medication, surgical intervention, or life style change.	Standard care, another intervention, or a placebo.	Mortality rate, number of days off work, pain, disability.
Prevention	Patient's risk factors and general health condition.	A preventive measure, e.g., a lifestyle change or medication.	Another preventative measure OR maybe not applicable.	Mortality rate, number of days off work, disease incidence.
Diagnosis	Specific disease or condition.	A diagnostic test or procedure.	Current "reference standard" or "gold standard" test for that disease or condition.	Measures of the test utility, i.e., sensitivity, specificity, odds ratio.
Prognosis (Forecast)	Duration and severity of main prognostic factor or clinical problem.	Usually time or "watchful waiting".	Usually not applicable.	Survival rates, mortality rates, rates of disease progression.
Etiology (Causation)	Patient's risk factors, current health disorders, or general health condition.	The intervention or exposure of interest. Includes an indication of the strength/dose of the risk factor and the duration of the exposure.	Usually not applicable.	Survival rates, mortality rates, rates of disease progression.

- Comparison or Control
- Outcome

In Table 2, basic elements are described:

When using the **PICO** framework, it is useful to think about what type of question pharmacists might have (is it about therapy, prevention, diagnosis, prognosis, etiology). Table 3 illustrates ways in which **P**roblems, **I**nterventions, **C**omparisons, and **O**utcomes vary according to the type (domain) of such a question.

Evidence-Based Practice in Health, University of Canberra, Library (accessed Aug 9, 2018)

Once PICO question is well formed, the best possible evidence should be found and applied to the individual patients' situation. That means that a pharmacist needs to know how to interpret collected data and apply the conclusion to the real-life situations (Schardt et al., 2007).

For example, when pharmacists find the evidence about drug–drug interactions in the literature, it is important to judge clinical significance in the patient case, individually. Not all interactions will obviously happen to anyone, so it is important to start from the facts and to modify interpretations according to the circumstances (e.g., age, gender, weight, kidney function, liver function, lifestyle, co-morbidities). Pharmacogenomic postulates can still change the decisions made in practice, as well as frequency of use and other conditions.

Once when decision is made and applied in real case, pharmacist should follow-up with the patient and review if the decision was right. In any case, patient opinion needs to be included and respected in the care process (Fineout-Overholt and Johnston, 2005).

Setting the Priorities

It could be that pharmacist will identify more than one problem in pharmacotherapy of the patient and will need to make clinical decision how to proceed with the patient case according to the urgency and order of interventions. We call that process prioritization.

Table 4 Choosing priorities in Patient care process

Was this problem a new issue, or did it occur earlier?
Why this is the problem right now?
If we do not solve the problem, what could happen to the patient?
Will there be side effects? If so—what side effects do we expect?
Will the overall state be out of control?
Can hospitalization occur?
Can a patient die?
What problems have to be addressed immediately?
What further problems can be expected?
Is the patient also recognizing the problem as a problem, or not?
Can we solve the problem without including someone else?
What do we need to solve the problem?

Source: A joint initiative of the American Pharmacists Association and the National Association of Chain Drug Stores Foundation, 2008

Deciding about priorities is a skill connected with time and risk management, especially connected with the patient safety and efficacy of the treatment. This process could be well supported by the potential electronic health records (if applicable), connecting more health-care professionals in the integrated care for the patient (Woolf, 2007).

In the process of prioritization, pharmacists can follow further scheme to make sure they are choosing right priorities to be primarily solved (**Table 4**):

Ability of the pharmacist to recognize that he cannot always set priorities without consulting other health-care professionals is also an important skill that can be developed with practice experience and teamwork.

Conducting Interventions

Once priorities are set, pharmacist should consider intervening. There is a whole range of interventions possible in the patient care process and again, it is a skill to recognize how and what to do.

One possibility is not to conduct any interventions. On the first sight that option might look as pharmacist do not take enough effort to do something for the patient, anticipating possible problems in communication, medical doctors' reactions, procedures in the health system, etc. But, sometimes "no intervention" can be the best solution for the patient. Those situations could be related with minor problems even at the end of antibiotic therapy or some acute disorders and intervention is actually not needed. Besides that, patient can decide that pharmacist do not intervene, for many various reasons. Sometimes, intervention is not possible, as it requires consultation with prescriber who might not be available or known. In pharmacy practice research, this situation should be noted and well interpreted, according to the circumstances.

Second option of intervention could be patient counseling and education, including practical instructions to the patients or just giving an educational leaflet to the patients. This intervention is most frequent, and it occurs in many situations that just do not require consultation with medical doctors. Research confirms that more than 50% of interventions fall into this category and problems are usually fully or at least partially solved, especially in chronic disease management (Ombini and Caserini, 2018).

Outcome of the intervention can be unknown, if patient does not come back for the follow-up, or pharmacists cannot track the progress of the individual patient for various reasons. With the pharmacists' intervention, problems can be fully solved, partially solved, or not solved, all for various reasons (agreement and support from medical doctor and patient might be missing, patient might lack understanding of the pharmacotherapy, some decisions could be made based on cultural, sociological, and religious beliefs of the patients or carer, etc.). It is very important to document all this outcomes and results and manage possible options to continue the process of care—that is also clinical skill, still to be fully developed for pharmacists all over the world. Pharmacists with developed clinical skills have to be able to choose research methods to publish their clinical data, also to make valuable conclusions and discuss the clinical outcomes of their intervention in neutral, unbiased way. From this type of research, we have today valuable information and proof how pharmacists' interventions can improve clinical, economical, and humanistic outcomes in the health care (Westerlund and Björk, 2006).

Planning the Process of Care

When all necessary data are collected and assessed, problems identified, priorities set, and intervention conducted, it is recommended to create individual care plan for the patient. The plan should focus on the patients' outcome and safety, considering the social profile of the patient, and desired life-style changes. The medication-related action plan will contain a list of recommendation for patients' self-management to achieve the desired goals. The care plan is an important component of the documentation and follow-up processes. To achieve the completion of the plan, the collaborative effort between the patient and the pharmacist is needed.

Often, the plan will contain goals that pharmacist and the patient can achieve without necessarily including other health-care professionals. Outstanding action items that still require physician or other health-care professionals' review or approval should be included in further plans. The patient can use the plan as a reminder and simple guide to track his own progress. He can take notes and fill the checklist that pharmacist has prepared for him, for better understanding and successful implementation. Patient can modify the plan according to the circumstances and possible outcomes of pharmacotherapy. Pharmacist needs to have a skill of education and guidance to the patient. It would be important that pharmacist count both on possible success or failure of the plan set, so that alternative plans could be predicted and implemented when needed. Therefore, follow-up is an important part of the care process. Plans and alternatives should be discussed in affirmative and assertive way with the patients to avoid any misunderstanding and safety risks for the patients.

(A joint initiative of the American Pharmacists Association and the National Association of Chain Drug Stores Foundation, 2008)

Managing the Risk

Risk management is a crucial part of effective and safe pharmaceutical care provided in pharmacy. It ensures that the health, safety, and well-being of patients are safeguarded, and risks are minimized.

Risk is defined as the chance or probability (high at one extreme and low at the other) that a person could be harmed or experience an adverse health outcome in pharmacotherapy process. It could be caused by medication error caused by medical doctor, pharmacist, or other health-care professional. The risk management is therefore very important. It involves:

- Efficient safety systems, including not just well-established process, but also skilled staff providing service, to minimize the likelihood of any harmful event
- Safety strategies and mechanisms to learn from situations where, despite all procedures implemented, something has gone wrong
- Management of minimizing the harm or adverse health outcomes if anything goes wrong as a result of a pharmacy's activities and services (Aronson, 2009).

Pharmacist need to have a skill to understand and manage the factors influencing risk and providing person-centered services in any activities in pharmacy. In this process, patients' health needs and vulnerability issues need to be considered. These activities should be conducted continuously and proceeded in sustainable way, not to allow any gaps in the process. Patient data should be collected in this process to track the impact of safety procedures. New potential risks should be considered on regular basis.

Some examples of the situations when risk management is beneficial are as follows:

- Internet-based orders and self-medication
- online counseling and giving instructions to the patients which might be misleading
- identity check
- lack of patient e-record or any other relevant information
- label checking systems
- communication with nursing homes or kindergartens
- universal rather than individual approach to the patient cases
- medication errors
- unsecure dispensing system
- lack of time
- insufficient number of the pharmacy staff
- lack of feedback to the pharmacy staff
- lack of reporting adverse drug reactions
- lack of the teamwork
- lack of self-confidence in pharmacy team, etc.

There are many resources to be used in implementing risk management in pharmacy, such as frameworks, tools, checklists, and guidelines, usually developed by national professional organizations of pharmacists working in hospital and community settings (General Pharmacy Council, 2016).

Communication, Motivation, and Counseling

Essential skill critically important to achieve outcomes in clinical practice is the ability of the pharmacist to communicate with the patient in professional way and to lead the conversation in nonjudgmental, nonthreatening way. Motivational interviewing is one of the skills that clinical pharmacist should develop to open the conversation in motivating and supportive way, especially when lifestyle change is involved. The skills needed for enabling communication in health care are, reflection, active listening, and open-ended questioning. Unlike Rogerian approaches, the technique can include elements of "direction" and is balanced with elements of "following". This shows a guiding style rather than the leading style seen traditionally in health-care consultations. Central to the motivational interviewing is the attitude of clinical pharmacist—belief in patients' inherent resources, rather than extrinsic problem solving, which include image of the patient as a partner in achieving the therapeutic goals.

Basic principles of motivational communication in the clinical setting are as follows:

- Showing empathy in the conversation is essential
- Motivation to change is elicited from patients, not imposed on them.
- It is designed to elicit, clarify, and resolve ambivalence.
- Resistance and denial is often a signal to modify motivational strategies.
- Eliciting and reinforcing patients' ability to carry out and succeed in achieving a specific goal is essential.
- The therapeutic relationship is a partnership that respects patient autonomy.
- It is both a set of techniques and counseling style.

(Miller and Rollnick, 2009)

It is also important that clinical pharmacist develop the skill to communicate collaboratively with medical doctors, nurses, and the whole pharmacy team. Assertive communication includes facts, feelings, and suggestions or requests. It sounds professional and opens the possibilities to collaborate interprofessionally, which is essential to achieve integrated care and comprehensive care for the patients.

Using the Clinical Guidelines

Using clinical practice guidelines is described as one of the basic competencies of the pharmacists in the FIP Global Competency Framework (International Pharmaceutical Federation FIP EDT, 2012).

Pharmacists should know how to find, use, interpret, and apply various clinical practice guidelines in their clinical practice and decision-making process for a variety of medical conditions. During practice experiences, students are often expected to quote an applicable guideline as justification for their clinical decisions. Recent Pharmacy students are usually knowledgeable in the latest guidelines for treating chronic diseases and conditions, and they are ready to use them in practice. Some students may learn those guidelines „by heart," not really thinking through the logic of choices that need to be made in patient care process. That means they would be memorizing clinical facts rather than learning clinical principles. Those who teach pharmacy, whether didactically or experientially, should be aware of this fact and use appropriate methods of teaching and learning to assure desired outcome.

For pharmacists to create sophisticated pharmacotherapeutic plans, they need to function beyond the written recommendations. With this goal in mind, it is time to consider the real role of clinical guidelines in the educational process and implement essential changes to the courses design and delivery (Brown, 2015).

Evaluation and Assessment of the Clinical Skills—How to Achieve it?

Both in undergraduate education and continuing professional development (CPD) for pharmacists, it is important to plan the learning, based on the real needs of clinical pharmacists. Needs can be assessed by reflection and self-evaluation, or by competency evaluation conducted by preceptors, professors at the faculty, or human resources experts, and managers at the work place.

Self-assessment is a skill in itself. It requires some experience in practice, good understanding of required standards and clinical procedures, objectivity, and self-motivation. Emotional and social intelligence is required for solid self-assessment, including the awareness, wish to advance in the profession, self-confidence, and ethical approach to the self-development process.

Some studies have shown that pharmacy students, even when attending faculty programs, which are strong in assessment and competency evaluation, do not always have the required skills for proper self-assessment. Their judgment appears not to be so accurate, even on senior levels of their degree, comparing with average assessments of their peers, standardized patients, and pharmacist-instructors. These differences are particularly visible and significant in the areas of showing empathy, and logic/focus/coherence of interviewing. It is evident that pharmacy schools in many parts of the World do not sufficiently prepare students to be life-long learners. Self-assessment of clinical competence should be a starting point in this process, as this skill will definitely be required for professional practice and continuous professional development (CPD) of clinical pharmacists (Austin and Gregory, 2007).

To maintain the licence or certificate for practicing clinically oriented pharmacists, continuing education (CE) activities are required in most countries. They are usually incorporated into the credentialing systems, where points to renew licence are just "hours-based." That would mean that for certain number of hours in the lectures or symposia, practitioners can "earn" certain number of points, collecting them to renew their licence (Tofade et al., 2015).

Accreditation Council for Pharmacy Education (ACPE) defines CPD as an ongoing, self-directed, structured, outcomes-focused learning cycle focused on maintaining and improving performance of professional practice. CPD cannot replace, but rather enhances CE in a broader approach ensuring improvement of pharmacist competence. CPD is rather dynamic than static learning process where the learner reflects, plans, learns, evaluates competencies, and applies gained knowledge and skills. That way, clinical pharmacist has the meaningful reason to learn. Central to each step in the CPD cycle is a personal learning portfolio where learners record self-evaluations, reflections, and further plans, as shown in **Fig. 1**.

As practicing roles and needs of clinical pharmacists are changing, their learning needs are changing too. The original concept of dynamic cycle and all components of CPD remain the same, but much greater focus has been given to the application of learning in

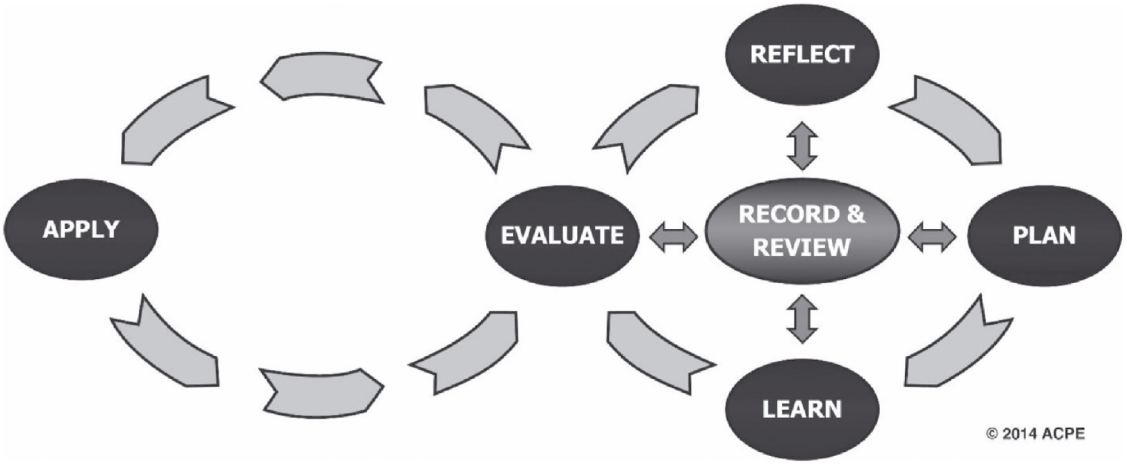


Figure 1 Continuing professional development cycle (ACPE, 2015).

everyday practice, connected with evaluation of the competencies before and after the application. Clinical skills can be developed only in this way, through the application and more reflection of the further learning needs. This approach will allow the clinical pharmacist to see individual benefits of his or her dedication to change and apply learning into practice. Seeing the impact of one's learning (especially in patients' outcomes and satisfaction) is always the strongest motivator for further advancements (Rouse et al., 2018).

No matter which methods are chosen to assess clinical skills, to start the process the competency list required for the desired level or aspects of practice should be available. It can serve as the checklist for the self-assessment (if required), and especially for the assessors, to define expectations in advance and to approach the assessment in organized, structured way. That means that all competencies should be well defined and described with the related behavioral statements. Both qualitative and quantitative methods could be applied to evaluate clinical pharmacists' behavior.

Competency framework for clinical pharmacists should be designed with all stakeholders' inputs, validated and piloted for quality assurance of the right context in certain organization, country, or region. It should be realistically aligned with educational programs and trainings, available for the pharmacists, both in undergraduate and CE programs. That way the clinical pharmacist can be encouraged to be assessed in objective, meaningful way, and objective goals and expectations could be set for the future development (Meadows et al., 2004).

Obviously, if behavior needs to be assessed, pharmacist should be ideally observed at his regular working place, where clinical skills are required and visible. If that is not applicable, there are some other methods to be used in the assessment of clinical skills and performance, such as OSCE-s (Objective structured clinical examination or mini CEX—Mini-Clinical Evaluation Exercise).

On Site Evaluation

Assessment in the working place can be organized in many different ways. It is highly recommended that the assessor has had the personal experience in practice to be able to assess the colleagues in the real situations. He could be known or unknown to the clinical pharmacists, and in both cases, there are some advantages and disadvantages, concerning bias in the evaluation, prejudices, and objectivity. Visits can be expected or unexpected, depending on the purpose of the evaluation and other circumstances. Also, assessor can be visible or invisible to the clinical pharmacist, which has been shown as a significant difference, as the fact that someone is observing, can cause behavioral changes in pharmacist's performance.

Checklist for evaluation can have different rating systems, but it is important to have some quantification, as qualitative, descriptive ratings are not easy to interpret, as well as measure and compare statistically. Whenever possible, qualitative aspects of the research should be portrait by numeric values, describing the level of competence. Some scales are designed to describe the frequency of achieved standard in repeated situations. In this case, we can say is the clinical pharmacists meets his expected standard always, often, rarely or never, using numbers 4, 3, 2 and 1 to rate the performance seen in practice.

During the assessment, assessor can interact with the pharmacists, asking additional questions, requiring additional explanations or making comments on the behavior just seen in practice. Before the assessor comes to the working place, it is recommended that pharmacist was introduced to the required standard, even better to conduct self-assessment, which can be then compared with assessor's ratings. Most common method of assessing the clinical pharmacist in practice is called "shadowing," when assessor follows the pharmacists and observe all aspects of his behavior (communication, time management, risk management, clinical approach and judgment, interprofessional collaboration, etc.).

Table 5 Mini-CEX evaluation examples

Delivery of patient care	
1. Patient consultation	Introduction to patient, conducting a patient-centered consultation, exploring the medical/surgical condition with the patient, considering the patient's own health beliefs, being aware of personal limitations, and making appropriate referrals
2. Need for drug	Establishing the patient's background, taking a drug history and gaining the necessary information from a range of sources in order to decide on the appropriateness of drug therapy
3. Selection of the drug	Appropriate consideration of evidence-based medicine and drug interactions (drug–drug, drug–disease, drug–patient)
4. Drug specific issues	Checking that the drug is prescribed correctly (route, formulation, dose, frequency, course length) and considering available results and what effect they have on drug therapy, e.g., U&Es, LFTs
5. Provision of drug product	Implementing an effective system for the supply of medicines
6. Medicines information and patient education	Provision of medicines and health advice to patients, carers, other pharmacy staff medical and nursing staff, and other health-care professionals
7. Professionalism	Identification and prioritization of medicines management issues, time management, patient confidentiality, appropriate application of guidelines such as formulary, therapeutic switching policies, etc
Problem solving	
8. Gathering information	Accessing and summarizing the information required and ensuring the information used is up-to-date
9. Knowledge	Knowledge of pathophysiology of common medical/surgical conditions encountered, pharmacology, side effects, and drug interactions
10. Analyzing information	Demonstrating the ability to evaluate information gathered (reliability or source, relevant to patient care), correctly identifying the problem, appraising options, making appropriate decisions, and demonstrating a logical approach
11. Overall clinical care	An assessment that summarizes all of the above in terms of outcome for the patient

Source: NHS Education for Scotland, 2014

Numerous factors within a pharmacy work system appear important to enable pharmacists to provide clinical services. To be successful in providing clinical services, pharmacists must be cognizant of the different components of the pharmacy work system and try to change environment to be optimal for clinical performance.

It is recommended that assessor share his observations with the pharmacist before the final marks are given. Sometimes, assessors and pharmacist's views are going to be different. In these cases, more resources should be considered to assure objectivity, such as additional interviewing or documentation sources available for the assessor to review. It would be ideal to achieve consensus in final record, but if it is not possible, it should be noted for the further analyses and procedures of assessment.

The site visit, when appropriately arranged, could be not just evaluation and assessment oriented, but also it could be beneficial for the pharmacist (Chui et al., 2012; Meštrović et al., 2011).

Mini CEX and CbD

If the random onsite evaluation is not possible or necessary, the mini-CEX (Mini-Clinical Evaluation Exercise) could be very appropriate to assess and evaluate clinical skills of pharmacists.

Mini-CEX originated in the United Kingdom and has been used within medicine for years. It was adapted for use within pharmacy in 2006, and then introduced into the Pharmacy Vocational Training Scheme to enhance learning, in 2011. A mini-CEX is a structured interactive examination based on the real-life case study. Following example can demonstrate what skills could be examined in Mini-CEX evaluation (**Table 5**).

Various rating scales could be used in the process. They should have large descriptive range, so the comparison can be made with what would be expected of any pharmacist at that stage of their vocational training or practice. The key part of mini-CEX is effective feedback and identifying learning needs. Here is one example, used in Scotland (**Table 6**):

Case-based Discussion (CbD) also adapted for use within pharmacy in 2006 by CoDEG (Competency Development & Evaluation Group). CbD is defined as a detailed discussion between the pharmacist and their assessor on a patient case. CbD can be suitable for more deep assessment of clinical reasoning and knowledge, such as discussing the pharmacokinetic or pharmacodynamics of a new medicine for a patient. Another example could be evidence base use of a drug in a particular patient, the legal or ethical issues around patient care, or behavioral changes with some social pharmacy aspects (NHS Education for Scotland, 2014).

Objective Structured Clinical Examination

The OSCE is an acronym for Objective Structured Clinical Examination, which has demonstrated validity and reliability for assessing medical and pharmacy students' and practitioners' clinical skills in various settings. Pharmacist is exposed to the unique clinical

Table 6 Rating scale in Mini-CEX process

Rating Scale	
Significantly below	Performs poorly; very rarely meets the standard expected
Below	Performs poorly; meets the standard required occasionally
Borderline	Performs satisfactorily; with appropriate support and direction should meet expectations
Meets expectations	Performs well and to the standard expected of a pharmacist at that stage in their training
Above	Performs to a standard higher than what you would expect from a pharmacist at that stage in their training
Significantly above	Performs to an excellent standard; trainee is ahead of his/her peer group
Unable to comment	Unable to comment as performance not observed while she/he was there

Source: NHS Education for Scotland, 2014

situation for evaluation of his clinical knowledge and competence, professional judgment, problem-solving skills, and interpersonal and communication skills.

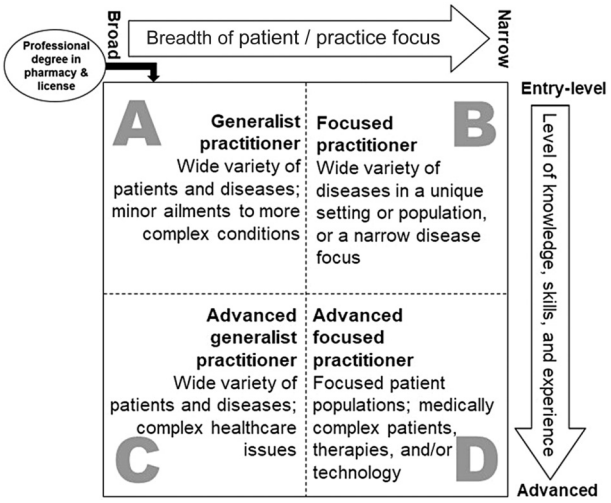
OSCEs are often used as part of certification at the end of specialization or as a part of licensing process. For instance, the United States Medical Licensing Examination and the Medical Council of Canada Qualifying Examination use OSCEs as part of their examination process.

The OSCE consists of various stations related to the direct patient care; so, the different competencies can be examined, depending on the learning (credential) needs and scope of pharmacists professional practice. Competencies such as collaboration and teamwork; ethical, legal, and professional responsibilities; drug, therapeutic, and practice information; communication and education; drug distribution; and management principles could be assessed and evaluated successfully.

Many pharmacy schools around the World are now used OSCEs in their curriculum, and this implementation is in progressive development. There are numerous publications proving the tremendous potential of using OSCE in clinical skills assessment (Urteaga et al., 2015).

Other Methods for Clinical Assessment

Various methods are available in pharmacy education to assess clinical competencies such as clinical counseling competitions, multiple choice questioners based on clinical cases, small group work, panels, poster presentations, seminars, etc. This area of assessment is under development, and new methodologies are emerging, both in undergraduate and postgraduate education.



Development of the Clinical Skills

The most important aspect of clinical skills development plan is the understanding that the clinical competences are much more than clinical knowledge in theory, as it was explained in the introduction of this chapter. It is clear that clinical skills, attitudes, and values are also important aspects of the clinical competences and should be taken into consideration when clinical competency development is concerned. The level of clinical pharmacists' performance varies depending upon scope of their practice at working place. Upon entry into the profession, pharmacy graduates are just starting to manage pharmacotherapy, and even if they have huge theoretical knowledge, the experience still needs to be gained. Due to some experiential learning during their program, they could be often able to competently perform basic clinical activities, but not always providing more complex clinical services.

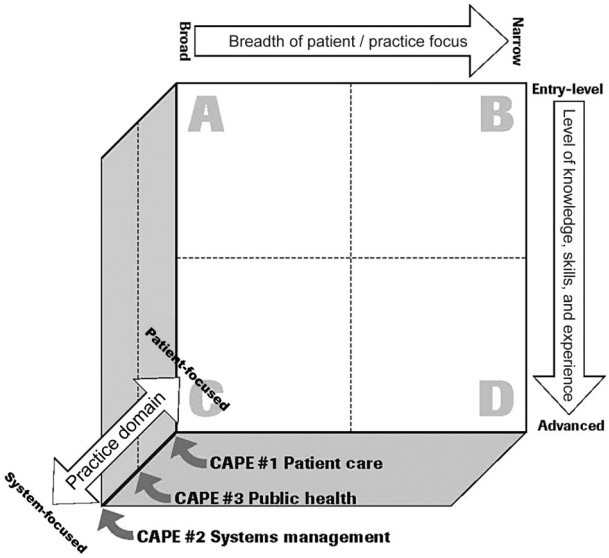


Figure 2 Development of the clinical skills (Paolini Albanese and Rouse, 2009).

In different countries, the clinical aspect of the pharmacy degree program varies. Only through continued clinical and additional learning opportunities, pharmacists can become proficient clinicians and experts in a field of practice. To conclude—clinical pharmacists develop proficiency through formal training and practice experience (Burke et al., 2008).

Later, in practice, the roles, responsibilities, and functions of clinical pharmacists could be developed in many different ways. The following concept was introduced by the US Council on Credentialing in Pharmacy to demonstrate how clinical skills in pharmacy could be developed on patient level, system management, and public health level. Looking from the different perspective: clinical pharmacist could advance as a general practitioner, but also as more focused on certain aspects of pharmacy practice (such as complex patient care, technology, pharmacogenetics, or specialized areas as oncology, paediatrics) (Fig. 2).

This concept cited sometimes as "Rouse cube" according to its conceptual author, demonstrate different dimensions and directions of clinical skills development. That is important in planning the learning of clinical pharmacist on individual, organizational, or even national and regional levels.

The axes of this three-dimensional framework lead to the planning and development of:

- breadth of patient or practice focus (x-axis)
- level of knowledge, skills, and experience (y-axis)
- practice domain (z-axis) of pharmacists

As explained in the Conceptual Framework for pharmacists' professional development in 2010, pharmacists are conceptually grouped in four quadrants, according to their practice and clinical skills development:

1. Generalist practitioner (quadrant A) covers different aspects of pharmaceutical care, but clinical approach does not have to be too complex. Majority of pharmacists develop and practice in this way.
2. Focused practitioners (quadrant B) serve patients with a wide variety of diseases but in a unique setting or population, or the practitioners have a narrow disease focus in their practice.
3. Advanced generalist practitioners (quadrant C) encounter a wide variety of patients and diseases for which the health-care issues are more complex. They need to develop clinical skills to the higher level of understanding and intervening.
4. Advanced focused practitioners (quadrant D) serve focused patient populations, with advanced approach and highest level of clinical skills, specialized in certain areas.

It is clear that for each of those groups, the CPD, training, specializations, assessment, and certifications, will aim to achieve and evaluate different competencies required for the pharmacist services provided (Rouse and Maddux, 2010).

Interprofessional Aspects of Clinical Skills in Pharmacy

Clinical pharmacists spend the majority of their time assuring that the pharmacotherapy is provided in a rational and safe way. Rarely, that could be achieved if they work independently, in isolation, more often the collaboration with other health-care providers is needed. In this context, the clinical skills are extremely important to be well demonstrated in daily communication.

Still not a large number of pharmacists have been educated and trained in interprofessional aspects of clinical pharmacy, meaning that they were not often learning in interactive communication settings with other health-care professionals. There is often one of the most important barriers that continue to prevent pharmacists from acting in the role as clinical pharmacists. Connected circumstances could encounter: inadequate leadership and management, failure to establish collaborative relationships with physicians and nurses, lack of reimbursement for clinical services, and provider status. Again, time in practice beyond pharmacy education and training is required to allow one to gain confidence in collaborative processes and experience with a wide range of medical problems and therapies, which require interprofessional cooperation in daily practice (Burke et al., 2008).

Teaching and Learning Clinical Skills

From the detailed and complex description what clinical skills for pharmacists are, and in which directions they are to be developed, it is clear that classic teaching approach (didactic lectures, teacher-directed learning, and guided instructions) will not be most appropriate teaching methodologies. As previously explained, in developing clinical competencies, all aspects of competencies must be addressed (knowledge, skills, attitudes, and values).

Knowledge should be properly addressed with solid foundational scientific facts and guidelines, following recent discoveries and updated information.

To develop clinical skills, learning should provide clear and evident links with real-life situations, as well as relevance and applicability to pharmacists' clinical practice. Clinical pharmacists learning needs can be met, only if they feel that the activity could be useful in and applicable to their daily work and if the instructor is personally experienced and skilled in the clinical pharmacy setting. Educational activities should include more interactive methods, such as small group discussions, round tables, problem-based learning including exchange of experience and workshops with practical examples. Moreover, it is crucially important that activities include demonstration of the practical aspects of the learning, with peers or teachers feedback (Tsingos et al., 2014).

Incorporating the ethical aspect in teaching process is important, both on undergraduate and postgraduate level. That way, the participants are also exploring their motives, values, and attitudes regarding clinical aspects of the patient care. Ethical issues should be addressed, providing clear solutions and answers, which allows pharmacists to develop decision-making skills and manage real-life situations. Behavior-shaping processes in education will increase motivation and professionalism and add an important value in the learning activities.

To achieve desired goals, teacher–practitioners should be included into the undergraduate and postgraduate educational programs and curricula designs must include clinical aspects of pharmacy practice in an innovative manner. Involving the patients or simulating real-life situations in the classroom could be successful, as well as interprofessional enhancement of the designed courses, including other health-care professionals as collaborative teachers and learners, together with the pharmacists (Meštrović and Rouse, 2015).

It is also important to keep in mind that for the clinical skills development, inspiring role models in practice are needed. Therefore, it would be recommended to set the criteria for preceptor selection and their education as high as possible. Working with competent mentor or tutor in practice, following not just the procedures but also their passion and dedication to achieve care plan goals for their patients is the key starting point to the clinical skills development. Students and practitioners need to believe in their capability to start getting out of their comfort zone.

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Dynamic Relationship Between Education, Regulation, and Practice

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Introduction

Pharmacists and health care workers are constantly faced with increasing and changing health care needs around the world. With the global strive toward universal health coverage—and with it the imperative for safe and effective use of and access to medicines for all—pharmacists are pressured to assess their current status, and advance and optimize their remits and practices to meet these demands. Re-professionalization is therefore an important path. However, there is no single definition of a "profession" in general, and while sociological interpretations of professions offer a solid foundation for theoretical understanding, their practical applications within the constantly changing health and pharmacy professions are limited. An alternative approach to the traditional theories of professions that can be used to analyze and identify challenges and improvement measures for the advancement of pharmacy was developed and validated. This new and simple conceptual framework redefines what constitutes a professional arena and lends itself as both a mapping tool and a diagnostic resource to support professional development and re-professionalization. This chapter presents the framework and refers to work of the authors to collate eight case studies and examples from around the world that have utilized the validated conceptual framework in their country or region to assess current professional challenges or successes, and identify drivers and barriers for advancement.

The conceptual framework describes that in any professional arena, there is a dynamic relationship between three interrelated professional sectors: practice, education, and regulation (International Pharmaceutical Federation (FIP), 2008, 2014). **Fig. 1** illustrates the conceptual framework, showing the relationship between its three principal components. "Education" refers to the sector of the profession that prepares members of the pharmacy workforce for practice; it includes both preservice entry-level education as well as continuing education (CE) and continuing professional development (CPD). "Practice" refers to the sector of the profession that provides a broad range of services to society in and from a variety of settings; practice varies according to country, context, or setting. "Regulation" refers to the sector that determines and enforces the statutory requirements for the organization and practice of pharmacy; regulation could be stemmed from within and/or outside the profession. In the chapter, accreditation of pharmacy education is included in the "regulation" sector.

The framework stipulates that any developments, changes, or innovations in any of these professional domains may drive, lead, or require an appropriately measured change or response from another. For example, changes in practice and service provision may force proportionate responses to be made in education; new regulations may impose new changes on the practice environment; and regulation changes, in the form of accreditation, may result in transformation in education provision. An appropriate "push-pull" relationship between these sectors (illustrated by the connection axes in **Fig. 1**) serves to advance the profession of pharmacy; and a disconnect or dysfunctional relationship between them usually results in complex professional challenges.

The framework illustrates that there is a dynamic relationship between the sectors; a relationship that could also be construed as a "tension" that continuously drives advancement and change. This tension or separation depicts "checks and balances" where a "push" from one sector or component can be checked (or opposed) by the other side. The absence of checks and balances between the three components may have a negative impact, for example, through conflict of interest or stagnation. It is also equally important that the separations between the sectors do not get too wide, or a complete disconnection may form. The lack of needed responsive changes by one professional domain can and should be challenged by another. Therefore, a proper "push-pull" relationship between these professional domains is crucial to advancing the profession; and disconnects between them may results in complex challenges and prove detrimental to the overall state of the profession.

The following examples may demonstrate these three relationships and how intersectoral disconnects may occur, but also how changes in one sector can drive innovation and development in another:

Practice-Education: If changes in the practice environment, such as, expansion in roles and service delivery are not met with appropriate responses by the education sector, the workforce may not be prepared to meet practice needs and hence pharmaceutical health care delivery may be negatively impacted. Alternatively, if educational institutions are not providing needs-based programs—exemplified by inappropriate adoption of foreign degrees locally—graduates of these programs may be disappointed to find that practice areas and sectors do not have the capacity to meet their expectation. Additionally, the workforce may be ill-prepared to meet real societal needs. In such situations, the educational institution fails to demonstrate social accountability. Another example strongly linking education and practice is training. Foundational training of the workforce is fundamental (and in many countries

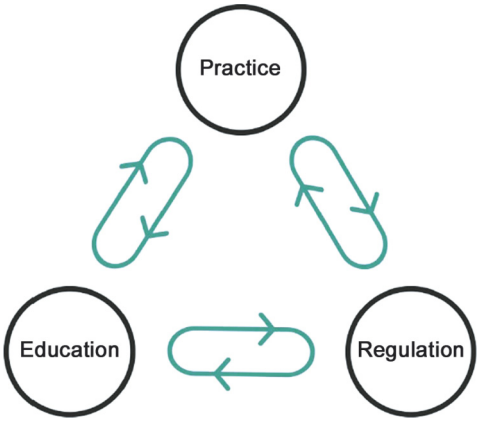

Figure 1 A conceptual framework depicting the dynamic relationships between practice, regulation, and education. *International Pharmaceutical Federation 2014, adapted with permission.*

required) for registration and practice. This results in the need for collaboration between the educational and practice sectors to provide optimal training opportunities; successful training program is one example that can demonstrate the positive impact a balanced practice-education relationship can have.

Regulation-Practice: General examples of the disconnect between regulation and practice may demonstrate the complexity and importance of this relationship too. Problems in practice may sometimes be traced to the lack of proper implementation or enforcement of regulations. Regulations may refer to practice laws, professional development and registration requirements, and medicines regulations. The "regulation" sector could, therefore, be a governmental or regulatory agency, the professional association, higher education ministries, drug authorities, etc. Improper implementation or enforcement in any of these areas results in problems with varying consequences, in some cases affecting the health and safety of patients. On the other hand, positive advancements and changes in practices may facilitate wider changes in regulations; for example, the development of advanced practice pathways starting in practice (e.g., private sector) could provide a proof of concept and therefore rationale for national strategic development of advanced practice systems.

Education-Regulation: The connections or disconnects between education and regulation can be described using the example of accreditation. Mandatory accreditation and quality assurance standards (i.e., regulations for education) established for pharmacy play an important role in shaping pharmacy education on a national level; the minimum standards of education can determine the overall quality of education. In this instance, educational regulators and stakeholders have a responsibility to regularly revise the standards established for pharmacy education to meet the national needs and changes in the profession. On the other hand—similarly to the practice-regulation relationship—advancements in education can positively impact regulation; a pharmacy school innovating in educational provision can trigger a healthy competitive effect on other institutions and force educational regulators to review and improve nationwide standards.

Existing challenges hindering the advancement of a profession may also be better understood by tracing them back to their corresponding "disconnected" axes. Hence, the framework may be used to "diagnose" existing challenges in development and prescriptive studies or initiatives. The framework may also be used to demonstrate a successful collaboration resulting in professional advances. In both cases, this diagnostic feature can facilitate the identification of barriers and facilitators, and assist to develop specific evidence-based policy-oriented recommendations or improvement measures.

The framework was first developed by author Rouse in the early 2000s as a result of his work with the Accreditation Council for Pharmacy Education (ACPE), the US national accreditation agency for pharmacy education. The conceptual framework was then used widely in presentations, depicting the need for collaboration and coordination between the entities responsible for practice, education, and regulation. The conceptual framework was first published in the Global Framework for Quality Assurance of Pharmacy Education (Version 1) which was adopted in 2008 by the International Pharmaceutical Federation (FIP)—the global leadership body for the pharmaceutical workforce worldwide (International Pharmaceutical Federation (FIP), 2008).

Between 2013 and 2014, the framework was validated and used in a country-level study in Jordan. Preliminary research resulted in the identification of eight major challenges facing the professional arena in Jordan. National stakeholders used the framework to map each of the challenges to the primary sector-to-sector disconnect that they perceived to explain it. Hence, the conceptual framework was used as a prescriptive tool. Stakeholders in Jordan used the tool to map the eight main challenges; this mapping exercise led to the identification of the primary source of the disconnect (professional challenges could be the result of multiple sectoral disconnects):

1. Unpreparedness of graduates for practice, which highlighted a disconnect between educational outcomes and practice needs (Education-Practice);
2. Inconsistencies of higher education accreditation and quality assurance mechanisms point toward a gap between educational regulations and their operationalization in educational institutions (Regulation-Education);

3. Unregulated and unorganized preregistration training is a result of a gap between appropriate training and regulation for practice placements (Regulation-Practice);
4. Absence of educational workforce development systems (i.e., CE and CPD) corresponds to a lack of regulatory policies on workforce education (Regulation-Education);
5. A growing supply of the workforce coupled with unclear market demands was identified as a symptom of a general lack of engagement between the educational and practice sectors (Education-Practice);
6. The reported occurrence of community pharmacists being paid below their nationally stipulated minimum wages is traced to the ineffective enforcement of minimum wage regulations in practice (Regulation-Practice);
7. The illegal dispensing by pharmacy assistants in community is another example of a regulation-practice gap (Regulation-Practice); and
8. A mismatch between the intended role of PharmD graduates and actual job fulfillment highlights another disconnect between the education and practice sectors (Education-Practice).

Using this participatory mapping approach, a list of evidence-based policy-oriented recommendations was developed for each of these challenges. Identifying the primary disconnect and related sectors helped formulate the most action-oriented and focused recommendations for solutions. It also helped identify the roles of different stakeholders in addressing the challenges; for example, in the case of Jordan, the national professional association carries regulatory responsibilities and the identification of "regulation" as a common source of a number of the challenges above further highlights the need for the association to review its roles and responsibilities—as well as its potential to lead reform and development. The results of this national study were published in 2016, and the conceptual framework became a global tool for identifying and analyzing challenges to the advancement of pharmacy (Bader et al., 2017).

Between 2017 and 2018, the authors further collected country and regional case studies using the tool. The purpose of this was to further utilize the tool's descriptive and prescriptive purposes in other countries around the world and to help national stakeholders reflect on successful developments and assess any existing challenges. An initial scoping survey was distributed to the authors' contacts around the world. The scoping survey served to identify preliminary case studies that were evaluated by the authors for inclusion in the Encyclopedia. A total of 10 initial submissions spanning 10 countries were received. In-depth case study templates were then sent to these country contacts and reminders were distributed. From this scoping survey, seven full case studies were received and results reported in a separate chapter in the Encyclopedia; these case studies span the following countries and regions: Brazil, Europe (with specific examples from Spain), Japan, Nigeria, Oman, Romania, and Taiwan. With the exception of South East Asia, all World Health Organization (WHO) regions are represented in this study. One additional case study from the USA was then purposively identified to provide an example of a country where a structure had been established to promote and facilitate active and ongoing communication, interaction and collaboration between the practice, education, and regulation sectors within the profession, thereby illustrating how the conceptual framework can and should work in a country. Fig. 2 depicts the dynamic relationships that are described in the case studies.

The case studies describe varying issues that touch on different sectors—demonstrating the usability of the whole conceptual framework. Each case study is accompanied by a descriptive, contextual background on education, regulation, and practice in the country or region and an analysis of the dynamic sectoral relationship(s) reported by the case study authors. Drivers and barriers to advancement, lessons learned, and implications for future planning are also discussed. The chapter authors carefully reviewed the case studies, edited them, and returned them back to their original authors for validation.

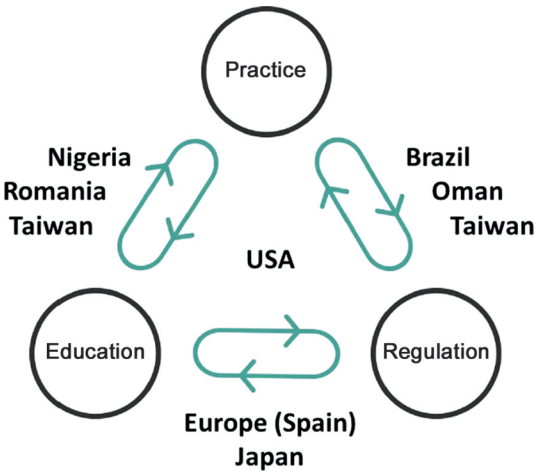

Figure 2 Summary of the dynamic relationships reported by the eight case studies.

Discussion and Conclusions

The Brazil case study demonstrated how the regulatory sector can be a positive driver for change in the practice sector, where changes in national legislation are resulting in broadened scope of practice for pharmacists; these resulting practice changes in turn drove responses from the education sector to cater to the new and expanded roles and services delivered by the workforce. In Brazil, a "domino effect" initiated by the regulatory sector demonstrates that a dynamic relationship indeed exists between education, regulation, and practice. At the same time, barriers to advancement in the country are interestingly also found within the regulatory sector, which shows that contradictory and complex forces usually exist within each sector and that strengthening drivers for advancement can support the successful impact of positive dynamics.

In Europe, as reported by examples from Spain, the effects of regional-level regulations (as stipulated by the European Union on its members) on harmonization of cross-country education is very prominent. "Soft regulations" that allow for relatively flexible adaptation as opposed to strict enforcement have proven to be a positive driver for changes in education. The regulatory harmony found in Europe has also carried a potentially positive effect on practice, via workforce mobility facilitated by mutual recognition. The Europe and Spain case study demonstrates successes of multinational frameworks and how they can be adopted and adapted based on country-level needs.

Regulation, in the form of accreditation of pharmacy programs, has had internal effects on institutional self-evaluation. In the case of Japan, the overreliance on external regulation has affected the dynamics of quality assurance in the educational sector. Institutions are dependent on external evaluation mechanisms to assure quality of educational programs, and in doing so are neglecting the establishment of strong internal quality assurance systems. While the recently established external (regulatory) accreditation has generally improved the national system for pharmacy education quality assurance in Japan, it has perhaps resulted in the unintended effect of weakened institutional-level, self-driven quality assurance, whereby "gaps" in the external evaluation system are not addressed in the internal system.

Nigeria reported an interesting case of multiple factors and drivers within education that have resulted in positive changes in the practice sectors. The case study demonstrates the importance of multinational collaboration and cross-country programs set up through strategic partnerships in catalyzing changes on a national level. It is important to note, however, that substantial donor funds have been a key factor in Nigeria's successful transitions. The prominent transformation in the provision of pharmacy education, namely its increased focus on clinical pharmaceutical care, has impacted positively on the provision of pharmaceutical care and the role of pharmacists in practice. Similarly, an international partnership with the support of funding between USA and Romania resulted in positive dynamics between education and practice in Romania.

In Oman, pharmacy regulations are not enforced effectively in all practice sectors and are sometimes in themselves lacking important elements to regulate practice. There is a high degree of variation between pharmacy practice in private versus public sectors. These factors, combined with the lack of a strategic vision for the profession, are negatively impacting the advancement of practice and the profession in general. However, acknowledgement by the Omani government of these issues—particularly of the sectoral disconnect—is considered one of the existing drivers for advancement. Despite this, review of the current regulatory enforcement process and of the regulations themselves is needed to drive positive change in practice.

An interesting case in Taiwan reported how changes in regulation drove advances in practice, advances which the education sector was not able to respond to as needed. The role of the professional body in successfully lobbying for the expansion of the role of pharmacists is evident in Taiwan. The advocacy efforts resulted in policy changes providing a wider scope of practice to pharmacists through the provision of pharmaceutical care and demonstrating the role of leadership in driving the profession forward. The positive changes on practice where especially evident in the community pharmacy sector, but educational institutions were not sufficiently preparing graduates to provide these patient-centered services. The close collaboration between the schools of pharmacy, however, coupled with the direction of the professional body may instigate the dynamic responses needed by the education sector.

The final case study from USA provides an example of a country, where a structure has been established to promote and facilitate dynamic relationships between the practice, education, and regulation sectors of the profession, which has been the focus of this chapter.

It is evident from the case studies that countries around the world report similar barriers and drivers to advancement. It is also evident that regulation plays a hugely important role in determining the status of the profession and its capacity to develop. In Brazil—the innovation in regulations drove changes in the two other sectors, showing the double relationships that can present themselves between all three sectors. Regulation in Europe, Japan, and Taiwan was also similarly seen as a positive driver. On the other hand, in Oman, the lack of regulations is a cause of professional problems nationwide. These results present important implications for pharmacy stakeholders that hold regulatory power and are consistent with findings from the validation study conducted in Jordan where regulation was also found to be a primary factor in many of the nation's challenges. Governments, regulatory agencies, higher education authorities, and professional associations with oversight responsibilities all should take note of these findings as they review their strategies and visions.

Common trends can be identified across all cases with cross-sectoral and, in some cases, multinational collaboration featuring as a prominent and main driver for positive changes across all sectors. Communication, collaboration, and concerted efforts by all stakeholders in pharmacy education, regulation, and practice are needed not only to drive positive changes in each sector but to also identify issues and barriers that need to be addressed through multistakeholder efforts. Leadership and strategic vision of a strong and stable professional leadership body, which closely works and aligns with the national government, is another driving factor for cross-sectoral collaboration.

Finally, the use of the conceptual framework by the case studies further proves its benefits in diagnosing and analyzing professional issues; by diagnosing the issues at hand, users of the framework can form specific and practical recommendations targeting the relevant stakeholders. Engaging with stakeholders to assess societal needs and professional standards is the key to ensuring that the recommendations, solutions, and improvement measures are implemented. This chapter demonstrated the dynamic relationships between education, regulation, and practice and describes how countries and institutions can use the framework for assessment of pharmacy professional challenges as well as successes.[1]

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[1] The tools and templates used by the country case study authors are available for wider use upon request from the authors.

Experiential Education for Clinical Pharmacists

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Background

Experiential education represents an indispensable part of pharmacy education, where, historically (and similarly to medicine) competencies have been developed through the apprenticeship model of teaching and learning. With the rapidly increasing knowledge base in biomedical sciences in 20th century, the need for development of more formal didactic curricula has been recognized which included traditional classroom instruction with significant proportion of practical laboratory sessions. More recently, with the changing professional roles of pharmacist, and shifting emphasis from medicines dispensing to medication therapy management and direct patient care, the need emerged for integration of theoretical knowledge and clinical experience in modern pharmacy curricula (GPhC, 2018a; Husband et al., 2014; Knoer et al., 2016; Zebroski, 2016).

Traditionally, experiential learning in pharmacy has been part of the mandatory preregistration training/traineeship which took place after graduation and was a prerequisite for professional licensure. Significant increase in the number of pharmacy graduates worldwide has been followed with the rising concerns about the consistency and quality of learning experiences provided throughout preregistration training. These concerns, accompanied with the general expectation that first pharmacy degree should be "entry-to-practice" level program (e.g. graduates exhibit professional competencies of an entry-level practitioner) resulted in the recommendations that professional practice placements should be integrated into pharmacy curricula. Thus, planning, organization, quality assurance and evaluation of experiential education become responsibility of the academic pharmacy departments (ACPE, 2015; GPhC, 2018b).

Experiential education should complement the didactic curricula and provide student pharmacists with the opportunity to better understand theoretical knowledge, integrate it and apply in direct contact with patients and other healthcare professionals, develop critical thinking and decision-making skills, and build confidence necessary for future professional practice. Development of experiential pharmacy education is topic of intensive scholarly activity, and numerous excellent publications can be find in peer-reviewed pharmacy journals. This chapter tends to provide general overview and guidance for further inquiry.

Educational Theories of Experiential Education

Experiential education, as defined by the Association for Experiential Education, is "a philosophy that informs many methodologies in which educators purposefully engage with learners in direct experience and focused reflection in order to increase knowledge, develop skills, clarify values, and develop people's capacity to contribute to their communities" (AEE, 2018).

The emphasis in experiential education is on authentic experience in the real practice settings, quality of experience, interaction, active participation, self-directed learning, and critical reflection. Thus, experiential education is related to several constructivist, social, and situational learning theories. Yardley et al. (2012) discussed different experiential learning theories as applied to medical education.

Constructivist Theory of Experiential Learning

Experiential education is based on the principles of constructivist learning theory introduced by John Dewey, Kurt Lewin, and Jean Piaget, which assume that individuals construct their own understanding and knowledge through experiencing things and reflecting on those experiences. David Kolb (1984) defined learning as "the process whereby knowledge is created through the transformation of experience". Kolb's experiential learning model is probably the most widely employed learning model in experiential education. It is represented by the four-stage learning spiral which includes: (1) concrete experience, (2) reflective observation, (3) abstract conceptualization, and (4) active experimentation. Although learning process can start at any of the four stages identified, the most often trigger for learning in clinical pharmacy is student's engagement in authentic professional practice situation (i.e. concrete experience). In order for effective learning to occur practical experience should be followed by reflection on what has happened and how it relates to past experience. This is expected to lead to critical thinking, generalization and new ideas to be tested in practice which, thus, provoke new experiences.

Sociocultural Theory of Experiential Learning

While constructivist theories focus on developing individual knowledge, sociocultural theory (Vygotsky, 1978) emphasize the importance of social dimension and describes learning as social process. Lave and Wenger (1991) argued that knowledge needs to be presented in authentic contexts, settings and situations that would normally involve that knowledge. They developed situated learning theory in which social interaction and collaboration are essential components. It assumes that learners are involved in a "community of practice" which provides the necessary guidance and encouragement. The term "legitimate peripheral participation" has been used to describe that "as the beginner or novice moves from the periphery of a community to its center, he or she becomes more active and engaged within the culture and eventually assumes the role of an expert" (Lave and Wenger, 1991). Word "legitimate" indicates that learner is accepted as a member of the working community by participating in simple and low-risk tasks that are nonetheless productive and necessary and further the goals of the community. Gradually, as newcomers advance and gain a recognized level of mastery, their participation takes forms that are more and more central to the functioning of the community. Closely related to this theory is the Experience based learning theory (ExBL) described by Dornan et al. (2014) as a model for medical students workplace learning. This educational process has been described as the "supported participation in practice", in which students are taking responsibility for seeking out and engaging in learning experiences; are actively involved in the context of the task being undertaken in the work situation; reflect on their learning experiences with mentors, supervisors, teachers, and peers; interact with colleagues and other members of the healthcare team; receive on-going feedback from mentors, supervisors, teachers, and peers. In order to denote students' progress, Dornan et al. (2009) describe four levels of participation: (1) passive observer, (2) active observer, (3) actor in rehearsal, and (4) actor in performance.

Reflective Practice in Experiential Education

Reflective practice is defined as methods and techniques that help individuals and groups reflect on their experiences and actions in order to engage in a process of continuous learning. It forms the basis of deep learning from past experiences, as critical reflection on an experience is a key element of a process that creates meaning out of an experience. The importance of reflective observation and reflective practice in pharmacy education has been elaborated by Tsingos et al. (2014). The authors concluded that "reflective practice offers to assist with the integration of theory with complexities of practice by promoting critical thinking, problem-solving, and self-directed and lifelong learning".

Experiential Education Framework

Quality experiential education is based on quality practice experience which has been defined as "a well-planned, outcomes-focused training experience with adequate supervision and assessment by a qualified preceptor within a learning-rich practice environment" (Haase et al., 2008a, Haase et al., 2008b). It is expected that structured practical placements in the real work setting, and in direct contact with patients, should enable students to integrate and apply knowledge and skills developed through the didactic part of the curriculum. While in the traditional experiential learning model student pharmacists have been expected to learn by observing

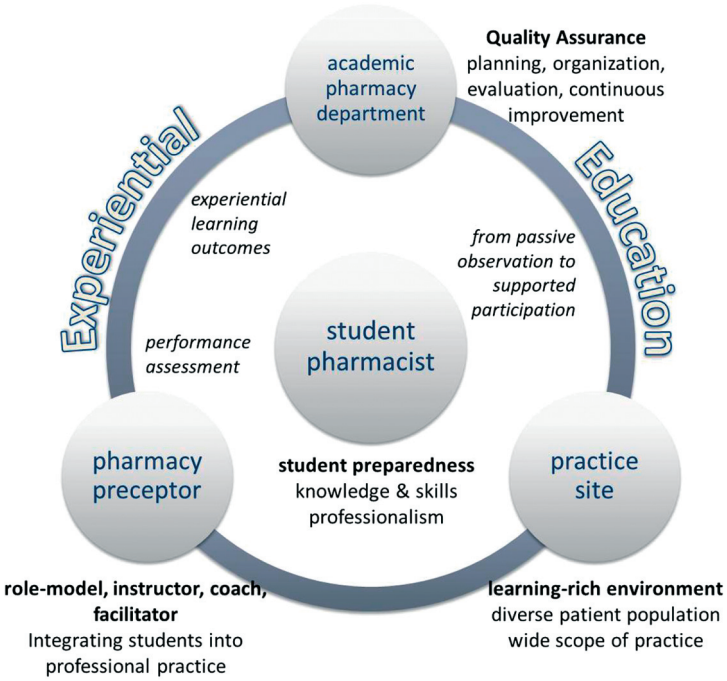

Figure 1 Framework for experiential pharmacy education.

skilled practitioners, in modern pharmacy curriculum they should engage in different professional activities including direct patient care. The importance of professional practice experiences in modern pharmacy education has been recognized and relevant guidelines and standards are provided by leading national and international professional organizations (ACPE, 2015; CCAPP, 2018; FIP, 2014; GPhC, 2011; PSI, 2013).

Development of framework for experiential education is challenging endeavor. While preregistration training in pharmacy is based, mainly, on the relationship between the recent graduate and relevant employer, experiential education model includes complex relationships and interactions in which higher education institutions, healthcare institutions, academic staff, clinical staff, students and patients are involved with their specific expectations, interests and challenges (Parojčić, 2014). General educational, professional and lawful standards and expectations related to the quantitative and qualitative aspects of experiential education, requirements for practice sites and preceptors development and qualification are outlined in the relevant quality standards (ACPE, 2015; FIP, 2014):

- practice experiences should be undertaken at approved practice sites under the supervision of appropriately qualified, experienced and trained preceptors;
- criteria for the selection, review and retention of preceptors and practice sites should be established and implemented in collaboration with the regulators of pharmacy practice;
- competency-based objectives for each pharmacy practice experience and the responsibilities of the student, preceptor, and practice site should be clearly defined and mutually agreed;
- relationship between the school and its preceptors should be clearly defined and articulated through a written agreement and/or appointment as a member of the academic staff of the school;
- practice experiences should include direct interaction with diverse patient populations in a variety of practice settings at a level appropriate to the education and experience of the student and in accordance with pharmacy practice regulations, and provide opportunities for communication and collaboration with other health care professionals.

Framework for experiential pharmacy education involves: (1) experiential learning curriculum; (2) professional practice sites; (3) pharmacy preceptors; (4) student pharmacists, and (5) academic pharmacy departments (**Fig. 1**). Overview of the relevant requirements, and responsibilities of each element are discussed in more details in separate sections.

Experiential Learning Curriculum

Experiential learning curriculum should be based on the well-defined educational outcomes which represent the basis for learning activities design and students assessment. Within the experiential curriculum, focus is shifted from teaching to learning - students are learning by observing, participating and reflecting on the experience, without much instruction received. The responsible academic staff and preceptors should jointly work on the development of experiential curriculum and define potential activities related to each

of the outcome statements. It is also important to generate practice site descriptions and reasonably define educational outcomes in line with the scope and extent of relevant professional practice.

Experiential learning should be initiated from the early stages of pharmacy curriculum (introductory professional practice experiences) and extended throughout the curriculum (advanced professional practice experiences). Learning activities should be carefully designed to accommodate increased level of student engagement from observation (at the beginning of experiential learning) to active participation in relevant professional activities and integration into the pharmacy practice model (ACPE, 2016; FIP, 2014; Hall et al., 2012; Kennerly and Weber, 2013).

EU Regulatory Framework for Experiential Pharmacy Education

In the European Union, in line with the EU Directive on the recognition of professional qualifications, "evidence of formal qualifications as a pharmacist shall attest to training of at least 5 years' duration, comprising at least: (1) 4 years of full-time theoretical and practical training at a university or at a higher institute of a level recognized as equivalent, or under the supervision of a university; (2) during or at the end of the theoretical and practical training, 6-month traineeship in a pharmacy which is open to the public or in a hospital under the supervision of that hospital's pharmaceutical department" (EU, 2013). While this directive provides common minimum standard, different models exist, and preregistration training of graduate pharmacist is still mandatory in some countries. However, the prevalent curriculum model is 5-year integrated Pharmacy program leading to the Master of Pharmacy (MPharm) degree. Integrated Pharmacy curriculum includes the requested minimum of 6-month practice placement and student pharmacists are entitled to take the licensure exam, and register as pharmacists upon obtaining the MPharm degree.

US Regulatory Framework for Experiential Pharmacy Education

In the US, pharmacy curriculum includes at least four academic years of professional studies following a minimum of two to three academic years of pre-professional, college-level study, leading to the Doctor of Pharmacy degree (PharmD). Experiential part of pharmacy curriculum in US includes at least 300 h of introductory pharmacy practice experiences (IPPE), and no less than 36 weeks (1440 h) of advanced pharmacy practice experiences (APPE) (ACPE, 2015). It has been reported that structured pharmacy practice experiences with increased complexity are being south as a strategy to provide student pharmacists with a set of skills and attitudes necessary for independent work (O'Sullivan and Sy, 2017).

The main focus of experiential pharmacy curriculum is direct patient care, where sufficient time must be provided for students to gain the core competencies in this domain. Extended periods of experiential learning placements are encouraged and may include variety of practice settings, beyond community and hospital pharmacies.

Experiential Learning Outcomes

Experiential learning outcomes should be defined in accordance with the overall programmatic outcomes of the pharmacy curriculum and aligned to professional activities at the particular practice site. Well defined educational outcomes serve as a guidance on teaching, learning and assessment for both students and practice preceptors. They should be timely communicated among all the interested parties—academic pharmacy department, students, and preceptors.

Experiential learning outcomes should be defined as clear statements of what student pharmacist is expected to be able to do after a period of practice placement within a particular learning environment, by integration of knowledge, skills and attitudes. They should be specific, relevant, attainable, and measurable. The importance of standardized learning outcomes has been emphasized in order to ensure that, although practice experiences may vary due to different site-specific activities and patient population encountered, student pharmacists will be expected to achieve similar goals. Outcomes statements are usually expressed in the form of relevant competencies, or abilities. More recently, the term "entrustable professional activities" has been introduced as a means to translate competencies into clinical practice in both medical and pharmacy education (Haines et al., 2017; Pittenger et al., 2016; Ten Cate et al., 2015). Entrustable professional activities (EPAs) are described as "units of professional practice or descriptors of work, defined as specific tasks or responsibilities that trainees are entrusted to perform without direct supervision once they have attained sufficient competence" (Ten Cate et al., 2015). It is expected that experiential learning outcomes defined in the form of entrustable professional activities may facilitate decision making about students' readiness for independent practice or progression to the next level of training (Pittenger et al., 2016).

Students Assessment

Students assessment in a complex and dynamic learning environment such as professional practice placement is challenging. Different performance-based assessment tools may be employed, as well as student portfolios (Beck, 2000; Monaghan and Jones, 2005; Swanson et al., 1995). Workplace-based assessment practices may include relevant in-training evaluation reports, mini-clinical evaluation exercises (mini-CEXs), patient reported outcomes, as well as direct observation of performance. However, students assessment generally requires highly standardized, reproducible exam environment. Therefore, performance-based assessments in health professions education are mostly based on simulated problems (case-based scenarios) from the real-world situations delivered in a form of an objective structured clinical examination (OSCE). OSCE is widely recognized as valid and reliable tool

for competency assessment, and can be used to complement traditional written tests, in order to assess students skills against the predetermined standards of performance (Austin et al., 2003; Kirton and Kravitz, 2011; Shirwaikar, 2015).

Introduction of OSCE in pharmacy curriculum is complex, resources intensive and time-consuming. It requires careful planning, and sufficient number of dedicated staff which will: (1) prepare relevant blueprint defining the number and topics to be covered at each OSCE station; (2) prepare database of relevant and realistic clinical case-based scenarios, and (3) provide training for all the examiners, as well as orientation of simulated/standardized patients engaged.

Student portfolios are widely used as both learning and assessment tool in experiential pharmacy education (Briceland and Hamilton, 2010; Driessen, 2017; Peeters, 2017; Plaza et al., 2007; Skrabal et al., 2012). It is expected that portfolio should provide comprehensive evidence of student's learning, performance and professional development. However, wider use of student portfolios has introduced certain criticism and controversy. Both students and teachers are sometimes reluctant to fully employ it. It has also been recognized that use of portfolios may become overly bureaucratic, and fail to meet the expected educational value. In order to be meaningful, portfolios should be integrated into curriculum as part of the assessment program, and contain diverse contents which can be used as the guide for discussion with preceptor, thus enabling relevant feedback and supporting further learning and progress (Eva et al., 2016).

Professional Practice Sites

It has been emphasized that "learning-rich" environment is one of the essential elements of quality experiential education. This is described as "practice site that allow the opportunity for students to engage in the direct care of a diverse population of patients and provide opportunities to interact with other healthcare professionals on a daily basis" (Haase et al., 2008a, Haase et al., 2008b).

Practice sites should be approved and continuously monitored by the academic pharmacy department. It has been stated in the relevant quality standards that "to support the pharmacy practice experiences in the curriculum and to collaboratively advance the patient care services of pharmacy practice experience sites, the school should establish and implement criteria for the selection of an adequate number and mix of practice facilities. The respective responsibilities, commitments, and expectations of the school and the practice site regarding the education and evaluation of students should be agreed and, ideally, formalized in a written agreement or contract" (FIP, 2014).

As mentioned in the previous section, student pharmacists can be placed in various practice settings. Mandatory placements include healthcare facilities involved in providing direct patient care, such as community and hospital pharmacy, as well as ambulatory patient care. Possibility for placements in pharmacy practice settings outside the traditional fields of community and hospital practice are also available, and referred to as alternative, role-emerging placements (Kassam et al., 2013). It should be taken into account that different practice sites may vary considerably with respect to services provided, patient population, number and professional structure of employees, preceptors experience, and opportunities for interprofessional interactions. Independent community pharmacy team, for example, can be quite small and with limited opportunities for student interaction with other health-care professionals, compared to large hospital pharmacy department. However, even the most advanced practice sites cannot secure per se that learning will occur if students are not looking for opportunities to learn and engage in work-based activities.

Pharmacy Preceptors

Qualified preceptors have vital role in experiential education. Pharmacy preceptor should demonstrate the ability to use clinical teaching roles, and act as instructor, role model, coach and facilitator. It has been recognized that, as instructors, preceptors encourage application of didactic knowledge through discussion with students during learning situations as they evolve, as role models, preceptors embody professional attitudes, values, and ethics by continually demonstrating these attributes over the course of the experience (Harris et al., 2012); as coaches, preceptors guide students through new experiences and difficult decision-making situations (Chase et al., 2015); as facilitators, preceptors create the infrastructure within a practice site that fosters and supports student learning (Littlefield et al., 2004).

Quality standards for pharmacy education state that schools should have "a sufficient number of preceptors to effectively deliver and evaluate students in the experiential component of the curriculum" (ACPE, 2015). It is also stated that "school should identify pharmacist preceptors who will be positive role models for students; who practice ethically and with compassion for patients; accept personal responsibility for patient's health outcomes; have professional training, experience, and competence commensurate with their position; have a desire to educate others; and have an aptitude to facilitate learning and evaluate the achievement of required competencies by students" (FIP, 2014).

In order to be effective instructors, preceptors must demonstrate expert knowledge and skills. Generally, preceptors should be recruited among the registered pharmacists who meet certain predefined criteria related to professional practice experience. They should attend initial orientation and periodical training and be certified by the academic pharmacy department. Further attributes of an excellent preceptor have been recognized as the ability to develop a relationship with the student, demonstrate skills and adaptability in teaching, encourage students to actively participate in discussion and problem-solving exercises, display positive preceptor attitude, and serve as a role model (O'Sullivan et al., 2015; Walter et al., 2017; Young et al., 2014). In the majority of studies, the importance of personal attributes of exemplary preceptors (rather than their credentials) has been highlighted. It has been emphasized that successful preceptors convey enthusiasm, professionalism, and knowledge of pharmacy to student pharmacists, and in doing so, enhance their own satisfaction and promote the profession (Skrabal et al., 2006). Being a preceptor should

be an expectation of the job. Preceptors should be provided protected time to educate students and be rewarded for their efforts (Cox, 2016).

Preceptor's responsibility is to engage student pharmacists in meaningful learning activities, ensure appropriate student interaction with patients, caregivers and other health professionals, support students and challenge them in a way that would make them "supported participants in practice at the highest level of involvement that their ability and the clinical situation permits, and adapt their behavior student-by-student and situation-by-situation" (Dornan et al., 2009). Preceptor is also expected to perform student assessment and confirm if student has attained the expected learning outcomes, as well as the level of achievement. Preceptor should clearly communicate relevant expectations, monitor student's progress and provide constructive and timely feedback. In order to serve as preceptors, pharmacy professionals should be prepared for the new role and challenges it might bring. While willingness and motivation to contribute to pharmacy education and advancement of the profession could be viewed as a prerequisite for successful preceptor, further re-training and orientation is necessary. Academic pharmacy departments are responsible for design of preceptor development programs which will address specific issues related to teaching and learning in clinical practice. These courses should be accredited continuing professional development courses and should be accompanied by regular preceptor orientation and development sessions.

Serving as preceptor is professionally rewarding and associated with certain advantages such as contribution to education of future pharmacy professionals and evolution of the profession, knowledge reinforcement through student interactions, continuing professional development and personal growth (Rathbun et al., 2012; Skrabal et al., 2006).

However, there are also numerous challenges related mainly to increased workload without financial remuneration, need to find the right balance between provision of direct patient care and students involvement, students assessment, and dealing with wide variations in student attitudes, knowledge and skills, as well as unprofessional students' behaviors. In order to successfully manage increased workload, precepting student pharmacists should be identified as job responsibility of the qualified preceptors and embedded in their professional practice. Academic pharmacy departments should provide continual support for pharmacy preceptors to develop "an advanced pharmacy practice patient care model where student learning is integral to the patient's care" (McGivney, 2009). Preceptors contribution to pharmacy education should be acknowledged by students and academic pharmacy departments, as well as professional organizations through relevant preceptors award and recognition program (Whalen et al., 2017; Worrall et al., 2016).

Student Pharmacists

Quality experiential education provide numerous benefits to student pharmacists. Experiential learning provides opportunity to better understand theoretical knowledge gained during the didactic part of the curriculum, integrate and apply it in direct contact with patients, develop critical thinking and decision-making skills, and build confidence necessary for future professional practice. Experiential education provides relevance, by focusing on real professional practice problems, active participation, feedback, individualization, interprofessional experience, career choice, and enhanced employment prospects, thus being a valuable professional and personal experience even for those student pharmacists who are not inclined toward clinical pharmacy career. In line with the current requirements that pharmacy graduates should be "practice ready", it is expected that through advanced professional practice placements student advance from competent to proficient practitioner.

Transition from the safe learning environment of the academic pharmacy department into real workplace may be quite challenging. Student pharmacists often develop anxiety and tension trying to cope with the differences in learning environment and teaching styles between the classroom setting and professional placement site. They may also worry about the workload and performance expectations, and making mistakes, as well. When involved in patient care delivery, responsibility for decision-making adds a dimension that turns mistakes from something that means a low grade to something that impacts a patient (Henman, 2015).

Therefore, student pharmacists should be well prepared for professional practice placements. Academic pharmacy department is responsible to provide students with the necessary orientation and support, and to assess student preparedness. In order to progress to professional placement, student pharmacists need to acquire certain competencies that facilitate experiential learning and assure patient safety. For that purpose, students must complete professional study modules determined by the academic pharmacy department, relevant orientation and readiness assessment. Different approaches based on early introduction of professional practice experiences into curricula, increased clinical contacts, and short transitional courses have been employed in health professions education in order to improve students preparedness for clinical practice. Chipchase et al. (2012) investigated clinical educators' views on the characteristics of health professions students that are important for preparedness for clinical learning. Six themes that can be used as indicators of student preparedness for the clinical learning environment have been identified as: (1) knowledge and understanding, (2) willingness, (3) professionalism, (4) communication and interaction, (5) personal attributes, and (6) professional and interpersonal skills (**Box 1**). Student pharmacists' professionalism is highly important for their integration into professional practice. Experiential learning provides excellent opportunities for improving student professionalism through interaction with role model preceptor, self-evaluation and feedback received (Hammer, 2006).

Academic pharmacy department should provide simulated experiences that provide students the opportunity to apply and practice concepts in a controlled environment before actually performing them (Hardya and Marshall, 2017; Lin et al., 2011). This may include interaction with simulated patients, or virtual patients. Simulated practice settings provide controlled learning environment which enables repetition, and where mistakes can be used to support learning. They should be used to develop

Box 1

Indicators of student preparedness for the clinical learning environment
(adopted from Chipchase et al., 2012)

- knowledge and understanding
- willingness
  i.e. to work as a team, ask questions, discuss, receive constructive criticisms, take responsibility to their own learning, etc
- professionalism
  understanding the code of conduct and ethics of the profession, timeliness, appropriate appearance, regular attendance, complies with confidentiality and other professional matters, etc
- communication and interaction
- personal attributes
  enthusiasm and interest, empathy, desire to learn, self reflection, helpfulness, politeness
- professional and interpersonal skills
  organizational and time management skills, social skills, problem-solving skills

communication and counseling skills and undertake performance assessments. Simulated practice settings can also be used to assess students preparedness to progress to experiential part of the curriculum. The need for standardized examination to document readiness for experiential learning has been recognized (Meszaros et al., 2009). In experiential learning, students are physically engaged in professional activities with real consequences (Hoberman and Mailick, 1994). Students learn by participating in the activities in the practice site, particularly ones that are challenging. According to the Experience-based learning model (ExBL), during experiential placement students progress through the four levels of participation starting from passive observation up to supervised care delivery (Dornan et al., 2009). It is expected that graduate pharmacist will exhibit intrinsic willingness and enthusiasm to entry professional practice; however, some student pharmacists may be somewhat less inclined to do so. For the majority of graduates, professional practice placement is a matter of choice, while some students may find it as additional, complex and demanding, curricular burden, especially if the individual is not inclined toward the pursuit of clinical pharmacy career.

Other challenges that student pharmacists may encounter during professional practice placements include situations in which students are perceived as burden, rather than a contributing member of the health care team, due to the fact that students often do not have clearly defined roles at practice site and they are not well integrated into the patient care, or working with preceptor who is being overprotective, allowing student virtually no independence, or working with an unprepared or inexperienced preceptor, which can also adversely affect the students' view of the profession.

In order to develop responsibility, self-confidence and professionalism, it is important that student pharmacists are recognized as part of the health-care team with tasks and activities which are defined in line with their level of competence, institutional rules and regulations, as well as relevant learning needs.

Quality Assurance in Experiential Education

In the modern pharmacy curriculum, experiential education is integrated with didactic teaching in such a way that on successful completion of the study program, graduates are eligible to apply for professional licensure. Academic pharmacy departments are responsible for planning, organization and quality assurance (QA) of experiential curricula, although its delivery is "outsourced" to other institutions. It is important to note that all standards of quality assurance in higher education pertinent to didactic curricula should be also met for the experiential education. Quality assessment of practice sites, preceptors and student's delivery of care is responsibility of the academic pharmacy department. Similarly to didactic curricula, consistency and quality across different placement sites should be accomplished in order to secure minimum common performance standards for all graduates (ACPE, 2015).

Quality assurance framework for experiential education is based on: (1) implementation of relevant standards related to practice sites and preceptors selection, subcontracting and evaluation, (2) assessment and certification of students compliance and readiness for practice placements, (3) monitoring preceptors and students performance (through regular site visits, timely communication and feedback obtained from students and preceptors), (4) periodical review, and (5) continuous quality improvement (**Fig. 2**).

Academic pharmacy department should define relevant standards based on the general quality standards available, and taking into account specific requirements and expectations related to national legislation, educational and health-care system.

Quality assurance framework for experiential education relies on a well-developed and maintained database and extensive documentation. Establishment of the appropriate e-platform is of great importance. Both students and preceptors should be informed in detail about the educational outcomes, curriculum, assessment and time frame of the practice experiences. Relevant information, procedures, QA documents and forms requested should be compiled in the guideline document (i.e. Experiential Education Manual/Handbook). Academic pharmacy department should timely provide necessary support for students, as well as preceptors, including relevant information, advise, students placements scheduling, remediation, or conflict resolution, when applicable.

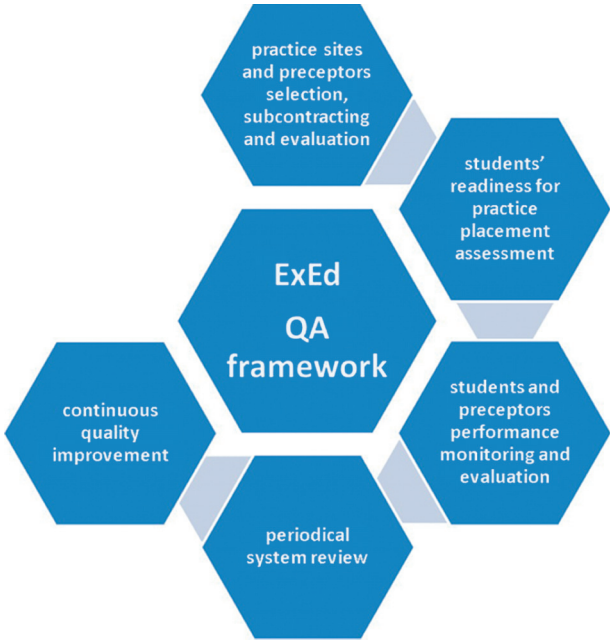

Figure 2 Quality assurance framework for experiential education.

In order to meet relevant quality standards, academic pharmacy departments have to provide financial and human resources necessary to operate a successful experiential education program (Danielson et al., 2014). Taking into account the complexity of activities related to management of professional practice placements and the adjacent workload, it is recommended to appoint person responsible for overall management and administration of experiential curricula, as well as to establish separate office/center with sufficient staff to take care of all the responsibilities.

Quality assurance of experiential education has been identified as priority area for improvement from a number of sources (Cox, 2016; Frail et al., 2017). ACCP Position Statement on ensuring quality experiential education (Haase et al., 2008a, Haase et al., 2008b) provides excellent reference for those aiming to establish new or improve the existing experiential curricula, as well as the more recent commentary on supporting quality in experiential education through enhanced faculty engagement by Frail et al. (2017).

Advancing Experiential Education in Clinical Pharmacy

In order to advance experiential education in clinical pharmacy, all the interested parties should share the common vision on the future prospects of pharmacy profession and emerging roles of pharmacists. Contribution to education of future pharmacists is one of the roles of pharmacists and should be considered professional responsibility and supported by employers, professional organizations, and regulators as advanced professional practice. Schools of pharmacy should act to instill this responsibility and professionalism in student pharmacists from the early stages of pharmacy education, and further nurture it through their professional career.

General concerns related to experiential learning in pharmacy education are that students are not actively involved in professional activities, but merely observing/shadowing, that they are most frequently engaged primarily in medicines dispensing, and that some placements sites do not provide level of pharmaceutical care which is requested in order to promote learning. However, contemporary pharmacy education is expected to prepare graduates to act as independent practitioners and provide patient care. Taking into account major challenges encountered within the experiential education framework, two points for action have been identified as crucial for further advancement and sustainability of experiential pharmacy education: (1) preceptor development program and (2) integrating students into professional pharmacy practice.

Preceptor Development Program

Quality experience and sustainability of experiential learning for student pharmacists depend on the availability and commitment of competent pharmacy preceptors. Preceptor development program should include recruitment, orientation, continuing professional development, evaluation, and recognition of qualified pharmacy preceptors. Academic pharmacy departments should collaborate with professional associations to develop comprehensive preceptor development program using variety of tools and methods

Box 2

Competency statements for pharmacy preceptors
(adopted from Walter et al., 2017)

- Demonstrate a commitment to teaching as a means for growth and skill development for each learner
- Create practice-based learning opportunities by promoting active collaboration in client care
- Engage in continuous reflection, self-assessment and lifelong learning to improve their effectiveness as educators
- Demonstrate effective communication skills
- Create professional relationships with students
- Adapt to students' learning needs
- Model best educational and clinical practices to facilitate development of skills
- Facilitate student development of critical thinking, problem solving and decision making skills
- Assess and document student pharmacist performance

of delivery (Assemi et al., 2011; Boyce et al., 2008; Worrall et al., 2016). It could include different online, and/or printed materials, e-learning modules, preceptor newsletter, as well as "face-to-face" training and networking events, including practice site visits (Vos and Trewet, 2012).

In order to develop core competencies of an effective preceptor and identify performance indicators to guide preceptor growth, Preceptor competency framework for pharmacists has been recently developed within the Canadian Experiential Education Project for Pharmacy (CanExEd). It is expected that this framework can serve as the foundation of a national preceptor development program, be integrated within the continuous professional development (CPD) process, serve as a critical component of experiential quality assurance programs (preceptor evaluation), help with identification and recruitment of quality preceptors, and be contributing criteria used for selection of preceptor awards and other recognitions (Walter et al., 2017). The list of proposed competency statements for pharmacy preceptors is presented in **Box 2**.

Recognition of excellent preceptors is important aspect of preceptor development program (Harris et al., 2012). The purpose of such program is to recognize preceptors for their sustained commitment to excellence in experiential education and professional practice. Criteria for candidates selection are based on demonstration of overall contribution to experiential education, pharmacy practice, and service to the profession. Majority of schools of pharmacy, as well as relevant professional organizations in US, have some preceptor recognition award established, such as the Master Preceptor Recognition Program established by the American Association of Colleges of Pharmacy (AACP) in 2014.

Integrating Students into Professional Pharmacy Practice

It has been recognized from a number of sources that effectiveness and sustainability of experiential pharmacy education can be achieved only if student pharmacists are adequately integrated into professional practice. It has been emphasized that "accommodating increased numbers of students for experiential training would only be possible if the hosting organizations perceived that they were receiving value in return for their contribution to the training of pharmacy students" (Hall et al., 2012). In order to achieve this, student pharmacists should be recognized as contributing members of the health care team. Reviews of the available literature on the value of student pharmacists in experiential education indicate that student pharmacists have positive impact on patient care through extended services, as well as positive economic impact through cost reductions (Mersfelder and Bouthillier, 2012; Whalen et al., 2017). Kennerly and Weber (2013) advocated that student pharmacists can assume an integrated and accountable role in the practice model by having defined responsibilities for patient care. Different ways to integrate students into clinical practice has been described as (1) stepwise incorporation into patient encounters, (2) planned integration into service-related activities, and independent projects (McGivney, 2009).

Incorporating students into patient encounters should be approached stepwise, beginning with a general overview of the patient service and the expectations of patients, preceptors, and other health professionals at the site. Independent projects can provide another level of learning for students at a clinical practice site. In addition to practice-related projects, students may be involved in other patient care-related activities, including responding to drug information questions and reviewing patient charts. Thoughtful planning of activities and integration of students into patient care can provide a wealth of resources to the site that enrich rather than overburden the faculty member (McGivney and Weber, 2009). Hall et al. (2012) argue that "experiential training would need to be designed to gradually increase, over the duration of pharmacy program, students' responsibility and accountability for patient outcomes associated with drug therapy". By assigning specific tasks to students, some of the time pressures placed on clinical pharmacists to perform these functions can be alleviated. In order to increase the accessibility, quality, quantity and variety of experiential learning opportunities, and promote and increase interprofessional and intraprofessional approaches to education and training, it is necessary to secure funding to design, evaluate, and disseminate best practices of experiential learning; create an inventory of best practices and examples of exemplary models in experiential learning; create, evaluate, and disseminate new learning models, and support mechanisms for practitioners to offer experiential learning opportunities (Task Force on a Blueprint for Pharmacy, 2008).

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Glossary

Academic Pharmacy Department - organizational unit within higher education institution, which is responsible for planning, administration and evaluation of experiential education (typically, Office of Experiential Pharmacy Education, or equivalent);
Entry-level practitioner - practitioner who has the competencies required to practice safely and independently as a newly licensed pharmacist;
Experiential Learning - structured or semi-structured learning activity that takes place in a practice setting, under supervision of an experienced practitioner, and in direct contact with patients and other healthcare professionals, that involves authentic/real-life situations and interpersonal interactions (term often used interchangeably with: practice-based learning, situated learning, clinical learning, experience-based learning, learning from experience, traineeship) (FIP, 2014);
Fitness to practice - demonstration of the skills, knowledge, attitudes and abilities required to practice safely and effectively as an independent practitioner (GPhC, 2018);
Practice site - healthcare institution, or other appropriate setting, which provides learning environment for experiential pharmacy education (FIP, 2014);
Preceptor - practitioner who teaches, supervises, and evaluates students in his or her professional practice setting (often used interchangeably with: teacher practitioner, clinical instructor, practice supervisor, mentor) (FIP, 2014);
Professionalism - the demonstration of ethics, attitudes, values, qualities, conduct, and behaviors that characterize a profession, are expected of its practitioners, and that underpin the trust that the public has in the profession (FIP, 2014);
Role-emerging placements - placements in practice settings outside the traditional fields of community and hospital pharmacy (Kassam et al., 2013);
Student pharmacist - student enrolled in a pharmacy degree program (the term is used intentionally to reflect the role and responsibility of the student as a member of the profession of pharmacy from the day a student is admitted to pharmacy study program) (APhA–ASP, 2016).

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List of Relevant Websites

Accreditation Council for Pharmacy Education: https://www.acpe-accredit.org/
Affiliation for Pharmacy Practice Experiential Learning: https://www.appel.ie/
American Society of Health-System Pharmacists: https://www.ashp.org/New-Practitioner/New-Practitioners-Forum/Resources/Mentoring-and-Preceptor-Development
Association for Experiential Education: http://www.aee.org/
Association of Faculties of Pharmacy of Canada: http://afpc.info/content/experiential-education-resources

Indicators of Quality of the Patient Care in Hospital and Community Settings

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Quality of Health-Care Services

Before implementation of indicators of quality of the patient care in hospital and community settings, it is important to understand the need to define, evaluate, and advance the quality of pharmacy practice.

Pharmaceutical care is the responsible pharmacist's practice, which provides safe and the best available therapy for the patient. It is the professional activity in which the pharmacist, using his knowledge and experience, identifies patients' needs, set priorities in the treatment process, and takes responsibility for a positive outcome of drug therapy (Hepler and Strand, 1990). That responsibility is shared with the medical doctor who has determined the diagnosis and prescribed therapy, but also with patients, encouraging them to compliance, frequent checks, and counseling about responsible treatment. There are many variations in providing patient care, but quality of services should ever be compromised.

Pharmaceutical care derives from the principles and postulates of clinical pharmacy; which pharmacists recognize as the scientific basis for intervention in the treatment of patients. The concept of clinical pharmacy clarifies the role of the pharmacist in the process of providing health care. It involves different ways of cooperation of health professionals in which science and practice can be linked to patient care. For such interventions to have the biggest impact possible, it is not only necessary to develop clinical knowledge, but also communication skills, judgment, and decision-making. Clinical practice should play an increasing role in the daily work of a pharmacist, instead of being just one of the possible options or specialty area of practice for a pharmacist (Hepler, 2004).

Today, the implementation of quality indicators for pharmacy practice will play a great role in the global effort of pharmacy advancement, while many countries are trying to incorporate clinical pharmacy and pharmaceutical care concepts in their health-care system. Although such attempts are of great interest to national and international pharmacy organizations, many challenges often appear in the implementation of this concept. Some of the difficulties may include: attitudes and opinions of other health professionals, lack of cooperation, and inadequate communication between them, and an insufficient number of pharmacists, space or equipment for the provision of pharmaceutical care, and the structure and organization of health care.

The quality indicators, when used to analyze those gaps in pharmacy practice, can provide a clear roadmap of implementation of pharmaceutical care, as well as the evidence that will help in closing the mentioned gaps.

Quality indicators can describe the possible ways to introduce innovations in pharmacy, shaping pharmacy future in a patient-oriented way. Innovative cognitive services are needed in rationalization of medicine therapy and patient education. Cognitive pharmaceutical services can be defined as professional services provided by pharmacists, who use their skills and knowledge to take an active role in patient health, through effective interaction with both patients and other health professionals. Various models of data collection, assessment tools and implementation strategies are needed to innovate and drive sustainable changes in pharmacy. All those aspects can be described and defined in the set of indicators (Smith et al., 2017).

Good Pharmacy Practice

Guidelines for Good pharmacy practice (GPP) were published by International Pharmaceutical Federation (FIP) and World Health Organization (WHO) with the intention to provide a description of ways in which pharmacists can improve access to health care, health promotion, and the use of medicines to the patients they serve (International Pharmaceutical Federation (FIP), 2011).

National pharmacy professional organizations are using the guidelines to implement them into their pharmacy practice, by setting national standards to assure the quality of services. The context of practice vary widely from country-to-country and each national pharmacy professional organization is adjusting the main principles to the local environment.

The vital element is the commitment of the pharmacy profession worldwide to promoting excellence and professionalism in practice for the benefit of the patients into practice in all settings, especially community and hospital pharmacy settings.

Besides the traditional role of pharmacists which is to prepare, procure, store, secure, distribute, expose, dispense medicines, and medical products, there are other roles described in those standards, such as role to provide rational pharmacotherapy to the patients. That would mean to assess the health status and needs of the patient, to manage the therapy processes, to monitor the outcomes of treatment and progression of the patients and to provide information on medications and treatment procedures. GPP also emphasize the need for pharmacists to achieve excellence and continuous improvement by planning and implementing continuous professional development for pharmacy competencies advancements. Public health aspect is described as the need for pharmacists to contribute to the effective functioning of the health system and public health activity by informing and educating patients about medicines, prevention and health, active involvement in the prevention, and treatment outcome procedures. There is to act in line with the national context, guidelines and legislation and to actively support and promote national strategies that aim at a good outcome of treatment and patient safety. FIP/WHO Guidelines on Good Pharmacy Practice (2011).

Indicators of Quality of Pharmaceutical Care

Indicators of quality of pharmaceutical care are equally appropriate for hospital and community settings, for hospital and community pharmacists, and other health-care professionals. The indicators should be applicable in any region of the world, providing information about the range, quantity, and quality of pharmaceutical care interventions/services delivered.

In the context of quality management, the pharmaceutical care is a process of medication therapy management and direct patient care, which is patient centered, drug focused and outcome oriented. The application of pharmaceutical care in various settings need to be standardized and measured to allow its management and improvement, and thus play a great role in setting smart standardized goals and a tool for measurement and improvement.

Indicators can help the pharmacists to organize to document and track the processes related to quality of care, to define benchmarking, decide on priorities, clarify accountability, set accreditation standards, and to ensure quality improvement.

In addition, the indicators provide information about the range, quantity, and quality of pharmaceutical care interventions/services delivered as well as an opportunity to gather in-depth knowledge on pharmaceutical care practices regionally, nationally, and internationally that will permit the sharing and follow-up of experiences over time by professional disciplines and the health sector in general, regionally, nationally, and internationally.

These indicators are rather broad, and can be further developed and refined over time, but they are easily understood and will help pharmacists, other health-care providers, and professional regulators to formalize and develop the pharmaceutical care philosophy and its working methods.

Indicators provide a quantification required to manage and improve the medication and patient care processes.

The pharmaceutical care concept is envisioned to assure the quality of services to maintain patient safety and achieving the outcomes through rational usage of medicines.

It is expected that pharmaceutical care programs will be reflecting positively on all health care programs within the strategic plans of many health-care systems in the world. Therefore, the competence of members of the pharmacy workforce is considered as the fundamental element to provide comprehensive and sustainable pharmaceutical care.

To achieve that, the strategy should be defined on the national, regional, and international levels. Indicators of quality of services should be developed for the current and targeted situations, with a concrete estimate of the desired level of implementation. The elements of regulation, education, and practice are described should be connected, in constant communication, to achieve the goal.

Classification of Quality Indicators in Health Care

In the era of universal health coverage, the indicators are the main tools that will provide a clear unified standardized roadmap for reimbursement based on performance (Joint Learning Network for Universal Health Coverage, 2018).

According to the Donabedian model, indicators can be used to assess the quality of a health care related to their structure, process, and outcomes. Those aspects could describe the setting of delivery of care, the procedures in health-care setting, and the effects of health-care services on the health status of patients and populations (Donabedian, 1983).

Structural measures indicate capacity of the health-care systems, and processes to provide care. Some examples are: the use of automation, electronic medical records, and medication order entry systems. Some indicators are describing the number of board-certified pharmacists, the ratio of number of pharmacists to the number of the patients.

The structural indicators are the measures that monitor variability in processes and focus on hospital or community pharmacy characteristics and need to have linkage to outcomes significant to the pharmaceutical care. If the quality improvement is the aim of the quality initiatives and monitoring, the indicators of the process need to be selected and implemented to the system of quality assurance. Interpreting process measures should be simple and more sensitive to small variability compared to the outcome indicators measurements (Mant, 2001).

Also, some processes, such as policies and procedures on medication reconciliation could be measured by indicators, as they are crucially important to assure patient safety (Van Sluisveld et al., 2012).

Other process measures can also indicate important compliance with standards, guidelines, and best pharmacy practice
Some examples could be:

- The percentage of patients receiving prophylaxis as indicated (immunizations).
- The percentage of patients that are treated according to first line guidelines.
- The percentage of patients with a certain disease for whom recommended laboratory tests are ordered.
- Percentage of encounters, where the pharmacist implemented guidelines

Outcome measures reflect the results of a certain service or intervention done for patients (Campbell et al., 2002)
For example:

- Mortality rates
- Hospital-acquired infections
- Patient satisfaction rate of a certain pharmacy services.

Indicators related to the outcomes are most useful for tracking care process given by high-volume providers over long periods of time, and for detecting problems in implementation of processes of care. Outcome indicators could be used when variations in health care might result in significant variations in health outcome of the patients, and where this occurrence is sufficiently common.

Palmer and Reilly (1979) recommended choosing outcomes measures if:

1. Outcomes can be measured that are affected by health care;
2. Long time-frames for measuring the outcomes are available;
3. Performance of the whole health-care systems should be studied;
4. High volume of cases is available.

A key consideration in the indicator's selection process is the practicality and capacity of its measurement. It is important that indicators can be understandable to the users, clear and precise, also applicable in the practice settings (Rubin et al., 2001).

Indicators are also used to measure the pharmacist's capacity, value, and importance in the health-care system. The indicators will allow many stakeholders to identify gaps and/or opportunities and threats to build a successful strategy to improve health-care services provision. Quality indicators are the first step in setting and operating a pharmacy service in a hospital setting. It is important to ensure that the members of the health-care team can assess all aspects of the health-care provision in the systematic way, to assure the awareness of quality analyses and improvements.

One of the most commonly used indicators classification in the health care are ECHO indicators. The abbreviation stands for Economic, Clinical, Humanistic and Outcomes and it could be applied in many sectors of the health care. There are tools developed to use the indicators and their rationale within the ECHO performance framework is explained, as well as some insights on their adequate use (Bunting, 2006).

A rate-based indicator lists compile the data about events that are expected to occur with some frequency. These can be expressed as proportions or rates (proportions within a given time period), ratios, or mean values for a sample population. To permit comparisons among providers or trends over time, proportion- or rate-based indicators need both a numerator and a denominator specifying the population at risk for an event and the period of time over which the event may take place.

A sentinel indicator identifies individual events or phenomena that are intrinsically undesirable, and always trigger further analysis and investigation. Each incident would trigger an investigation. Sentinel events represent the extreme of poor performance and they are generally used for risk management (Ansari and Collopy, 1997).

Examples of rate-based and sentinel indicators

Rate-based indicators	*Sentinel indicators*
Clean and contaminated wound infection	Numbers of patients who die during surgery
Hospital-acquired infections	Numbers of patients who die during the perinatal period
Contaminated intravenous preparation	Numbers of near miss
	Number of patient with MDR cultures

Generic indicators measure aspects of care that are relevant to the most patients, while disease-specific indicators are diagnosis-specific and measure particular aspects of care related to specific diseases.

Examples of generic and disease-specific indicators

Generic-specific indicators	*Disease-specific indicators*
Ratio of pharmacists to other health-care professionals	Ratio of patients with stroke treated with thrombocyte inhibitor <24 h after admission
STAT Medication ratio delayed more than 30 min	Ratio of patients dead after 30 days of antimicrobial treatment
Readmission within 15 days	Ratio of patients who receive restricted medications

How to Validate and Adopt the Set of Indicators in Different Pharmacy Settings?

The process of developing indicators will provide a framework that clarify accountability, allows benchmarking, and identifies areas for improvement of services in certain pharmacy setting. Set of indicators should be determined by the local context and national health strategies.

For every indictor it is recommended to set a benchmark (Fernandes et al., 2015). This can be done either by using historical data from the work setting or from literature, to set the baseline target.

The steps of developing indicators will involve:

1. Meeting and interviewing stakeholders (looking for what is critical for them)
2. Meeting with the pharmacy practitioners from different settings
3. Performing a workshop with panel group to summarize the critical to quality indicators mentioned by stakeholders and to establish a list of indicators
4. Compile the list of a draft of agreed indicators by the consensus
5. Meeting with quality department and top management to take official approval
6. Outlines of the set of indicators, determination of data collection, analysis and action plan
7. Indicators' implementation needs to be piloted for 3-month period
8. Revaluating the indicators after the 3 months period and reporting to top management, deciding on the future plan of action

An ideal indicator would have the following key characteristics:

1. Indicator is well defined and described in the indicator identification card
2. Indicator is specific and sensitive
3. Indicator is valid and reliable
4. Indicator is relevant to clinical pharmacy practice
5. Indicator permits useful benchmarking
6. Indicator is evidence-based.

A major focus need to be drawn to the validity and the reliability of the indicator, where validity is the degree to which the result of a measurement corresponds to the true state of what is being measured and Reliability is the extent to which repeated measurements show results that have no statistical significance (Sackett et al., 2000).

Fernandes et al. (2015) stated that the indicator should be:

1. Reflecting a desired quality of practice
2. Linked to the direct patient care
3. Evidence based
4. Pharmacy- or pharmacist-sensitive
5. Measurable

Incorporating indicators in Failure Mode and Effects Analysis (FMEA) processes will allow a new dimension of redesigning patient care and medication management process. FMEA is a structured approach to discovering potential failures that may exist within the design of a product or process.

Measurement and Documentation

The methods of measurements, evaluation, and documentation should be defined. In some cases, indicators can be defined as key performance indicators (KPI) and to be a part of the quality assurance systems in hospitals and community pharmacies.

Indicators can be described in the form of questions (e.g., Are pharmacists checking adherence when dispensing the medication?) or statements (Pharmacists are checking adherence when dispensing the medication.). To rate (measure) the indicators of quality for pharmacy services, they need to be quantified. Evaluation can be done with selected scale (e.g., Likert scale, a psychometric scale commonly involved in research that employs questionnaires). Ratings can be done in more descriptive way (e.g. What kind of improvement is needed (substantial, minor, etc.).

The results of measurement and documentation, when collected and analyzed in form of indicators ratios, will allow pharmacists to interpret the current situation and to plan the improvements (Bruchet et al., 2011).

When focusing on continuous improvement pharmacy practitioners will also need to balance the use of outcome and process indicators and to identify and build the link between process and outcomes of their services.

Pharmacy Services and Indicators of Quality—Some Examples

In the following text, some examples of quality indicators for pharmacy services will be described (Council of Europe (EDQM), 2017).

When the catalog of indicators is created, some of the further aspects can be selected:

CPD/CE Activities of the Pharmacy Workforce

Despite the differences in CE/CPD requirements all over the globe, it is expected that pharmacy workforce is well trained and updated in their knowledge and skills to provide quality services in different settings of health care. To assure quality of services, education, and training of pharmacists and their teams should be specific, self-directed, related to their daily practice, and applied to improve the quality of their performance. It is a good indicator if pharmacists and pharmacy technicians completed the specialized courses and training to even expand the scope of their practice and offer more services to their patients. Some of the examples might be: Immunization courses, Medicine therapy management trainings, Patient care process courses for various chronic diseases, Smoking cessation training courses, etc. It is especially visible if the pharmacy staff is changing and improving their communication and approach as the essential part of the patient care after completing the communication skills training, especially Motivational interviewing courses. What also makes difference in the quality of services is the existence of the competency and performance assessment of their learning and implementation in the practice. If pharmacists and pharmacy technicians are expected to be evaluated and encouraged to develop, if they are required to maintain the learning portfolio to plan and track their learning and application into practice, the quality of services will be higher (Bader et al., 2017).

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

CPD/CE activities of the pharmacy workforce
Are pharmacists attending internally organized education activities?
Are pharmacists attending any other pharmaceutical care courses?
Does pharmacy team have enough number of specialists in pharmaceutical care or clinical pharmacy?
Are pharmacists regularly assessed to identify the level of competencies and to plan the improvements?
Are pharmacists maintaining a CPD learning portfolio?
Are pharmacists planning their individual learning?

Patient Safety

One of the most important indicators of quality of services is the existence of the patient safety policies and procedures in community and hospital pharmacy settings.

Patient safety should never be compromised; therefore, the system should assure that pharmacists and pharmacy technicians have standardized operating procedures to follow and to assure the patient safety is maintained during offering the services of the patient care.

Patient safety could be compromised on many levels of service delivery, such as storing and preparing the medicines, during administration and dispensing of medicines, during documentation process and discharge from the hospital, including both individual and organizational factors to influence the safety (Pronovost et al., 2006).

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Patient safety
Are medication safety programs, policies and procedures established and applied in the institution?
Are the symptoms that require physician/doctor intervention explored and identified before supplying medication?
Is the appropriateness of the medicine for the actual patient assessed before deciding whether or not to dispense the medicine?

Patient safety (cont.)
Are quality reports submitted regularly?
Are supplies arranged in a code-wise system?
Are items properly labeled (expiry dates, alerts, and special warnings)?
Does the institution have sufficient and adequate storage space, that comply with required specifications?
Are cleaning and hygienic standards obtained and checked regularly?
Is patient identity checked properly?
Is patient's understanding of dispensed drug checked and maintained?
Are pharmacists using evidence-based resources regularly?

Rational Pharmacotherapy

Pharmacists should take medication history from the patients regularly in primary, secondary, and tertiary care, setting the priorities in therapy management when they identify drug-related problems (DRP). All pharmacists should be able to set the priority using clinical guidelines and tools, such as START and STOPP criteria, to contribute in the rational pharmacotherapy and patient outcomes. It is important that individual therapeutic plan for patients is created in a structured and evidence-based way. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact (Hill-Taylor et al., 2013).

Using Donabedian's framework, the majority of quality indicators related to the rational pharmacotherapy are process indicators, existing and used for the nervous system (ATC code: N), followed by anti-infectives for systemic use (J) and cardiovascular system (C). The most common indicators to document DRP were related to the 'drug selection', followed by 'monitoring pharmacotherapy' and 'drug use process' (Fujita et al., 2018).

A checklist for medicine therapy management could also be helpful, as some pharmacists are not focused on checking on patient adherence, drug–drug interaction, adverse drug reactions etc. These procedures should be in a primary focus of pharmacists in the health-care centers and community, as patients who are out of the hospitals need guidance, follow up and education. Pharmacists should check device usage regularly, and be are confident in the interpretation of laboratory results. More focus on the patient outcomes would help to improve all indicators in this cluster.

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Rational pharmacotherapy
Are pharmacists taking medication history from the patients?
Are pharmacists assessing and identifying DRP?
Are pharmacists able to set priorities in therapy management?
Are pharmacists creating individual therapeutic plans for the patients?
Are pharmacists reporting adverse drug reactions?
Are pharmacists identifying and preventing drug–drug, drug–food and drug–disease interactions?
Are pharmacists checking patient's adherence?
Are pharmacist taking into consideration relevant LAB tests?
Are pharmacists using START and STOPP criteria list for potentially inappropriate medications in elderly and other group of patients?
Are pharmacists checking device usage in appropriate way? (inhalation technique, etc.)
Are pharmacists performing medication review?
Are pharmacists educating the patients about rational drug usage?

Prevention and Public Health

Taking care of the prevention and public health are very important indicators of pharmaceutical care implementation and quality of services. There is great potential for quality improvement, taking into consideration that lifestyle changes, regular health checks, nutrition and physical activity are crucial in achievement of therapy outcomes and patient safety. Public health campaigns should be incorporated within national and/or international public health priorities and strategies to get more visibility and attention in the health care.

Often, patients are treated without considering what are their nutrition, sleeping, lifestyle habits and needs. Pharmacists should close that gap in the patient care processes. Standardized forms and leaflets, promotions and public health campaigns could be helpful in developing this important component of pharmaceutical care. Educating the patients and improving patients' health literacy is crucially important for their benefits and health improvements (EDQM, 2017).

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Prevention and public health
When counseling during medicines dispensing, is the medication regimen discussed taking into consideration patient's lifestyle and desired quality of life, needs, and expectations?
Does the patients attend an educational session before they are discharged from the hospital?
Are pharmacists offering advice about healthy lifestyle?
Are patients provided with leaflets, materials, self-control diaries?
Are patients included in the smoking cessation activities when needed?

Strategy, Management, and Organization

Clear strategy and organization in any pharmacy setting are needed in terms of time management, job description definition, skill mix usage and shared responsibility, open communication, human resources engagement, and standardization of processes. This cluster of pharmaceutical care indicators has great potential for improvement all around the globe. Rules and standards are in place in some hospitals in a very successful way, but not everywhere national standards are in place. Quality indicators, competency assessment, and patient care procedures should be nationally adopted and developed.

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Strategy, management, and organization
Are the standards for determining staff requirements and job descriptions existing and is implementation visible at all health care levels?
Is the existence and implementation of rules regulating the delivery of drug information and organizing drug promotion activities visible?
Are standards to assess pharmacists' competence and performance in place?
Are standards to evaluate the pharmaceutical services quality approved?
Are the management of time and resources well achieved?
Is the career advancement and criteria well described and transparent?
Is the patients' satisfaction obtained and measured?
Are incidences of drug shortages in the pharmacy/wards reduced to the minimum?

Interprofessional Collaboration and Integrated Patient Care

It is important to achieve interprofessional collaboration and integrated patient care in all community pharmacies and hospitals, as pharmacists' roles are becoming more and more clinically oriented. New working places are opening for clinical pharmacists in primary, secondary, and tertiary care, and that trend is likely to grow. Not all medical doctors are open to this collaboration on the same level, but some examples are showing great potential. Pharmacists should document and present more of their interventions and contribution to the other colleagues in the health care. Some hospitals and community pharmacy centers provide a good example by establishing a drug Information centers in the pharmacies, which are open to all health-care professionals in the system; the number of questions and requests is rapidly increasing, especially by the nurses, but also by medical doctors.

Common educational activities with other health-care professionals are still rare and not always well attended by the medical doctors. A multidisciplinary approach to prevention activities could be more implemented in all areas of practice and care.

It is also possible to observe the development of integrated care including other health-care professions, such as nutritionists, aromatherapists, physiotherapists, nurses, and others to provide integrated approach to the complex patients (International Pharmaceutical Federation (FIP), 2015).

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Interprofessional collaboration and integrated care
Are regular health-related interactions (calls, visits, etc.) with other health professionals and pharmacists in place?
Is the collaboration with other health-care professionals and primary care organizations established for the benefit of the patients?
Are any health prevention or other programs for the patients including multidisciplinary team (pharmacists, nurses, medical doctors, nutritionists?) organized and available to the patients?
Are common educational activities with other health-care professionals organized and attended?

Follow up and Documentation

The follow up and documentation aspect of the patient care services is usually neglected and far from achieving the real potential. Connection between primary, secondary, and tertiary care should be properly established, including data collection and sharing of results of their contribution. Patient follow up is the core activity in the pharmaceutical care process and should be maintained and documented at all levels of care. IT tools and facilities should be used more in these processes and results collected and presented. Pharmacists on all levels of practice should regularly check the outcomes of the treatment for the patients and arrange the follow up to maintain the focus of care and to achieve the outcomes.

To assess the indicators of quality in this area, some of the following questions might be used for the self-assessment or peer-assessment in community and hospital settings:

Follow up and documentation
Are pharmacists checking regularly the outcomes of the treatment for the patients?
Is patient follow-up after hospital discharge or leaving HC performed in the pharmacy (by phone or in the pharmacy)?
Are the key features of the explanation and recommended follow-up actions, interventions, including referrals to the physician/doctor documented on the service record form?
Are IT facilities in patient care process used (reminders, apps, personal records, etc.)?

Point of Care and Screenings in Community Pharmacy

Innovations are visible in point-of-care testing in various pharmacy setting, including rapid tests for important clinical parameters. Screening tests and questionnaires are in place for many indications and preventive programs. As laboratory testing cannot always be conducted close to the site of patient care, this is how some orientation testing is offered on the most accessible place for the patients. Recent advances in technology have made such testing possible for certain disease screening and prevention, across a wide range of conditions in virtually any setting. Numerous concerns have arisen about the quality and accuracy of such tests, comparability between multiple tests for the same endpoint, interpretation of test results, and whether and how results should be used for therapeutic decisions and included in a patient's medical record.

The pharmacist is well-positioned to manage and interpret POCT performed outside of the usual clinical settings. Educational and regulatory changes are needed to enable pharmacists to take on this emerging activity effectively (Kehrer, 2016).

Commonly used tests
- Blood glucose
- Blood gases/electrolytes
- Activated clotting time for high dose heparin monitoring
- Urine dipsticks including pregnancy
- Occult blood
- Hemoglobin
- Rapid strep

Available but variable use
- Cardiac markers
- Drug/toxicology
- INR/PT
- Heparin
- PSA, CRP
- D-Dimer test for thromboembolism
- Magnesium
- Lactate
- Transcutaneous bilirubin
- Lipids
- Hemoglobin A1c
- Microalbumin, creatinine
- HIV
- Influenza
- *H. pylori*
- Other bacteria

Emerging and future tests
- Complete blood count
- White blood cell count
- Coagulation for transfusion algorithms

(*Continued*)

- Platelet function
- Microbiology—outbreaks, epidemics, MRSA
- Endocrine testing to guide surgical therapy
- Parathyroid hormone
- ACTH
- Gastrin
- Growth hormone
- Testosterone
- Sepsis markers
- Stroke markers
- Cancer markers
- DNA testing

Conclusion, Summary, and Way Forward

The list of quality indicators should not only be presented as an evaluation tool, but also as a developmental and educational tool, helping the pharmacists to plan their improvement. Many organizations are using the indicators' list to plan in which areas of practice they can reach quality improvement. Pharmacists, both in hospital and community settings have shown an interest and great motivation to use indicators in their practice. Quality evaluation and improvement should be in the center of health-care leadership attention, on organizational, national, and international level.

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Interprofessional Clinical Education

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Introduction

Advancements in medical technologies, therapies, and models for health-care delivery over the last century have required enhanced education and training for professionals to prepare for a highly complex practice environment. When the expertise of each professional is optimally integrated, the overall quality of care is maximized, and patient outcomes are improved. Better chronic disease management, reduction in medical errors, and overall improvements in health outcomes have been widely demonstrated through effective collaborative practice including pharmacists as part of the team (Briggs 1999; Feldman et al., 2012; Giberson et al., 2011; Hirsch et al., 2017; Holland 2015; Hwang et al., 2017; Lovely et al., 2014; Manias 2018).

> "Collaborative practice happens when multiple health workers from different professional backgrounds work together with patients, families, careers and communities to deliver the highest quality of care. It allows health workers to engage any individual whose skills can help achieve local health goals" (Health Professions Network Nursing and Midwifery Office, 2010)

The recognition that interprofessional collaborative practice (IPCP) improves patient outcome emphasizes the need for a workforce that is prepared to work in a team environment. The landmark report from the Lancet in 2010, "Health professionals for a new century: Transforming education to strengthen health systems in an interdependent world," highlights the importance of the timing, duration, and relevance of Interprofessional Education (IPE) in promoting behavior changes among individual health professionals. IPE is a necessary response to the pressing needs of our increasingly complex and interdependent health-care systems and populations (Frenk et al., 2010).

IPE is seen as critical to both practice and education throughout the world to develop a collaborative practice-ready workforce. According to the World Health Organization (WHO), "Interprofessional education (IPE) occurs when students from two or more professions learn about, from and with each other to enable effective collaboration and improve health outcomes" (Gilbert et al., 2010). **Fig. 1** demonstrates the complicated interweaving of interprofessional training leading to collaborative practitioners. WHO emphasizes that an effective model of interprofessional collaboration should be regionally distinct, taking into account the unique needs and sensitivities of particular environments while striving to maintain the highest standards of care. Programs of excellence in preparing practitioners through interprofessional training, in both developed and developing countries, provide models that are being adopted and expanded through networks of academic and health-care institutions (Herath et al., 2017).

History of the Interprofessional Education Movement

Since the turn of the 21st century there has been an intensifying focus on IPE and collaborative practice. Among the causes for this are the shift to a chronic care model of health (National Center for Health Statistics, 2016), the defragmentation of care (Thomas and Wise, 2015), and a focus on cost efficiency (Porter, 2009). Calls for shifting health professions education to promote greater collaboration and team-based practice, however, have existed for over 50 years.

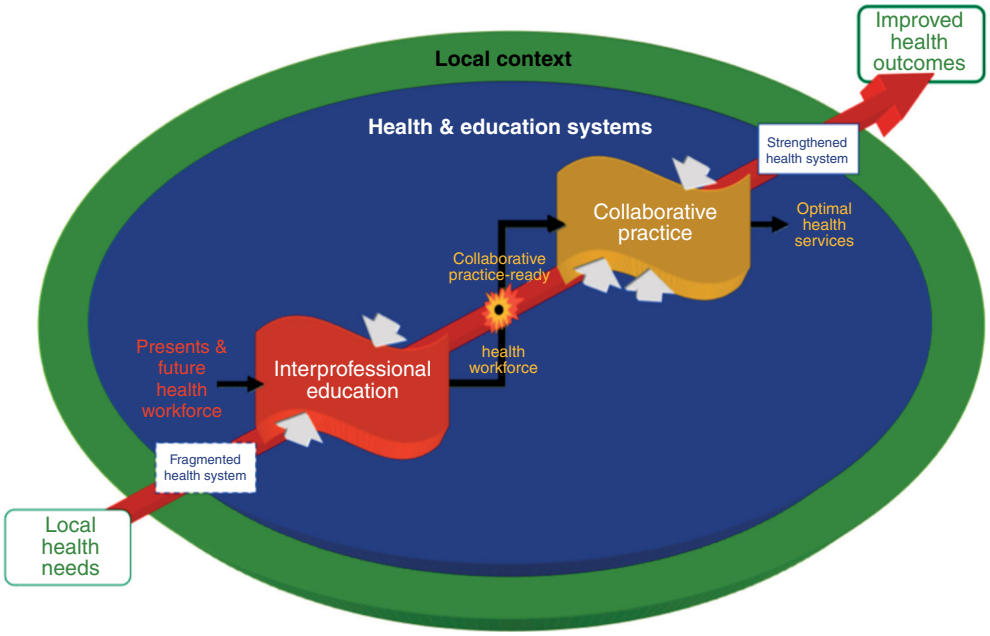

Figure 1 WHO: Framework for Action on interprofessional education and collaborative practice, 2010.

One of the earliest discussions of IPE was a conference on the interrelationships of educational programs for health professions sponsored by the Institute of Medicine. It was held in 1972 and resulted in 12 recommendations that focus on IPE in both clinical and nonclinical environments, development of faculty to teach new IPE skills, and the development of IPE competencies that promote collaborative practice and better patient care (Institute of Medicine. 1972). Although the vision was clear, implementation proved to be very difficult, especially at the prelicense level.

There are a number of examples of collaborative teams forming in clinical practice around the time the IOM was convening the 1972 conference. Surgery and emergency departments are two areas that recognized the need to develop integrated interprofessional teams to improve care delivery. Some teams were developed (e.g., Advanced Life Support) but most developed through on-the-job training.

The WHO noted the importance of training health workers to function as a team at its international Primary Health Care conference in 1978 (World health Organization, 1978). The report specifically recommended that effective health care " . . . relies . . . on health workers . . . suitably trained [both] socially and technically to work as a health team . . . ."(p5). The recommendation was primarily focused on practitioners, but there were strong implications for prelicense training programs.

In its 2010 report on IPE and Collaborative Practice, the WHO describes the need to integrate workforce planning and policy making in order to support IPE and collaborative practice. The report's call to action is primarily aimed at national and international policy makers and decision makers. However, it also recognizes the need for major changes in health professions education systems in an environment with severe shortages of health workers (Health Professions Network Nursing and Midwifery Office, 2010).

One of the first organizations that focused on IPE, The Centre for the Advancement of Interprofessional Education (CAIPE), was founded in 1987 in Great Britain and published the Interprofessional Capability Framework (Walsh et al., 2005) in 2004.

Over the last two decades, a number of events have catalyzed continued efforts to develop collaborative practice and IPE (Fig. 2) (International Pharmaceutical Federation, 2015), and a significant increase in conferences, organizations, and publications have coalesced to support expanding networks for advancing IPE efforts (Table 1).

Evolution of IPE: The Case of the United States

The IOM Quality of Health Care in America Project Impact on IPE

The evolution of IPCP in the United States is linked to political and social efforts for health reform. The stark contrast of health-care spending in the United States, compared to other countries, raised the alarm to address an unsustainable amount of spending while the quality of care was dropping. It is therefore important to look at IPE and IPCP development in terms of its unique context.

In June 1998, the Institute of Medicine formed the Quality of Health Care in America Committee. The charge of the committee was to develop a strategy that would result in a "threshold improvement" in quality during the following decade. It was their initial report, "To Err is Human," that captured the attention of providers, payors, policy makers, and the general public (Institute of Medicine, 2000). One of the more startling statistics from the committee's review of the literature was that as many as 98,000 deaths occured each year due to medical errors, with a significant proportion related to medications. They noted that the patient safety crisis

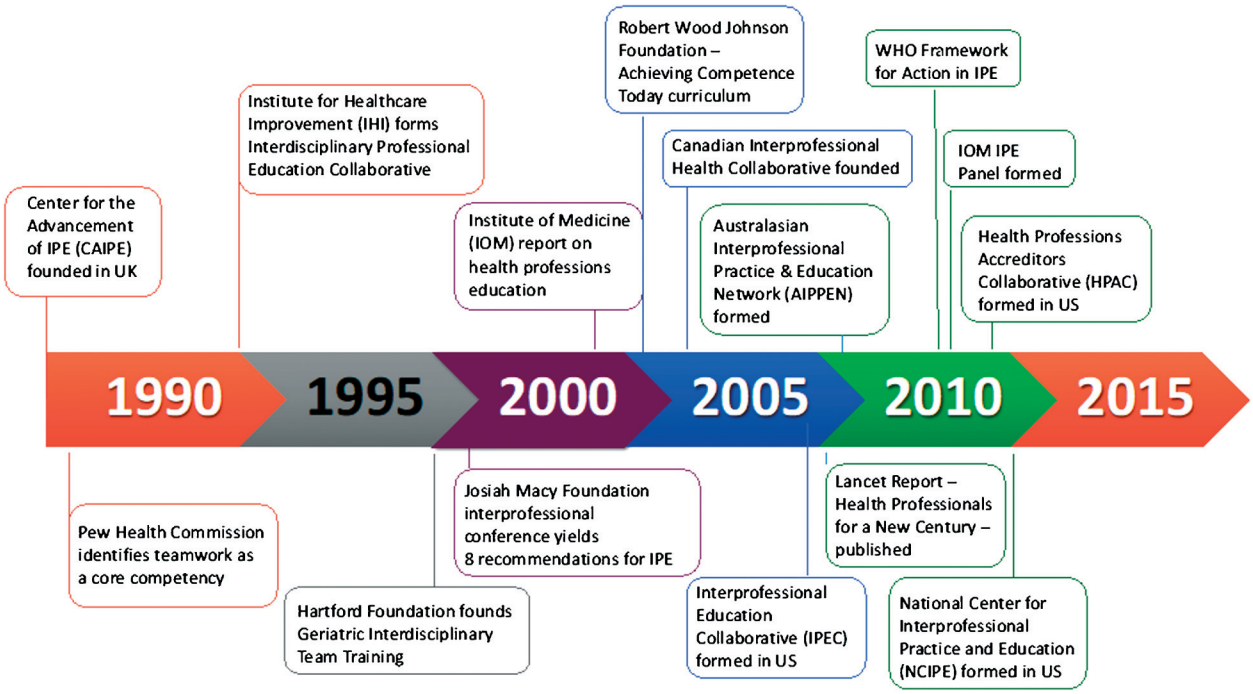

Figure 2 Timeline of select IPE events.

Table 1 Interprofessional education resources and current initiatives

A number of organizations, conference series, landmark documents, and journals have evolved over the last two decades supporting networking opportunities to facilitate development, implementation, and enhancement of interprofessional education. Most have shared focused for academics, practice, and policy surrounding IPE. Below is a brief summary of contemporary resources.

Resource

1. **All Together Better Health (ATBH)** is a biannual conference that started in 1997 devoted to sharing best practice, research outcomes and debate regarding IPE and collaborative practice. The World Coordinating Committee ATBH (https://waipe.net) consists of representatives from the following organizations.
   a. **AFRIPEN** - The Sub-Saharan African Interprofessional Education Network
   b. **AIHC** - The American Interprofessional Health Collaborative (USA), www.aihc-us.org/
   c. **AIPPEN** - The Australasian Interprofessional Practice and Education Network (Australia and New Zealand), www.aippen.net
   d. **CAIPE** - The (UK) Centre for the Advancement of Interprofessional Education, www.caipe.org.uk
   e. **CIHC** - The Canadian Interprofessional Health Collaborative, www.cihc.ca/
   f. **EIPEN** - The European Interprofessional Practice and Education Network, www.eipen.org
   g. **JAIPE** - The Japan Association for Interprofessional Education, www.jaipe.jp/
   h. **JIPWEN** - The Japan Interprofessional Working and Education Network, jipwen.dept.showa.gunma-u.ac.jp/
   i. **NIPNET** - The Nordic Interprofessional Network (Nordic countries in Europe), www.nipnet.org
2. **Collaborating Across Borders** is a North America interprofessional health-care education and collaborative practice conference through a joint effort between AIHC and CIHC. It has occurred biennially since 2007 (opposite ATBH) and has attracted participants from across the globe.
3. **Interprofessional Professionalism Collaborative (IPC)** has the collaboration of 12 American professional or practice organizations representing a variety of health disciplines. The purpose of IPC is to develop a definition of interprofessional professionalism, design and pilot an interprofessional professionalism assessment (IPA) instrument focused on health professions' entry into practice, and to develop educational resources for teaching interprofessional professionalism (IPP). http://www.interprofessionalprofessionalism.org/
4. **Interprofessional Education Collaborative (IPEC)** Founded in 2009 by six national associations of schools of health professions. Their purpose is to promote and encourage constituent efforts that would advance substantive interprofessional learning experiences. As of 2016–17, IPEC has 20 American association members representing schools of health professions. The mission of IPEC is "working in collaboration with academic institutions, will promote, encourage and support efforts to prepare future health professionals so that they enter the workforce ready for interprofessional collaborative practice that helps to ensure the health of individuals and populations." In 2011, and updated in 2016, IPEC published interprofessional collaborative competencies that are widely used in IPE.
5. **National Center for Interprofessional Practice and Education** (NEXUS) is a "unique public–private partnership charged by its funders to provide the leadership, evidence and resources needed to guide the US on the use of IPE and collaborative practice as a way to enhance the experience of health care, improve population health and reduce the overall cost of care." The National Center for IPE's website (https://nexusipe.org) provides resources that include free webinars, national data center repository, IPECP measurement instruments, forums and discussions with opportunities for collaboration, real stories about the implementation of IPECP with patients, students, networking with experts and organizations, and much more.

(*Continued*)

Table 1 Interprofessional education resources and current initiatives (*cont.*)

6. **World Health Organization (WHO) Interprofessional Education and Collaborative Practice** The Who developed the Framework for action on interprofessional education and collaborative practice in 2010, highlighting interprofessional collaboration around, identifying mechanisms to shape successful collaborative teamwork and outlining a series of action items that policy makers can apply within their local health system. "The goal of the Framework is to provide strategies and ideas that will help health policy-makers implement the elements of IPECP that will be most beneficial in their own jurisdiction". http://www.who.int/hrh/resources/framework_action/en/
7. **Institute for Healthcare Improvement (IHI) Open School** is a global learning community for students. It provides online education, local Chapters, and guided improvement projects. There have been more than 500,000 interprofessional learners from universities, organizations, and health systems around the world who have participated in building core skills in improvement, safety, system design, and leadership. http://www.ihi.org/education/ihiopenschool/Pages/default.aspx
8. **Selected Journals with a Focus on Interprofessionalism**
   a. Education for Health—www.educationforhealth.net/
   b. Focus on Health Professional Education: A Multidisciplinary Journal—https://www.anzahpe.org/journal
   c. Journal of Interprofessional Care—https://www.tandfonline.com/toc/ijic20/current
   d. Journal of the Allied Health Professions—http://www.asahp.org/journal-of-allied-health/
   e. Journal of Continuing Education in the Health Professions—https://journals.lww.com/jcehp/pages/default.aspx
   f. Journal of Research in Interprofessional Education—www.jripe.org/
   g. Journal of Interprofessional Education & Practice—http://www.journals.elsevier.com/journal-of-interprofessional-education-and-practice
   h. Medical Education—https://onlinelibrary.wiley.com/journal/13652923
   i. Medical Teacher—www.informahealthcare.com/mte
   j. The Clinical Teacher—http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1743-498X

is multicausal but much of the problem is related to outdated and failed systems of care delivery. Among their recommendations is a call to " . . . establish interdisciplinary team training programs for providers that incorporate proven methods of team training . . . " (p. 14). The second part of the committee's report, released a year later, focused on designing a new health-care delivery system to address a range of quality issues (Institute of Medicine, 2001). This report emphasized the need to reexamine our current system of education of the health-care work force. A model of shared responsibility and team-based care requires a set of competencies that are ideally taught through IPE.

The third report in the Quality Chasm Series focused directly on the health-care workforce and the need for significant transformation in order to function effectively in the proposed 21st century delivery system (Institute of Medicine, 2003). The report identifies five competencies for all health-care professionals: (1) Provide patient-centered care, (2) work in interdisciplinary teams, (3) employ evidence-based practice, (4) apply quality improvement, and (5) utilize informatics. These competencies are interrelated and, taken together, provide a model improving patient care.

IPEC Competencies for Interprofessional Education and Collaborative Practice

After the reports from the first decade of the 21st century, the initiatives for IPE for most US trained health-care professions began to gain momentum. Among the several groups that began to coalesce around IPE and CP were the Institute for Healthcare Improvement (IHI), the Interprofessional Education Collaborative (IPEC), and the Josiah Macy Jr. Foundation. Donald Berwick, MD (founding President of IHI), and George Thibault, MD (President of the Josiah Macy Jr. Foundation) were the two most visible leaders of this early work. Their voices were channeled through IPEC to develop educational IPE competencies and to, subsequently, impact professional education. IPEC, formed in 2009, was a coalition of six accrediting bodies. They included: Accreditation Council for Pharmacy Education, Commission on Collegiate Nursing Education, Commission on Dental Accreditation, Commission on Osteopathic College Accreditation, Council on Education for Public Health, Liaison Committee for Medical Education.

IPEC developed a set of core educational competencies for interprofessional collaborative practice that were widely disseminated in 2011 (Interprofessional Education Collaborative Expert Panel, 2011). In addition to specifically identifying four competency domains and 38 specific subcompetencies, it also proposed the new field of "Interprofessionality." The report defined this concept as " . . . the field of interprofessional practice and interprofessional education." (p. 9). Tethering education and practice fostered a single discussion that includes learner, as well as, patient outcomes. It also expanded the participants in the discussion. The concept of interprofessionality was founded on the principle that working together with other providers and professionals needed to be deliberate and purposeful.

The four competency domains from the 2011 report include:

- Competency Domain 1: Values/Ethics for Interprofessional Practice (Work with individuals of other professions to maintain a climate of mutual respect and shared values.)
- Competency Domain 2: Roles/Responsibilities (Use the knowledge of one's own role and those of other professions to appropriately assess and address the health-care needs of the patients and populations served.)
- Competency Domain 3: Interprofessional Communication (Communicate with patients, families, communities, and other health professionals in a responsive and responsible manner that supports a team approach to the maintenance of health and the treatment of disease.)

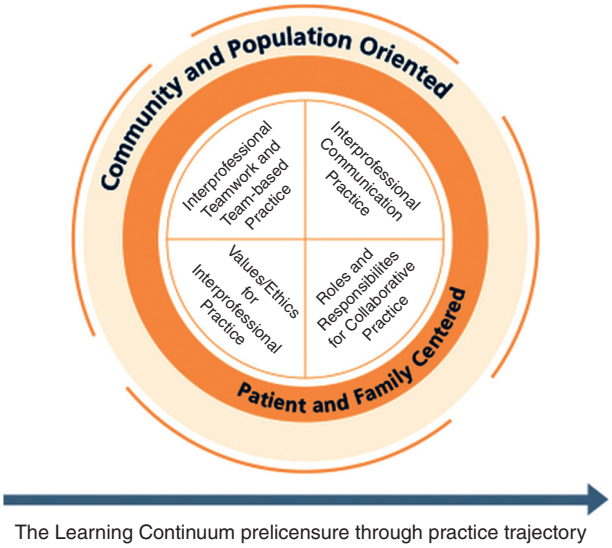

Figure 3 IPEC Framework for 2016 Revised Competencies for Interprofessional Collaboration.

- Competency Domain 4: Teams and Teamwork (Apply relationship-building values and the principles of team dynamics to perform effectively in different team roles to plan and deliver patient-/population-centered care that is safe, timely, efficient, effective, and equitable.)

The expanded model (Fig. 3) embeds the four competencies within a framework of patient- and family-centered care which, in turn, is embedded in a broader orientation of community and population health.

Dissemination and Revision of the 2011 IPEC Core Competencies

In 2014, the Health Professions Accreditors Collaborative (HPAC) was established to coordinate licensure-level training programs' IPE programs to ensure that the graduates were adequately prepared to practice in an interprofessional health-care environment. In 2017, there were 23 HPEC organizational members; almost a fourfold increase from the original six accrediting organizations.

Over the five succeeding years from the release of the 2011 IPEC competencies, three additional institutional members joined the original six founding organizations. They included the Association of Schools of Allied Health Professions (ASAHP), the Council on Social Work Education (CSWE), and the Physician Assistant Education Association (PAEA). Additionally, over 60 disciplines have sent representatives to IPEC-sponsored faculty development training programs.

In 2016, IPEC released a revision of the original core competencies and subcompetencies that reflected population health goals and the inclusion of many additional professions involved in health (Interprofessional Education Collaborative Expert Panel, 2011).

The revisions to the competencies and subcompetencies represent an expanded view of interprofessional collaboration that encompasses patient, family, and community health. While it is not clear whether the expanded focus is a cause of the many diverse organizations endorsing the domains or a consequence of the additional organizations, the ability to impact health can be found in many more professions that would not have been considered "health related" in the past. The 2016 IPEC revisions incorporate population health and health policy (Interprofessional Education Collaborative, 2016)

A Proposal to Change Pharmacy Practice for Improved Patient and Population Health

Pharmacists have had an escalating role in managing medication for patients over the last several decades. In the United States, prior to 1955, there were less than 200 FDA-approved medications. Today, in addition to multiple formulations and generics, there are more than 19,000 FDA-approved prescription products (FDA. Fact Sheet: FDA at a Glance.), and the growing number of treatments offers many more options for patients medical needs. It has also resulted in a number of complex medication-related issues to provide optimal care for patients, such as optimal medication selections, minimizing drug interactions and adverse effects, and selecting cost-effective therapies Pharmacists, have taken on many of these responsibilities within the health-care team. This has commanded changes over the decades in pharmacist education and training with enhanced clinical focus in addition to foundational scientific knowledge of medications. In the United States, the Doctor of Pharmacy (Pharm D) became the entry level degree for practice in the year 2000. A number of schools throughout the world have adopted the Pharm D degree (Accreditation Council for Pharmacy Education International Programs by Country), while others have revised their curriculum to become more clinically

rigorous or offer postgraduate Master's degree in a focused area such as hospital or clinical pharmacy (e.g., Europe, Australia). Postgraduate training (e.g., pharmacy residency programs) and credentialing (e.g., Board of Pharmaceutical Specialty) is also becoming preferred for many direct patient care positions.

Over the last 50 years, clinical pharmacy practice in hospitals and health systems has become a standard with pharmacists not only overseeing the medication distribution services but also being physically present on patient care units providing medication expertise and interacting with other health professionals and patients (Saavedra-Mitjans et al., 2018; Schneider et al., 2018; Vermeulen et al., 2018, Homsted) (Schneider et al., 2018). Ambulatory care practice is exploding with pharmacists integrated into the clinic setting providing advanced collaborative pharmacy services as part of a clinical team (Homsted et al., 2016, Buxton et al., 2015). Community practice has also advanced practice through a variety of models by not only providing medications to patients but also education, monitoring, and managing chronic diseases such as diabetes, hypercholesterolemia, and tobacco cessation (Alsaidan et al., 2018; Dokbua et al., 2018; Mansell et al., 2017; Saavedra-Mitjans et al., 2018). Evidence of improved patient outcomes is well documented when the pharmacist is included as part of the health-care team in these various settings.

These evolutionary changes have set the stage of pharmacists to be integrated fully into interprofessional collaborative practice at multiple levels and a variety of practice settings. In the United States, there were a number of other changes in health-care delivery that occurred during the time period from about 2008 through 2012 that further impacted pharmacists' role in the direct delivery of care and the spread of IPE and collaborative practice. The Affordable Care Act, enacted in March of 2010, expanded the number of individuals with health insurance by many million. It immediately created a critical shortage of providers, especially in primary care. Pharmacy education had already revised its license-level training programs to greatly expand direct patient care skills as described above. In a 2011 US Public Health Service report to the Surgeon General, a detailed plan was proposed to improve patient and health-care delivery system outcomes through advanced pharmacy practice. The plan included four focus areas: (1) Pharmacists integrated as health-care providers, (2) expanded recognition of pharmacists as independent health-care providers (including advanced practice models), (3) appropriate compensation mechanisms, and (4) evidence-based alignment with health reform (Giberson et al., 2011).

Implementation of IPE

Barriers and Success Factors

Several notable barriers have been identified in attempts to develop new IPE activities or programs. Differences in professional cultures, curriculum rigidity, scheduling challenges, distance in physical location, lack of common IPE vision, limited resources, and lack of leadership are commonly recognized challenges (Sunguya et al., 2014). Attitudinal differences regarding IPE are often present at multiple levels within in institutions including administration, faculty, and/or students. Despite these obstacles, many institutions have succeeded in implementing IPE, and there are a growing number of national and international resources available to support program development and improvement (**Table 1**).

There is a heightened global recognition regarding the value of IPE. Many countries have begun initiatives for supporting or requiring IPE through accreditation standards for pharmacy such as Australia (Dunston et al., 2018), Japan, multiple countries in the Middle East (El-Awaisi et al., 2017b), Canada (The Canadian Council for Accreditation of Pharmacy Programs), United States (Zorek and Raehl, 2013), and Great Britain (General Pharmacutical Council 2011). For pharmacy, the International Federation Pharmaceutical (FIP) hosted a landmark conference in November, 2016 "Global Conference on Pharmacy and Pharmaceutical Sciences Education," which included a focus on the importance of interprofessional collaboration in both the Nanjing statements and the Work Development Goals (Bader et al., 2017).

Several roadmaps are being developed for programs that are initiating or expanding their IPE efforts. Considerations for implementing a successful program have been described and identify key planning elements (**Table 2**) (Buring et al., 2009).

Development of IPE Programs

The delivery of a designated interprofessional curriculum in college and university programs throughout the world has been accomplished through a variety of modalities (Fox et al., 2018). After identifying interprofessional partner(s), a critical next step is agreement on IPE competencies. The five most cited frameworks are described in **Table 3**. While in the United States, the IPEC competencies are standardly used by schools of pharmacy, UK, Canada, Australia, and Japan have developed their own frameworks. All of the published IPE frameworks have content overlap as well as some unique domains. An international consensus statement on the assessment of interprofessional learning outcomes recommend assessment of the interprofessional learner in the following domains: role understanding, interprofessional communication interprofessional values, coordination, and collaborative decision making, reflexivity,and teamwork (Rogers et al., 2017)

Defining Competence

One of the differences among the frameworks is in terminology, especially around the term "competency." Early in the 1960s, a shift began from learning objectives to competencies to define behavioral objectives. Competency was then tied to learners having to demonstrate that they have mastered a set of skills or a body of knowledge (Carraccio et al., 2002). IPE competencies are typically directed at skills that complement uniprofessional expertise, but must be adaptable for life-long collaborative practice. IPE

Table 2 Elements critical for implementing interprofessional education

- Identify interprofessional education (IPE) as a goal of your college/school of pharmacy
- Identify administrative and faculty champions at your college/school to lead and support IPE initiatives
- Establish relationships with other health-care programs, considering geographical locations, university ownership/affiliation, and existing relationships
  - Schools/colleges of pharmacy without other health profession programs at their institution can still accomplish effective IPE by partnering with other institutions of higher education that may or may not be within the geographical area
- Identify the administrative and faculty champions at each of the partnering programs
- Establish an IPE planning team with engagement from every player
  - Choose IPE curricular theme
  - Evaluate equivalent levels of education; match students based on education level and maturity
  - Determine when and where this IPE will occur in the curricular schedule and who will teach/facilitate the interprofessional curriculum
  - Gradually implement based on level of preparedness (start small and go slow)
  - IPE planning team members must advocate for the acceptance of IPE curriculum at their individual schools/colleges
- Offer faculty development programs to support faculty teaching in IPE
- Establish faculty rewards and recognition for IPE involvement
- Determine an assessment strategy to evaluate the IPE initiative and share results with internal and external stakeholders, as well as the academic community via scholarship

Reproduced from Buring et al. with permission (Buring et al., 2009)

Table 3 Interprofessional competency frameworks

Competency framework	*Terminology used*	*Framework domains*
Interprofessional Capability Framework (U.K.), 2004	Capabilities	• Ethical Practice • Knowledge in Practice • Interprofessional working • Reflection
Canadian Interprofessional Health Collaborative (CIHC), Canada, 2010	Competencies	• Interprofessional communication • Patient/client-centered care • Role clarification • Team functioning • Collaborative leadership • Interprofessional conflict resolution
Core competencies for interprofessional collaborative practice, IPEC, U.S. 2011	Competencies	• Values and ethics • Roles and responsibilities • Interprofessional communication • Teamwork and team-based care
Interprofessional Capability Framework Australia, 2011	Capabilities	• Communication • Team function • Role clarification • Conflict resolution • Reflection

Interprofessional Competency Framework (Japan) 2018	Competencies	• Core Domains
		  ◦ Patient-/Client-/Family-/Community-centered
		  ◦ Interprofessional Communication
		• Peripheral Domains
		  ◦ Role Contribution
		  ◦ Facilitation of Relationship
		  ◦ Reflection
		  ◦ Understanding of Others

competency statements "identify specific knowledge, skills, attitudes, values and judgments that are dynamic, developmental, and evolutionary" (Bainbridge et al., 2010), which support the need to continually update curricula to meet the changing needs of populations over time. While some IPE frameworks use "competencies," there is a lack of consensus regarding the definition of "competence" (Nicolas et al., 2012) and some scholars have deemed "competence' too static for the dynamic nature of IPE. "*Capability*" has been used in preference to *competence* in other IPE frameworks, to encompass a more adaptive ability to meet the needs of a changing health-care environment (Walsh et al., 2005). IPE frameworks that have been developed throughout the world are described in **Table 3**.

Once competencies have been agreed upon, there are many available strategies for implementing IPE training programs. Barriers described above often result in a gradual building process for IPE programs. Abu-Rish and colleagues (Abu-Rish et al., 2012)

reviewed current trends in IPE. Of the 83 eligible studies they examined, small group discussions and problem-based learning were the most used strategies, followed by clinical teaching and simulation-based learning. There were a wide variety of instructional design formats being used across the curriculum. Some programs initiated entrée into IPE by having a single program, an IPE "day," or a series of activities for two or more professions. Knowledge-based IPE competencies are often addressed early in the curriculum through didactic/interactive classroom teaching, team-based projects, or case-based study. For more advanced learners, IPE practice simulations and clinical service learning have been integrated. Fox and colleagues (Fox et al., 2018) had similar findings regarding multitude of pedagogy and assessment strategies. In this work, almost all of the IPE implemented resulted in positive changes in student's perceptions and attitudes regarding IPE and practice.

Because of the wide variety, it is difficult to assess the overall impact of the numerous IPE strategies. **Table 4** provides a brief description of select published approaches and strategies to IPE including pharmacy learners.

Table 4 Brief description of example IPE initiatives and strategies including pharmacy learners

Single or Series of IPE events
• Singer et al. (2018) describe an "IPE Day" which devotes a full day of events designed to build toward IPE competencies with 438 first year students representing four professions. Through this experience, students demonstrated significant improvement of self-ratings using the Interprofessional Collaborative Competencies Attainment Survey (ICCAS).
• Nagge et al. (2017) in also had positive outcomes in their Healthcare Interprofessional Education Day (HIPED) among 2nd year pharmacy students and 1st year medical students with collaborative activities focused on communication, patient interviewing, and prescribing.
• El-Awaisi et al. (2017a) focused on a single event with a specific topic, delivering tobacco cessation content as well as highlighting professional roles. They engaged 50 students from four disciplines (pharmacy, pharmacy technician, medicine, and public health). Prepost assessment with Readiness for Interprofessional Learning Scale (RIPLS) indicated that students already had positive perceptions regarding IPE and further increased after event.
• Hadley et al. (2018) recently developed a pilot workshop with occupational therapy, physical therapy, pharmacy, and physician assistant students. The program included an ice breaker and a case-based activity with a jigsaw design. Student feedback and perceptions were positive based upon this experience.
• Lehrer et al. (2015) provided an interesting perspective with an analysis of a series of peer-led problem based learning (PBL) in IPE. The IPE perceptions of medicine and pharmacy students that participated in a weekly one-hour problem-based learning seminar over 16 weeks were compared, in a case–control design, to the perceptions of student who did not participate. Using the Interdisciplinary Education Perception Scale (IEPS), data showed significant higher perception of professional cooperation among medical and pharmacy students who attended seminars versus those who did not.
Interprofessional Courses
• Simko et al. (2016) developed a 3-hour credit course with a focus on pain management. Learners over two course offerings were 25 junior pharmacy and 35 senior nursing students. Instruction by multiple professionals as well as group IPE assignments was held throughout the semester. Activities included developing and presenting a patient care plan as well as simulations with a standardized patient as IP team. Significant improvement was seen in the IEPS, Collaboration and Satisfaction about Care Decisions (CSACD), and reported knowledge of the other profession for both nursing and pharmacy students.
• Kim et al. (2017) involved senior students (402) from nursing, pharmacy, allied health, and medicine completed an interprofessional course dedicated to critical event/disaster response. After completing online coursework, a 4-h synchronous team simulation focused on resuscitation, decontamination, and mass casualty triage. Pre/post evaluations resulted in improvement in team participation values, critical event knowledge, and 94% of participants reported learning useful skills. Most frequent qualitative response was value of interprofessional experiences in team communication and desire to incorporate this kind of education earlier in curriculum.
• Peeters et al. (2017) described first year health science students (554) from eight professions engaged in an impressive 14-week required course focused on the IPEC competencies. Activities included case-based communications exercises, standardized-patient interviews, simulations, vital signs training, and patient safety rotations. Student's self-assessed competency of course learning objectives based on Kirkpatrick's levels, student satisfaction with the course, and perceptions of other participating professions via word cloud. Competencies and satisfaction were significantly improved and there was change in students' perceptions of other professions.
• Shrader and colleagues involved pharmacy students longitudinally with IPE activities through a pharmacy-based clinical assessment course (Shrader and Griggs, 2014). Third year (71) pharmacy students engaged in 9 separate IPE activities as part of the course. The IPE events included participation of physician assistant, medicine, nursing students. Sixteen of the 18 items improved on the pre- vs postcourse Interdisciplinary Education Perception Scale (IEPS) score.
• Truong et al. (2018) reported an inter-institutional effort (Eastern Shore Collaborative for Interprofessional Education-ESCIPE), multiple intervention with nine disciplines to develop IPE toward IPEC competencies among nine disciplines (including pharmacy) and 18 faculty. Multiple activities were included in this effort such as an emergency preparedness point-of-dispensing (POD) drill, patient management laboratory simulation, geriatric assessment interdisciplinary team workshop, medical mission as public/global health rotation and service-learning program, rural health fair, and annual university health festival for community outreach at different stages of learning throughout the curriculums. Feedback has been positive and program evaluation plans are underway.
• Rotz et al. (2016) developed an impressive 6-semester experiential course series involving first and second year pharmacy and medical students. The courses consisted of a combination of teaching methods: orientation, reflective sessions, hybrid didactic/active-learning activities, and experiential component at student-run clinic and other practice sites. Students had both profession-oriented and IPE goals throughout the series. While still early in the course implementation, the results of standardized assessments so far showed that students expressed positive perceptions of interprofessional collaboration with respect to teamwork, roles and responsibilities, and patient outcomes, student perception scores, high team performance of collaborative behaviors, and a majority of teams demonstrated appropriate competence with respect to interprofessional communication and teamwork.
• Thompson et al. (2016) combined longitudinal, interactive classroom and interprofessional clinic experience with serving an inner-city charitable clinic. Eighty students representing 13 professions, worked together for an academic year. Pre/post assessments with RIPLS, T-TAQ, showed significant improvement in interprofessional attitudes. Results of the health-care professionals circles diagrams indicated increases in students' perceptions of the types of interprofessional team members, relationships, and communication between professions to provide medical care to patients.

Table 4 Brief description of example IPE initiatives and strategies including pharmacy learners (*cont.*)

Case-Based Interprofessional Learning

- Case-based learning has been utilized throughout the curricular levels and in both classroom and clinical settings.
- Posey et al. (2018) designed a case competition for Level 5 nursing students and third-year pharmacy students to work together as a pilot in the development of their IPE program. In addition to developing the clinical components of the case, participants were asked specific questions regarding interprofessional learning. A modified version of the Interprofessional Education Collaborative (IPEC) Competency Survey and the RIPLS Questionnaire were administered before and after the activity and demonstrated improved engagement with other health-care professionals.
- Nasir et al. (2017) implemented case-based interprofessional learning for undergraduate health-care professionals in the clinical setting teaching scenarios of real patients with student groups of four and including at least two professions. There were 329 students from 9 professional that attended one session during the academic year. One of the outcomes observed included that 70% of respondents stated they would alter their future professional behavior as the result of this learning.

Health Care Team Challenge™

- The Health Care Team Challenge (HCTC™) (Newton et al., 2013) is an innovative interprofessional learning activity that was created at The British Columbia University over 20 years ago. It is a case-based competition between two or more IP teams of students, representing at least two disciplines. A patient case is assigned prior to the event and, collaboratively, the teams develop a patient-centered plan of care. The teams present of their plan of care occur in front of a live audience and then are provided with additional relevant information pertaining to their case. While on stage, the team is asked to adjust their care plan accordingly. A panel of judges evaluates teams on both quality of care and IP collaboration. A number of programs (University of Queensland, University of Minnesota, Clarion, University of Washington, University of Toronto, Jikei Institute, Graduate School of Health Care Sciences, International Interprofessional Collaborative 2012: Kobe Japan) have adapted this activity and tailored it to their specific need. Through its broad implementation, the use of the HCTC™ has demonstrated impact on improved knowledge and attitudes toward collaborative practice, sustained changes in beliefs, behaviors, and attitudes related to socialization. An education research collaboration has been developed to further elucidate the role of HCTC™ in IPE.

Simulation

- Palaganas et al. (2016) reviewed the literature of simulation in IPE and concluded that while there is growing literature with some positive outcomes, data are still too limited to recommend how to best use simulation within IPE. Simulation IPE may include mannequin-based, standardized patients embedded-simulation persons, virtual platforms, or role play. Benefits of simulation include that it bypasses some of the challenges of being in a clinical environment, allows more control of the experience, and can be tailored to the level and type of learners; however, logistics of scheduling, costs, and alignment of goals and desired outcomes are some of the hurdles related to IPE simulation.

IPE Online and Distance Learning

- Online engagement of interprofessional students is becoming more prevalent.
- Evans et al. (2018) recently reviewed experiences of faculty facilitating online exchanges. Asynchronous group discussions were reported as the most common online approach, faculty perceived this to be a valuable approach despite challenges of involving all learners in this venue.
- Dow et al. (2016) developed a web-based case system for IPE training. During academic year 2012–13, 80 teams composed of 522 students from medicine, nursing, pharmacy, and social work participated were assigned to interprofessional virtual teams. Each team member had profession-specific information and was responsible for providing a summary of this information into the case system's electronic medical record. Each team member also answered knowledge questions about the case individually and then collaborated asynchronously to answer the same questions as a team. Team scores were significantly higher than individual scores. Students and teams with higher knowledge scores had higher case activity measures. Team score was most highly correlated with number of message board posts/replies and was not correlated with number of views of message board posts.
- Mccutcheon et al. (2017) reviewed the current status of IPE via distance learning. Based upon three questions: (1) Is this study implementing IPE? (2) Is this study utilizing the instructional delivery method of distance education? and (3) Does this study contain students from two or more health-care professions?, 15 of the 478 articles originally identified met inclusion criteria. Five of these including pharmacy students. Key finding from this review included that there were positive outcomes IPE outcomes such as recognizing roles of other professions, interprofessional teamwork, and interprofessional socialization, however, experiences varied by study. Further, some negatives identified were lack of personal contact, cumbersome programmatic layers, and technical difficulties. Facilitators sometimes lacked training and the online development was more time-consuming the in-person teaching. There were a wide variety of teaching models used including virtual towns, online learning communities, virtual interactive patients, and synchronous and asynchronous group forums.

TeamSTEPPS®

- TeamSTEPPS® is a teamwork system designed for health-care professionals to improve quality and safety of patient care developed by the Department of Defense's Patient Safety Program in collaboration with the Agency for Healthcare Research and Quality. Use of this tool has been used in numerous programs facilitating teamwork skills for students and practitioners (Welsch et al., 2018).
- Jernigan et al. (2018) engaged 715 first year learners from fifteen professions in the Level 1 TeamSTEPPS® program. Significantly positive attitude changes were documented among learners as well as increased appreciation for interprofessional communication and better understanding of the roles of other health-care professions. Other programs have also observed improvement in knowledge and attitudes when using this teaching tool in the acute care hospital setting (Fowler et al., 2018) as well as student-faculty primary care practices (Weinstein et al., 2018).

Student Run Clinics (SRC)

- Student-run clinics (SRC) have the advantage of providing a service while offering a learning environment, often to individuals in underserved settings.
- Haggarty and Dalcin (2014) described the growing number of voluntary SRCs that have developed in Canada over the last two decades with both IPE training and service to the community. The clinics have shown to provide similar outcomes to usual care and, while the IPE competency outcomes were limited, students were immersed in interprofessional care.

(*Continued*)

Table 4 Brief description of example IPE initiatives and strategies including pharmacy learners (*cont.*)

- Farlow et al. (2015), from the United States, similarly promoted SRC as an excellent IPE learning model.
- Lie et al. (2016) proposed a framework for understanding student learning during team-based care in an interprofessional SRC serving underserved patients. Analysis of the student focused groups resulted in six common themes about learning content from uniprofessional groups: role recognition, team-based care appreciation, patient experience, advocacy-/systems-based models, personal skills, and career choices. The authors also reported that "synthesis of themes from all groups suggests a learning continuum that begins with the team huddle and continues with shared patient care and social interactions. Opportunity to observe and interact with other professions in action is key to the learning process."

Clinical Practice IPE Experiences

- Nuffer et al. (2015) reported on the sustainability of a practice-based Interprofessional Introductory Pharmacy Practice (IPPE) experience course. The program has been ongoing for 13 years where third-year PharmD students were paired with community-based providers. The experience was a series of half-day visits for a semester and the learning objectives focused on enhancing the students' abilities to communicate and work closely with non-pharmacist health-care professionals and to gain an appreciation for the workplace pressures faced by those practitioners. Both pharmacy class size and the number of provider partnerships grew over the 13 years, with 154 students and 194 partners at the time of writing. Students consistently affirmed achieving the stated goals through the years and improved self-assessed level of confidence as a result of working with a non-pharmacist health-care practitioner. The authors conclude "The study provides indirect evidence through the long-term sustainability of the course that third-year pharmacy students have the competency to integrate themselves into medical and nursing practice sites and to contribute to patient care. It also provides evidence that the course is useful in socializing pharmacy students in the context of interprofessional health care teams".
- Boland et al. (2016) created an interprofessional immersion experience with 24 pharmacy, psychology, nursing, and family medicine trainees. The program was 1 week long side-by-side training focused on the IPEC core competency domains. Interprofessional teams observed, learned, and practiced working in teams. Upon completion, trainees reported more confidence regarding ability to work within an IP team a more likely to use the team-based approach.
- Anderson and Thorpe (2014) qualitatively assessed practice-staff, patients, and facilitators on how mid-level interprofession students team learning impacted practice. Results indicated that the students provided positive value, offered solutions to improve quality of care and propelled practitioners to maintain high professional standards.
- Brewer and Stewart-Wynne (2013) implemented a 2–3 week clinical placement for students from eight professions focused on six beds in a general ward. Authors reported the students attitudes improved overall regarding interprofessional education and the student's acquisition of a high level of interprofessional practice capabilities. Qualitative data from students and clients were very positive as well.
- Stubbs et al. (2017) developed an inter-institutional, community-based IPE student experience. Thirty students from 10 professions dentistry, dietetics, divinity, medicine, nursing, occupational therapy, pharmacy, public health, social work, and speech and hearing sciences worked in IP groups of six. The program included both a didactic, 2-month preparatory phase and a 4-month service-learning phase. The service-learning involved teams facilitating focus groups, interviews, and informal discussions with clients and organizations to identify specific needs and priorities and then working collaboratively to provide solutions. Significant improvements were observed in students' comfort working with others, value in working with others, and self-perceived ability by standardized assessments.

A recent report from the American Association of Colleges of Pharmacy Task Force on Intentional Interprofessional Education in Experiential Education (IIEE) (Grice et al., 2018) defined IIEE as "the explicit effort by preceptors and practice sites to create/foster educational opportunities or activities designed specifically to achieve interprofessional educational competencies." While there are many examples in the literature experiential-based IPE, the task force assessed that most occur in a nondeliberate manner. This group particularly highlighted opportunities in advanced pharmacy practice experiences (APPE), noting that an APPE that occurs in an interprofessional environment is not necessarily IIEE. The intentionality comes with targeting IPE competencies in design/developmental phases and building on previous IPE concepts in the curriculum. The task force challenged academic scholars for further advancement in IIEE.

Most institutions have aspirations of an IPE program that is multifaceted with longitudinal and is integrated throughout the curriculum to prepare practice-ready graduates. Some programs have made significant progress toward this goal and have become centers of excellence and share their resources. A sample of these progressive institutions includes University of Toronto (http://www.ipe.utoronto.ca/interprofessional-education-curriculum), University of British Columbia (https://health.ubc.ca/integrated-education/interprofessional-curriculum), University of Washington (https://collaborate.uw.edu), and University of Minnesota (https://www.health.umn.edu/our-impact/interprofessional-education).

Evaluation of IPE

Evaluation of IPE is essential for determining the effectiveness of educational goals and IPE competencies. Evaluation strategies work best when they are part of the curriculum development process. Recent reports from the IOM have called for both formative and summative assessments of IPE using qualitative and quantitative methods (Hovland et al., 2018; Zomorodi 2018).

A critical development of an overall assessment map of IPE programs is the evaluation of which IPE competencies are met by each program. Simmons and colleagues (Simmons et al., 2016) have proposed some reflective insights that are useful for planning and implementing IPE assessments. These included the fact that IPE "is a complex activity due to its involvement of both individuals as well as interprofessional teams/groups" and "[as part of] designing an IPE assessment a series of key questions needs to be posed and addressed, including, what is the purpose of the assessment? What is one going to assess? and How is the assessment to be

Table 5 Outcomes of interprofessional education

1 Reaction	Learners' views on the learning experience and its interprofessional nature.
2a Modification of attitudes/perceptions	Changes in reciprocal attitudes or perceptions between perceptions participant groups. Changes in perception or attitude toward the value and/or use of team approaches to caring for a specific client group.
2b Acquisition of knowledge/skills	Including knowledge and skills linked to interprofessional collaboration.
3 Behavioral change	Identifies individuals' transfer of interprofessional learning to their practice setting and changed professional practice.
4a Change in organizational practice	Wider changes in the organization and delivery of care.
4b Benefits to patients/clients	Improvements in health or well-being of patients/clients.

Modified Kirkpatrick's Model of Educational Outcomes for IPE, reproduced with permission (from Freeth et al. (2002, p. 14).(Freeth, D., Hammick, M., Koppel, I, Reeves, S., Barr, H. 2002)

performed?" It was suggested that an assessment blueprint is "vital to linking proposed learning outcomes with methods of assessment" and "the use of an assessment matrix can effectively collate key elements related to the assessment of IPE." Lastly, "entrustable professional activities and milestones are promising techniques to use in in IPE assessment."

It is essential for the evaluation to generate an understanding of the range of intended learning outcomes expected from an IPE activity. In measurable terms, an assessment needs to be made of knowledge, skills, attitudes, and beliefs, which can be focused on the individual learner, the learning community the institution, or the system as a whole. The modified Kirkpatrick's outcomes typology described in **Table 5** has been widely incorporated as an outcome-based framework for evaluating IPE, especially in the pharmacy literature. The original Kirkpatrick model had four levels: 1-reaction, 2-learning, 3-beahavior, and 4-results. It was expanded to the present version by adding two outcomes at levels 2 and 4 (Freeth et al., 2002) to further clarify the progression and distinguish between outcomes that relate to people and those that have an impact on service delivery. The complexity of behavioral change increases as evaluation of the interventions ascends in the hierarchy, and the model represents a sequence of strategies to evaluate programs.

A novel approach to the assessment of interprofessional competencies began at University of British Columbia (Charles et al., 2010). Their model was built on Miller's Learning Pyramid: "knows"(knowledge); "knows how"(competence); "shows how" (performance), and "does"(action) (Miller 1990). Early efforts for building IPE competencies focus on the knowledge and awareness and evolve into application and integration into professional practice. They proposed the process of exposure, immersion, and mastery for development of IPE competencies. The University of Toronto adopted a similar approach based on the preparation of their learners building from *exposure* (introduction) to *immersion* (development) to *competence* (entry-to-practice). **Table 6** demonstrates an example of assessment strategies applied to this IPE program. For both hierarchical learning models, the highest form of learning outcome is performance in practice on a daily basis in complex systems—a learned ability linked to formal training or the development of expertise over time.

A number of assessment tools have been developed for IPE competency domains. Areas of assessment include learner reactions, attitudinal shifts, behavioral changes, knowledge and skills acquisition, organizational practice changes, and benefits to patients (Bookey-Bassett et al., 2016; Oates and Davidson, 2015; Shoemaker et al., 2016; Shrader et al., 2017). **Table 7** lists some commonly used tools. While there are a few instruments that measure higher level learning, most tools and research have been focused on student attitudes toward, and readiness for, IPE as well as their achievement of individual IPE activity goals. Standardized approach to assessment with IPE is needed, yet there is still limited data to determine the best strategy. Continued focus on expanding research toward evaluating the impact of the IPE training on teamwork and patient care is needed.

Table 6 University of Toronto Assessment Strategy

Level	*Assessment*	*Notes (Domains and Format)*	*WHO*
Exposure	Quiz	Knowledge of foundational values, communication, collaboration	Faculty (via Learning Management System)
Exposure	Reflective writing	Values—Uploaded to Peer Scholar	Peer feedback
Exposure to Immersion	Reflective writing assignments (x3)	Reflective assignments (Values and Ethics, Communication and Collaboration)	Faculty
Exposure to Immersion	AITCS Assessment of Interprofessional Team Collaboration in Student Learning	Group process scale embedded in the Pain Curriculum (is being piloted in other group-based learning activities)	Group—Peer (guided by a facilitator)
Immersion	ICAR Modified Interprofessional Collaborator Assessment Rubric	Individual feedback embedded in the Pain Curriculum	Self and peer
Competence	IPCA Interprofessional Collaborator Assessment	Performance-based 360° assessment in a practice setting	Practicing team members

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Table 7 Selected evaluation/assessment tools for interprofessional education based on Kirkpatrick model toward IPEC domains

Level	*Tool name*	*IPEC domain*
1a. Reaction	Readiness for Interprofessional Learning Scale (Parsell and Bligh, 1999)	Roles/responsibilities Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice
1a. Reaction	Interprofessional Attitudes Scale (IPAS) (Norris et al., 2015)	Roles/responsibilities Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice
1a. Reaction 2a. Modification of attitudes/perception	Collaborative Healthcare Interdisciplinary Planning Scale (CHIRP) (Hollar et al., 2012)	Teams and teamwork Values/ethics for interprofessional practice
1a. Reaction 2a. Modification of attitudes/perception	Interdisciplinary Education Perception Scale (IEPS) (Hawk et al., 2002)	Roles/responsibilities Teams and teamwork Values/ethics for interprofessional practice
1a. Reaction 2b. Acquisition of knowledge and/or skills (when used as part of TeamSTEPPS training)	TeamSTEPPS Teamwork Attitudes Questionnaire (T-TAQ) (Baker et al., 2008)	Roles/responsibilities Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice
2a. Modification of attitudes/perceptions	Attitudes Toward Health Care Teams Scale (ATHCT) (Heinemann et al., 1999)	Roles/Responsibilities
2a. Modification of attitudes/perception	Student Perceptions of Physician-Pharmacist Interprofessional Clinical Education (SPICE-2) (Zorek et al., 2016)	Roles/responsibilities Teams and teamwork Values/ethics for interprofessional practice
3. Behavioral change	Assessment of Interprofessional Team Collaboration Scale (AITCS) (Orchard et al., 2012)	Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice
3. Behavioral change	IPEC Competency Survey Instrument (Dow et al., 2014)	Roles/responsibilities Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice
4a. Change in organizational practice	Index for Interdisciplinary Collaboration (IIC) (Oliver et al., 2007)	Teams and teamwork Values/ethics for interprofessional practice
4a. Change in organizational practice	Interprofessional Socialization and Valuing Scale (ISVS) (King et al., 2010)	Roles/responsibilities Interprofessional communication Teams and teamwork Values/ethics for interprofessional practice

Faculty Development

Faculties play a critical role in IPCP and IPE; thus, they need to understand IPE and have skills for facilitating IP learners (Egan-Lee et al., 2011; Simmons et al., 2011; Steinert, 2005). A majority of published descriptions of IP training have focused on the learner. There are limited outcome data on effective methods for faculty training. The timing of and resources for faculty development appear to be relevant to initiation and sustaining IPE. Ratka and colleagues (Ratka et al., 2017) provided an overview of faculty development programs for IPE. Based on their overview, five characteristics of an effective IPE faculty development program emerged: (1) institutional support, (2) objectives and outcomes based on interprofessional core principles, (3) focus on consensus building and group facilitation skills, (4) flexibility based on institution and participant-specific characteristics, and (5) incorporation of an assessment strategy. A variety of approaches including didactic, experiential, in-person, online, blended methods, and capstone projects have been used for faculty development. A standardized approach should be used for each institutional program, and strategies should be developed that are tailored to the needs of the organization.

Summary

IPE and collaborative practice have become not only helpful but also necessary for providing quality health care to patients and for promoting population health. The explosion of medical and biological sciences, the rapid growth of new health-care professions, and the shift from critical care to chronic care are among the most critical variables that have changed the nature of health and health care.

It is easy to see how a holistic approach to caring for patients became increasingly difficult and inefficient over time. In fact, the health-care delivery system itself became a common cause of morbidity and mortality. An examination of this alarming finding concluded that practitioner incompetence was a very small part of the problem. The system, itself, was the primary cause of most of the errors that resulted in patient harm. This growing problem is a global one, but countries with sophisticated and complex health-care delivery systems have felt the consequences more acutely. Professional organizations responsible for both training and professional practice in many different health professions have come together in search of solutions, and it has become clear that interprofessional collaboration is essential to improving care.

The discussions among the major health professions identified two major components to improving interprofessional collaboration: Training and Practice. While training and practice are closely linked, the recommended solutions are very different. Both areas, however, are served by the creation of competencies for health-care professionals. The approaches to implementing the competencies vary across the training and practice environments. The practice environment has focused on a wide range of quality initiatives that focus on patient outcomes, quality metrics, and system changes. There are also a number of training programs, such as TeamSTEPPS®, that support these efforts for practicing professionals.

The larger challenge, however, has been changing the training programs at the prelicense level to prepare professionals for lifelong team practice. Most professions have been siloed since their inception. With the recent revolution in health care, IPE initiatives have begun at academic health centers, and educators began to recognize that both students and faculty knew very little about the training of their colleagues in other professions. Institutions with successful IPE programs usually have IPE centers that stand apart from any individual health professions school. New IPE curricula, faculty training programs, and facilities are becoming more commonplace at academic health centers and many accrediting bodies now require it.

A parallel development to the rapid rise in IPE training and collaborative practice models has been the growing number of professional organizations, publications, and research in these areas. In addition to important manuscripts appearing in mainstream education and practice journals such as Academic Medicine, Lancet, and the Journal of the American Medical Association (JAMA), a number of new journals have emerged whose primary focus has been iIPE and practice as described earlier.

These multifaceted advancements are particularly important as more experience and research is needed to determine optimal models for IPCP and the best IPE strategies to achieve them. Both IPCP and IPE will continue to expand as health care continues to evolve.

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Further Reading

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Leadership in Pharmacy

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Introduction

The title of this chapter is Leadership in Pharmacy. You may have chosen to read this chapter because you want to become a leader in the profession. This is good news. We are entering a period of what could, and likely should, be great change in health care. Whenever change is needed, we have an even greater need for leadership. And the more transformational the nature of the change, the stronger and more flexible that leadership must be. We definitely need to develop and recognize leadership across many aspects of pharmacy practice and clinical pharmacy.

Before you read further, however, we want to make it very clear that it is beyond the scope of any book, video, or website to make a person into a leader. One can learn about leadership from such resources. Learning about leadership means being introduced to the underlying tenets and reviewing the key theories that describe and predict leadership behaviors. One can also learn from the stories told by leaders. Leadership stories that illustrate not only the successes but also the setbacks experienced along the way can be particularly valuable. Further, one can learn from other leaders and with other aspiring leaders. The most humbling and powerful way to develop skill is to invest in hands-on training that includes time spent practicing the often-difficult actions associated with leadership and then getting feedback from others on these actions. So, while reading this chapter will not, by itself, make you a great leader, we hope that it will be a positive influence on your personal leadership journey.

Our authoring team represents leaders across a range of career stages with experience in a variety of aspects of pharmacy practice across three different continents. Each of our journeys has been different, but despite this, we have taken comfort in some

commonalities along the way. It is these that we will share with you. Indeed, we have attempted to distill a great deal of pharmacy leadership information for you by focusing on the following key questions:

- How do pharmacy leaders come to be?
- How can you discover and document your pharmacy leadership abilities?
- What theories support leadership in pharmacy?
- What style of leadership is best suited for you, your audiences, and for the pharmacy decisions you face?
- How have other leaders approached challenges in pharmacy?
- Where can you go to continue your pharmacy leadership journey?

We hope that this approach will assist those of you who are interested in becoming pharmacy leaders and even those of you who have been placed into leadership roles by a supervisor or by peers. We also hope it will inspire you to discover your inner leader, learn more about what that inner leader needs to grow, and most importantly, connect with others who are striving in this area.

How do Pharmacy Leaders Come to be?

A longstanding debate swirls around the question of whether leaders are "born" (i.e., with innate leadership skills) or "made" (i.e., via purposeful development over time). One of the original philosophies of leadership is known as the "great man" theory. This theory, proposed in the 1840s by Thomas Carlyle (2008), suggests that leaders, who at that point in documented history would likely all have been men, are born with certain skills of power and influence. Despite a lack of rigorous studies to support this theory in the modern context, it is comforting to think that superhero-style leaders appear fully formed to save the day when a need arises. If we are not born as one of these superheroes, then we never have to face that responsibility.

In almost no aspect of work in health care are our inborn traits the primary driver of our successes. We were not born possessing the medication knowledge and clinical skills needed to care for patients. Rather, becoming a pharmacist is a journey that we undertake and refine in order to reach and improve that goal. This suggests that the likelihood that pharmacy leadership is solely an inborn skill is low. If it then follows that pharmacists become leaders through development over time, one would expect to find a clear definition of this leadership target. Interestingly, there are more than 4000 documented definitions of leadership and even more when you include some of the overlapping concepts from management in this mix. For the purposes of this chapter, we will define leadership as the framework of skills and abilities that are necessary for an individual to drive team success (Azad et al., 2017).

Pharmacists care for patients, guiding them directly or indirectly through the maze of appropriate medication use. Pharmacists must be persistent problem solvers, managing processes to formulate the best course of action for a specific patient in a specific care scenario. Pharmacists are responsible—according to legal requirements, corporate policies, and professional expectations—for the health and safety of patients. This chapter is written in the context that all pharmacists act as leaders at various points throughout their days, their positions, and their careers. In the next section, we will discuss how to better discover, develop, and foster that leadership to improve the systems in which we work.

How Can You Discover and Document Your Leadership Abilities?

Our individual personalities, tendencies and proclivities, in addition to our education and experience, all contribute to our leadership personas. Yet every pharmacy leader has a starting point from which that leadership persona emerges. The aphorism, "Know Thyself" was inscribed over the ancient Greek temple at Delphi and philosophers such as Socrates used it to emphasize that we must know ourselves deeply in order to fully develop (Ryff and Singer, 2006). This is also true for pharmacy leadership.

Throughout a given week, we may be offered glimpses into our specific personality traits, perhaps in the form of a social media survey that identifies which color, direction, animal, or Harry Potter character we are most like. These can be fun to complete and inherent in them are the more rigorous measures of (A) personality, (B) strengths/skills/talents, and (C) styles from which they have been adapted. While a multitude of these self-assessment tools exist, some open access and others, proprietary; **Table 1** offers a representative sample for your review. Many employers offer education and training programs that are founded in tools such as these. Consulting with your human resources representative to determine which may be available to you and potentially the teams who work with you is an excellent idea.

Once you have completed these self-assessments, where should you go next? We recommend creating a leadership portfolio to not only aggregate the results of these types of assessments, but also to place them into context. This can be done in printed format or electronically, using software like DropBox® or Evernote®. The creation of a portfolio and the reflection on the components included in it may highlight which leadership attributes are innate and which must be developed. It may also allow an individual to analyze where they are now and where they wish to be. Finally, the leadership portfolio can serve to document leadership development over time. This will aid you internally but may also help with any documentation required for continuing professional development activities, such as achievement of advanced practice status.

Table 1 Representative "know thyself" assessments

Personality Assessments	Myers-Briggs Type Indicator® http://www.myersbriggs.org/my-mbti-personality-type/mbti-basics/ Emotional Intelligence (EQ) http://www.talentsmart.com/about/emotional-intelligence.php DiSC® Profile https://www.discprofile.com/what-is-disc/overview/ Animal-based personality tests DOPE (dove, owl, peacock, eagle) http://richardstep.com/dope-personality-type-quiz/ Lion, Otter, Golden Retriever, Beaver http://smalley.cc/images/Personality-Test.pdf
Strengths/Skills/Talents	StrengthsFinder® https://www.gallupstrengthscenter.com/home/en-US/Index Leadership Skills Inventory Northouse, PG. (2012) Leadership Theory and Practice. Fifth edition. Thousand Oaks: Sage Publications. Leadership Assessment Tool Inventory Exercises http://www.kellogg.northwestern.edu/faculty/uzzi/htm/teaching-leadership.htm
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What Theories Support Leadership in Pharmacy?

As mentioned, there are more than 4000 documented definitions of leadership (Azad et al., 2017). Despite this, leadership is an under-researched abstraction within the pharmacy profession. Theory can both describe and predict effects so an understanding of leadership theories can assist in the leadership development process. For the purposes of this section, we will draw parallels from the wider health care domain but when possible, we will provide pharmacy-specific examples.

It is difficult to isolate exact qualities and behaviors that make good leaders. This is because the overall effectiveness of a leader is based on their traits, skills, and behaviors matched to the situation with which they are faced. Today, leadership theories have been broadly placed into five (at times overlapping) core groups:

- Trait theories—What type of person makes a good leader?
- Behavioral theories—What does a good leader do?
- Contingency theories—How does the situation influence good leadership?
- Power and influence theories—What is the source of the leader's power?
- Other theories—What more contributes to good leadership?

Trait Theories

Trait leadership is defined as integrated patterns of personal characteristics that reflect a range of individual differences and foster consistent leader effectiveness across a variety of group and organizational situations (Zaccaro et al., 2004). Trait theory is based on the assumption that we can identify a set of traits common to all leaders. This has proved more difficult than it sounds. A considerable number of studies have recognized certain traits; however, these results are neither comprehensive nor conclusive (Bolden et al., 2003). Another assumption of the theory is that the absence of these traits means that the individual is not a leader. Again, this has not proven true. Despite criticism, researchers continue to explore the correlation between various personality traits and skills with leadership effectiveness, the most widely explored of these being charisma. In an extensive review, Stogdill (1974) found some traits and skills of leadership that appeared more frequently than others. These are described in **Table 2**.

Behavioral Theories

Behaviorists view leadership as a key set of actions instead of as personal characteristics. To determine these behaviors, researchers evaluated what successful leaders did, developed a taxonomy, and identified broad patterns. Behavioral leadership theory incorporates B.F. Skinner's (1991) notions that reward and punishment are powerful mechanisms for leading. An example of this is a manager who motivates desired behavior by scolding employees who arrive late to meetings and showing appreciation when they are on time. There are several types of behavioral leadership theories, including those proposed by Kurt Lewin and Rensis Likert.

Table 2 Leadership traits and skills

Traits	*Skills*
Adaptable to situations	Clever
Alert to social environment	Conceptually skilled
Ambitious and achievement- orientated	Creative
Assertive	Diplomatic and tactful
Cooperative	Fluent in speaking
Decisive	Knowledgeable about group task
Dependable	Organized
Dominant	Persuasive
Energetic	Socially skilled
Persistent	
Self-confident	
Tolerant of stress	
Willing to assume responsibility	

Source: Stogdill (1974)

Lewin's Leadership Styles of Decision-Making

Kurt Lewin's leadership styles framework dates back to the 1930s and focuses on how leaders involve others in making decisions. He was a pioneering social psychologist who identified three different approaches (Gastill, 1994):

1. Authoritarian leaders, also known as autocratic leaders, make decisions and direct activities without any participation from others.
2. Participative leaders, also known as democratic leaders, involve their peers, team, coworkers in the decision-making process.
3. Delegative leaders, also known as laissez-faire leaders, give full autonomy to make decisions to their teams.

Likert's Leadership Systems

Rensis Likert, another pioneering social psychologist, expanded Lewin's work around the decision-making process and the degree to which people are involved in the decision to include four different leadership styles or systems (Katz et al., 1950):

1. Exploitative Authoritative—The leader has a low concern for people, using fear and threats to achieve outcomes. Communication is top down with all decisions made at the top.
2. Benevolent Authoritative—The leader is authoritative but has concern for people, using reward to encourage performance. Communication is better in this style; but almost all major decisions are made at the top.
3. Consultative—The leader makes an effort to listen to others; however, many decisions are still made at the top and the upward flow of information is still somewhat idealized.
4. Participative—The leader engages in participative methods, engaging all members of the team in decision-making. Communication flows both ways.

Contingency Theories

Contingency theorists suggest that there is no one leadership style, rather the uniqueness of each situation requires a different approach. Some examples of contingency theories include Fiedler's Least Preferred Co-worker Theory, Cognitive Resource Theory, Strategic Contingencies Theory, Path Goal Theory, and the Hersey-Blanchard Leadership Theory.

Contingency theories often see leadership on the continuum of relationships and tasks, sliding back and forth depending upon the speed required, the level of stress encountered, the motivation needed, and the perceived competence of the followers. Although these theories have subtle differences in their definitions and tools, in general they advocate that the effective leader adapts and interchanges their style in any given situation (Fiedler, 1967; Fiedler and Garcia, 1987; Hickson et al., 1971; Gill, 2011; House and Mitchell, 1974; Hersey et al., 2007)

Power and Influence Theories

Power theories involve influencing people via authority. This influence can manifest in the form of rewards or punishments and/or through personal and positional power. Two of the most common power and influence theories are transactional and transformational leadership, which both originated from the work of Burns (1978). **Table 3** summarizes key differences between the two approaches (Covey, 1992).

Table 3 Transactional vs transformational leadership

Transactional leadership	*Transformational leadership*
Builds on a man's need to get a job done and make a living	Builds on a man's need for meaning
Is preoccupied with power and position, politics and perks	Is preoccupied with purposes and values, morals and ethics
Is mired in daily affairs	Transcends daily affairs
Is short-term and hard data orientated	Is orientated toward long-term goals without compromising human values and principles
Focuses on tactical issues	Focuses more on missions and strategies
Relies on human relations to lubricate human interactions	Releases human potential—identifying and developing new talent
Follows and fulfils role expectations by striving to work effectively within current systems	Designs and redesigns jobs to make them meaningful and challenging
Supports structures and systems that reinforce the bottom line, maximize efficiency and guarantee short term profits	Aligns internal structures and systems to reinforce overarching values and goals

Source: Covey (1992)

Transactional Leadership

Transactional leadership occurs when there is an exchange of performance for either reward or penalty (Burns, 1978). Transactional leaders give followers something they want in exchange for something the leaders want (Kuhnert and Lewis, 1987). Transactional leadership is task-oriented, works within set organizational boundaries, and suggests a management focus for the leader.

Transformational Leadership

Transformational leadership is future-oriented; focusing on motivating followers to become leaders through a vision for the future. It suggests a more visionary focus for the leader. Burns (1978) defined transformational leadership as "the relationship of mutual stimulation and elevation that converts followers into leaders and may convert leaders into moral agents." His work was adapted by Bass and Avolio (1994), who described the integral role a leader plays in transforming their followers. Specifically, "the goal of transformational leadership is to transform people and organizations in a literal sense—to change them in mind and heart; enlarge vision, insight and understanding; clarify purposes; make behavior congruent with beliefs, principles or values; and bring about changes that are permanent, self-perpetuating, and momentum building."

Other Theories

Exemplary Leadership

Kouzes and Posner (2012) extended the theory of transformational leadership to identify transformational leadership behaviors, specifically, the following Five Practices of Exemplary Leadership that can be used to develop others as leaders:

1. Model the Way—Establish principles concerning the way people should be treated and goals should be pursued. Because complex change can overwhelm people, set interim goals so that followers can achieve small wins on the way to larger objectives.
2. Inspire a Shared Vision—Envision the future, creating an ideal image of what the organization can become. Enlist others in the dream to get people to see exciting possibilities for the future.
3. Challenge the Process—Search for opportunities to change the status quo, taking some risks along the way. Accept mistakes and disappointments as learning opportunities.
4. Enable Others to Act—Foster collaboration and build spirited teams. Create an atmosphere of trust. Strengthen others, making each person feel capable.
5. Encourage the Heart—Recognize the contributions that people make. Celebrate accomplishments to make people feel like heroes.

Servant Leadership

In medicine, nursing and pharmacy, the theory of servant leadership has received substantial attention because it aligns well with the professional and ethical duties of all health care providers—to serve their patients. Servant leadership is the desire to serve the needs of others even before aspiring to lead them (Greenleaf, 1970). This moral core of service represents a different calling as compared to that experienced by those who are drawn first to lead. Another aspect of servant leadership that is consistent with health care is a focus on "the least privileged in society" (Greenleaf, 1970). More recently, Trastek et al. (2014) have suggested that because there should be alignment with how we treat patients and how we work together as staff, there is a case for servant leadership becoming a more dominant model in delivering high value care.

There are more leadership theories than it is possible to discuss in this chapter. We have attempted to focus on those most commonly associated with the practice of health care professionals and those with overlapping constructs that may strengthen their applications to leadership development.

What Style of Leadership is Best Suited for You, the Audience, and for the Pharmacy Challenges You Face?

You may have identified with one or more of the leadership theories discussed above. To put these theories into action, however, we typically speak in terms of leadership "styles". There are several styles that have emerged directly from leadership theories (and may even share a common name) and others which combine elements of multiple theories (which may then have distinct or overlapping names). Some leadership styles are broad and linked to associated frameworks. Others prioritize a single construct. For example, servant leaders focus solely on using generosity to create the positive culture necessary for teamwork.

Table 4 summarizes the leadership styles that are most commonly described in health care, highlighting the best audiences for and potential pitfalls of each (Trastek et al., 2014; Faraci et al., 2013).

Table 4 Summary of advantages/disadvantages of key leadership styles

Leadership style	*Description*	*Advantages*	*Disadvantages*
DIRECTIVE	The team leader makes the decision based on their ideas.	• Style will work best with a newly formed team. • Style will work best with a team facing an unfamiliar situation. • Style needs an experienced leader in-order to combat difficult situations.	• Team members may experience lower self-esteem. • Team members will be "told" what to do, to which may result in lack of initiative, creativity, or self-confidence. ◦ Overcome disadvantage by: Using a researched directive leadership approach, where any necessary information is obtained from colleagues prior to decision making.
CONSULTATIVE	The team leader makes the decision based on everyone's ideas (including their own).	• Style will take other views into account. • Style will work best with a developing team. • Style will increase the knowledge and utilization of members.	• Overuse of this style can be seen as poor decision-making on the part of the leader. • Style can be time consuming. ◦ Overcome disadvantage by: Using a group consultative leadership approach.
DELEGATIVE	Team members make the decision based on their ideas.	• Style can be valuable when working with an experienced team that may have greater technical expertise, than the leader in different tasks.	• Underuse of the style can result in too little sharing of responsibility, which can lead to overload of tasks for the leader. • Overuse of style can lead to lack of control and loss of authority. • Overuse of style can result in less respect for the leader and increased amount of stress for the team members. ◦ Overcome disadvantage by: Using an informed delegative leadership process where the leader meets colleagues to provide them with necessary information, expectations, and objectives. The team can then proceed autonomously with problem-solving but keeping the leader informed about the work in progress.
CONSENSUAL	Decision is made by including everyone's idea.	• Style stimulates ownership and commitment throughout an experienced team. • Style is best used when facing situations that need to viewed through multiple perspectives.	• Insufficient use of this style can result in loss of team skills and involvement. • Overuse of the style can lead to a perceived lack of clear leadership role. • Style can discredit a leader. The leader will be displayed as being incapable to make their own decision without referring to others. ◦ Overcome disadvantage by: Using a chaired consensual leadership approach in which the leader will lead a collaborative process whereby all team members participate in making the decisions.

Table 4 Summary of advantages/disadvantages of key leadership styles (*cont.*)

Leadership style	*Description*	*Advantages*	*Disadvantages*
TRANSACTIONAL	Transactional leaders set goals and performance standards for their employees and in return promise to provide rewards if those standards are met, or punishment if not met.	• Style motivates the employees to contribute and perform their best (personal interest).	• Style does not require a leader to take the ethical and moral road, which may disengage members with ethical principles. • The transactional leadership model is unable to account for the complex motivations of health care providers and the professional and ethical duties to their patients. ◦ Overcome disadvantage by: Transactional leaders can offer tasks with some intrinsic rewards to cater to the team members who have high ethical morale. Leaders can forgo rewards and sanctions and incorporate a more transformational approach.
ADAPTIVE	Adaptive leaders enable a group to overcome challenges created by changes.	• Style is best used when situations and problems are constantly changing/evolving. • Style helps team members and organizations adapt and thrive in challenging environments.	• Style can put a tremendous amount of pressure on the leader to help organization successfully adapt, especially during an extremely difficult situation. ◦ Overcome disadvantage by: Enlightening the team members regarding the change and receiving input from all members on ways to evolve during the change.
TRANSFORMATIONAL	Transformational leaders inspire their followers to look past their own self-interest and to perform above expectations to promote team and organizational interests.	• Style involves leaders' providing large- scale inspiration and motivation for a new vision or mission that is incorporated to the company. • Style will allow members to perform beyond expectations and deliver lasting results, once they embrace the particular vision of the leader.	• Style requires the leader to advocate/ persuade followers to participate in the vision by their charismatic nature. • Style requires the leader to challenge the members to fully embrace the mission, and to give up old values in competition with the new mission. • Style imposes great importance on the vision since the leader's vision is central to the model. ◦ Overcome disadvantage by: Creating a shared vision with the team members, that will have a lasting effect on healthcare system. Leader should attend leadership seminars/classes that will aid them in improving their motivational skills.
SERVANT	Servant leaders serve the highest needs of others in an effort to help others achieve their goals.	• Style will contribute to strong relationships and trust between leaders and their members. • Style will promote leaders to inspire high performance and innovation throughout health care.	• Style requires leaders to develop great qualities/ characteristics such as: listening, empathy, healing, awareness, persuasion, conceptualization, foresight, stewardship, commitment to the growth of people, and building community which takes times. ◦ Overcome disadvantage by: Participating in a leadership development program to develop the desired characteristics

Source: Faraci et al. (2013), Hamilton (2008), Heifetz and Laurie (1997), Kreps (1997), Mark et al. (2014), Schwartz and Tumblin (2002), Scott (2016), Spears (2004), Trastek et al. (2014) and Zilz et al. (2008).

This is where the situation gets a bit confusing, though. The most effective leaders have the ability to move between styles depending on the needs of the situation. They have the aptitude and emotional intelligence to choose the right style for a given situation. Emotions play such an important role in leadership that Daniel Goleman (2000) highlighted six emotional leadership styles which overlap somewhat with an earlier three-style model suggested by Lewin.

1. Commanding (also called coercive or autocratic)—The commanding leader is demanding; "do what I tell you". This can be very effective in crisis management. Coercive style relies on order giving and the leader having a very tight control of their team.
2. Visionary (also called authoritative)—The best phrase to describe this style is "come with me". The leader states the overall goal but gives their followers the freedom to choose how they will achieve that goal, thereby using their own initiative. Empathy is the most important aspect of this style of leadership.

3. Affiliative—Affiliative leaders believe that "people come first". This style builds team morale and harmony and has a huge emphasis on emotional connectivity. This type of leader must have an enormous amount of emotional intelligence as they need to be aware of and value the feelings of others.
4. Democratic—"What do you think?" is the most appropriate phrase to summarize this leadership style. There is a huge focus on collaboration, giving followers a voice and giving the opportunity to generate fresh ideas. This is achieved by including team members in the decision-making and problem-solving processes.
5. Pacesetting—The pacesetting leader says "do as I do, now". This style emphasizes high performance and expects excellence from the team. This type of leader will step in to ensure that high standards are met.
6. Coaching—The approach of this style is "try this"; connecting team members' personal goals and values with that of the organization. This leadership style focuses on personal development.

How have Other Leaders Approached Challenges in Pharmacy?

So far, we have focused on how to self-assess your skills and strengths and then connect these to various theories and styles of leadership. We have also emphasized that the best leaders are those who are able to adapt their style to the challenge at hand. With this in mind, there are some key principles, for example, delegation, time management, mentors, networks, and work/life balance, that are associated with good leadership regardless of style. Table 5 summarises these shared principles and strategies for using them successfully (Mark, 2013).

Although all of these principles are important, the authoring team wants to bring some additional attention to the principle of work/life balance. Inexperienced leaders often feel pressure (internally or externally) to devote their full attention to work-related matters. However, self-care is a critical aspect of pharmacy leadership. Having a healthy approach to life is good for both leaders and their followers. If you have ever flown on a plane before, you will likely remember the flight attendant saying something like, "In case of emergency, air masks will drop from the ceiling...please put on your own mask before assisting others." If you aren't getting enough oxygen to your own brain, you should not be fooled into thinking that you can help anyone else. Taking time to ensure your environment is safe, positive, and inspiring will ensure that you can focus your attention on leading your team.

Table 5 Principles for all leadership styles

Principle	*What to do*	*What NOT to do*
Delegation	• Delegate, because one person cannot complete all the tasks by themselves, and a leader's success depends on the contributions of their followers. • Clearly articulate the needed outcome.	• Delegate as an afterthought. • Fail to explain the importance of the task and how it fits into the "big picture". • Delegate to the employees with the assumption that the employees are incapable of finishing the task. • Get into the habit of delegating to the same person.
Time management	• Organize your work and develop a system that caters to your liking. • Prioritize your work. • Delegate tasks. • Maximize email tools/ filters/reminders.	• Try to tackle all tasks at once. • Rank every assignment as high priority. • Let your paperwork/task manage you.
Work/Life balance	• Set professional and personal goals and protect them/pursue them equally. • Schedule your activities accordingly. • Create firm boundaries between time devoted to work and time allotted to personal activities. • Schedule buffer times for "thinking".	• Assume all responsibilities for the problems at work. • Self-impose pressure on yourself to achieve certain goals that will require you to work long hours many nights in a row.
Mentors	• Try to provide mentorship and receive mentorship. • Seek mentorship from a variety of sources, companies, and industries. • Have mentors for each aspect of your career or aspirations.	• Artificially constrain yourself with available mentors in pharmacy.
Networks	• Take advantage of networking. • Seek out good opportunities for networking, both planned and spontaneous.	• Go to a networking event without any preparation. • Go anywhere without copies of your resume or business cards. • Forget to thank everyone in your network who has been helpful to you.

Source: Mark (2013), *Mark et al. (2014)*, *Scott (2016)*.

Learning from and Leading through Failure

Despite extensive study and planning, all leaders will fail at some point. These failures can be humbling but are also important opportunities for strengthening one's resolve and personal growth. A leader who has never failed has probably also never achieved as much as they could have. This means while we should not strive for failure, we also should not fear it. A variety of circumstances can result in leadership failure. For example, some leaders struggle to blend tactics flexibly around the needs of a situation. Others may be frustrated when the direction of an organization changes. A leader may realize their efforts to complete a project are requiring much more energy than anticipated. These types of challenges signal a need for reflection about areas for further development. In the next section, we have outlined some of the most common leadership mistakes so that pharmacy leaders can avoid these "failures" from becoming repeated and career-limiting habits.

Failure to Communicate Clear Expectations

Failure to set clear expectations with team members is likely the most common leadership mistake. If the organizational goals change, the leader must communicate a credible plan to the team. Devising a clear set of expectations to meet a new goal involves considerable time, which may be the reason many leaders fail. Leaders should involve others in the development of the plan and when confirmed, there should be confidence in delivering the specifics. The expectations should be measurable and include as much background information as appropriate. Without clear explanations, teams may create rumors and spread misinformation about the scope of the project. Leaders should be consistent and steadfast in how they share expectations, ensuring that goals are not overreaching or unrealistic. Sharing personal goals as well as team goals may enhance employee engagement. Finally, the tone of voice and cadence when delivering expectations is important. For example, ending an expectation phrase with "if you possibly can" is counter-productive to the desire to produce solid results.

Failure to Follow through on Measuring and Presenting Results

As leaders share expectations and goals, they should also begin measuring the results. When consistency occurs in sharing results back with the team, it encourages team morale and the desire to push towards the goal. The leader loses credibility when commitments are made to measure and there is no follow through. Positive results are worth reporting often and negative results can also inform the team of focus areas that are needed. Leaders must be willing to change tactics if trends show progress is not realistic.

Failure to Delegate Appropriately

As expectations are clearly defined and measurements are put into place, the leader should decide on delegated tasks and make those known. Waiting until a deadline approaches and delegating in a panic may not prove effective. Additionally, when a leader is delegating, it should be with confidence and clarity. This is not the time to accept reverse assignments from a team member. Without such a focus on communication, the leader may walk away with more assignments than anticipated. Leaders should delegate often and perfect their ability to be descriptive instead of prescriptive. Information should not be withheld or minimized to belittle the recipient of the delegation. Instead they should be empowered and encouraged when approaching their assignment.

Failure to Hold Team Members Accountable

After delegation has occurred, leaders should not excuse team members from meeting deadlines. Often, leaders give benefit of the doubt and wait longer than necessary on others to prepare, plan, and execute. Leaders eventually may take the assignment back and complete it on their own. This can lead to burn out and/or passive aggressive tendencies towards the team. Instead, encourage individuals who have difficulty with closing out a big task to take smaller steps towards the goal. Failure should be encouraged as long as productive efforts are underway to produce results. Minimizing risk but using trial and error may offer early payoff toward achievement of a goal.

Failure to Use Coaching Strategies

Leaders are expected to coach their team when opportunities for improvement exist. But sometimes this does not result in individual behavior change. Inadequate coaching strategies include lecturing instead of listening, provoking resistance, and dampening the individual's personality. Instead a leader should explain the reason for the coaching session honestly. This can be difficult but is a necessity for transparency and changing of the unwanted behavior. After this, the leader should invite the individual to provide feedback. This feedback will include valuable insight on strategies for motivating this team member. Careful balance is needed to motivate without enabling the negative behavior. Leaders have to keep honesty at the center of their communications. When a poor performer is rewarded with the same benefits as strong performers, this enables the behavior and demotivates the team.

Consequences should be discussed and follow through must occur. Absence of any action from the leader also promotes low performance. As with all communication methods, consideration of the individual employee is important as similar words can evoke different emotions. Addressing an individual's ability barrier is key and suggesting strategies for them to overcome these is encouraging.

Failure to Engage in Mentoring and Networking

Leadership skills are not developed in one day or one week. The life experiences of the leaders and those around them build the character necessary for a successful leadership journey. Formal and informal mentors are important for emulating healthy skills. Watching and learning from others will demonstrate that having courage, perseverance, and benevolence are consistent in an effective leader. Honesty and integrity are developed through sharing honestly with oneself and with the team. Consistency fosters team engagement and teams work harder when treated with respect. These philosophies are witnessed when leaders surround themselves with other leaders and see the results. Leaders can learn how best to make hard decisions by talking with others who have faced similar challenges. Optimizing patient care is the core of decision making in pharmacy but must be balanced with resources and ability. Decision making skills are better observed than described. Therefore, having a mentor to walk through leadership experiences is vital for the development of the leader. Networking in pharmacy associations regionally, nationally, and even internationally is invaluable to the growth of a leader. Pharmacy leaders are usually very willing to share their successes and even their failures with others. As with clinical skills, leadership skills must be honed indefinitely. Things are ever changing and a leader must make intentional efforts to read literature, attend conferences, and engage in continuous professional development. Mentoring and networking should not only occur inside the profession of pharmacy. Other disciplines and professions offer meaningful insight and lessons in avoiding leadership pitfalls.

Failure to Balance Priorities

The overarching theme for leaders is balance in all things. Leaders may define work/life balance differently across a career. The following types of balance are key to address consistently:

- Coworker and friendship balance—A leader should get to know each team member and their role on the team. However, the leader plays a different role from other team members. Because of this, a leader must recognize when personal and professional issues may overlap. A leader will appreciate friendships but may also be asked to make hard decisions with upper management that could cause tension in the group. Having healthy boundaries for leader roles and staff relationships can protect unnecessary personal hurt and disappointment.
- Responsiveness and deadline balance—Leaders should prioritize their work related deadlines while maintaining credibility with their team. Perhaps responding to phone calls and emails is reasonable within 48 h instead of 24 h, and therefore, those parameters should be shared with staff. It is important to be realistic with what expectations a leader commits to in order to avoid burn out.
- Goals and resources balance—Leaders are routinely required to set and modify goals for their organization. The leader must balance resources to support team goals, even, at times, competing ones. Human resources and automation decisions are often difficult as both are costly and require some maintenance. Leaders should be optimistic but not unrealistic about such matters.

For a chance to assess your knowledge of leadership, in particular, learning from and leading through failure, review the case study and analysis shown in Fig. 1.

Where Can You go to Continue Your Pharmacy Leadership Journey?

Leadership is a journey, not a destination. The best leaders continue to grow and develop new skills over time. They learn to describe and predict results based on theory. They welcome feedback from supervisors and colleagues. They learn from their mistakes. They seek different types of mentors for different stages of their careers. They expand their networks to include leaders from other fields.

We began this chapter suggesting that it is not possible to master leadership by reading a book, watching a video, or accessing a website. Then we extended this by saying that one can learn about leadership from a variety of resources—alone or in groups with others who share the interest. One great way to engage with leadership development opportunities is to join a professional organization. This will increase access to leadership materials and activities developed specifically for health care and pharmacy situations. It will also help form connections between other new and experienced leaders.

There are many different options worldwide and there are advantages and disadvantages to each. Some are accessible freely, others are a condition of membership, and others require an additional fee. You should make the choice based on your needs and situation. We have summarized some representative English language opportunities in Further Resources.

Flu Vaccine ServiceImplementation

Description

M.J. is a community pharmacy owner. She employs a highly productive staff pharmacist, B.P. M.J. is busy with facilitating new marketing efforts for her store including signage and local news campaigns. Therefore, as flu season approaches, she delegates the responsibility of coordinating this year's vaccine efforts to B.P. She tasks B.P. with visiting with local physicians to encourage their referral of patients to the store. Additionally, she asks B.P. to ensure vaccine is ordered, all staff are trained, and the message of the details for the service is clear to all involved, including patients. B.P. is overwhelmed and not sure where to begin. He can tell M.J. is very busy and therefore, he attempts to proceed without further direction. B.P. thinks about the logistics of the vaccine service and gets input from the other pharmacy team members about steps to take to implement the initiative. B.P. and a technician visit several physicians and encourage them to send patients to the pharmacy. They also order 500 flu vaccines in June. B.P. has a staff meeting with the team and shares the information about expecting more volume this year than last year for flu vaccines. He tells the cashier they will charge $12 for each vaccine which is $2 higher than last year.

Analysis

M.J. used a delegation leadership style and trusted B.P. with the specifics of the implementation. Perhaps her delegation could have included written instructions with deadlines, including data to use for making decisions. For example, M.J. has a file with last year's flu vaccine volumes included. She also has information regarding vaccine manufacturer, and the deadline for best price purchasing for early delivery options. B.P. used a consensual leadership style where he engaged his team members but may not have checked in with his leader, M.J., as often as necessary to confirm his direction.

Impact

There is value and the opportunity to be very effective when using delegation and consensual leadership styles. However, the leader must be mindful not to compromise the integrity of the project with missed opportunity for communications. The flu vaccine program could have included a collaborative practice agreement with a few physicians to ensure the referrals were continued and aligned with State Board of Pharmacy regulations. Because the order was placed in June, the pharmacy did not receive those until October, which is after the competition has started their flu campaigns. The late order caused the cost of each vaccine to be more than anticipated at $20 per vaccine. This cost was below the charge to the patient so the pharmacy had an overall negative financial impact from the flu vaccine project. While logistics were communicated to the staff, clinical situations such as allergies were not anticipated and addressed. Overall, M.J. and B.P. were able to address issues throughout flu season to compensate for missed opportunity during planning, but many lessons were learned regarding careful leadership tactics that could have avoided the mistakes. Communication and repetition in planning sessions and follow up could have enhanced the campaign launch.

Figure 1 Leadership Case Study.

Further Resources

- Harvard Business Review (HBR) Newsletters—offers free, online information about leadership, management, and strategy; can set individual preferences for frequency—https://hbr.org/email-newsletters
- American College of Clinical Pharmacy (ACCP) Academy Leadership and Management Certificate Program—https://www.accp.com/academy/leadershipAndManagement.aspx
- American Pharmacists Association's (APhA) Leadership360 Institute—http://www.pharmacist.com/leadership
- Center for Health-System Pharmacy Leadership—offered by the American Society of Health-System Pharmacists (ASHP) and the ASHP Foundation, multiple programs and resources available to students, residents, and pharmacists http://www.ashpfoundation.org/MainMenuCategories/CenterforPharmacyLeadership
- Pharmacy Leadership Education Institute (PLEI)—established by the Phi Delta Chi Pharmacy Fraternity, PLEI is a foundation to advance the leadership, educational, and other benevolent missions of the Fraternity—http://plei.org/
- Phi Lambda Sigma, The Pharmacy Leadership Society—dedicated to recognizing and developing leaders, provides resources available to students and pharmacists to develop leaders—http://philambdasigma.org
- Royal Pharmaceutical Society Leadership Development Framework—outlines the behaviors of effective, engaging leadership—https://www.rpharms.com/resources/frameworks/leadership-development-framework
- National Health Service (NHS) Leadership Academy—offers a range of tools, models, programs to support leadership development—https://www.leadershipacademy.nhs.uk/
- HealthLEADS Australia—outlines the Australian health leadership framework—https://www.aims.org.au/documents/item/352

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Learning and Teaching Methods to Develop Clinical Skills in Pharmacy

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Learning and Teaching

There is a variety of methods that can be used by students to assist their learning. Teaching does not necessarily result in learning in that we know what is being taught but not what is being, or has been, learnt by the student. The focus needs to be on the learning. There are a variety of approaches that are used to facilitate learning, the choice of which is influenced by many factors including what we want our students to learn, for example, knowledge or a skill, and how we are assessing the learner. The alignment of learning with the methods of assessment is sometimes overlooked. Constructive alignment (Biggs and Tang, 2011) is a term used that acknowledges that students learn by constructing their own learning through appropriate learning activities and that the teacher helps to create an environment in which appropriate learning takes place. All elements of the curriculum, including the learning activities, desired learning outcomes, or competencies, and assessment methods are aligned. Further, the student is supported to achieve the required outcomes by the teacher/facilitator.

There are four steps associated with constructive alignment, namely

1. Defining the intended learning outcomes;
2. Selecting teaching and/or learning activities likely to lead to achieving the outcomes;
3. Assessing students' learning to see if and/or how well they match what was intended; and
4. Arriving at a final grade or determining the student has passed (reached the required standard) or has failed to reach the standard.

What Do We Mean by Clinical Skills?

Clinical skills have been defined in many ways. For example, a clinical skill is any discrete, observable act performed by an individual involved in direct patient care at any point during a patient's care. The following skills are examples of clinical skills within pharmacy contexts: communication/consultation skills, physical assessment skills (e.g., measurement of blood pressure, pulse, peak flow), handwashing/hygiene, and, increasingly, vaccinations and testing body fluids. Venepuncture and basic life support would be other examples. It is accepted that there are significant differences in the clinical skills routinely practiced within countries as well as between countries. Safe and effective clinical skills are often assessed and monitored due to their potential negative impact on patient safety.

Levels of Learning

Miller's pyramid (or Miller's triangle) describes four levels of learning (Miller, 1990). This approach has been applied widely in relation to assessing clinical skills in healthcare.

Level 1—Knows/knows about the skill, including any underlying theory

Level 2—Knows how to perform the skill

Level 3—Shows how: the student can demonstrate that skill and the demonstration could take place in a simulated or clinical environment. Demonstration of that skill on one occasion is usually considered as sufficient to demonstrate that the student has "shown how".

Level 4—Does: the student can independently perform the skill safely and effectively in a clinical environment

The method of assessment would depend on the level of learning, and considering the principles of constructive alignment, the methods of teaching and learning. That is, the learning activities need to be appropriate for the level of learning.

UK Example

The pharmacy regulator in Great Britain, the General Pharmaceutical Council (GPhC, 2018), has produced standards for the initial education and training of pharmacists. The GPhC accredits pharmacy programs in Great Britain. Typically, students in the UK undertake a four year MPharm degree and after graduation spend an additional 12 months as a pre-registration pharmacist under supervision. (A small minority of students undertake an integrated 5 year program where the 12 months professional training is incorporated together with the degree so that they graduate and qualify as a pharmacist co-terminously after 5 years.)

Students must demonstrate achieving a number of learning outcomes and these are listed in the professional standards document. The level (using Miller's pyramid) that must be achieved for each outcome is identified by the GB regulator, the GPhC. So, for example, the GPhC requires individuals to "Obtain and record relevant patient medical, social and family history." For an MPharm student the required level is "shows how," so a student before graduating must be able to demonstrate that he/she is capable of demonstrating this skill (within a classroom or simulated environment). For pre-registration pharmacists, however, before they can register as pharmacists, they must demonstrate that they can demonstrate this outcome at the "does" level. So, in a clinical context within a healthcare setting (e.g., community, primary/ambulatory care and hospital) they can independently perform this skill safely and effectively, and are observed so doing.

So using this example, "Defining the intended learning outcomes" of constructive alignment (Biggs and Tang 2011) the learning outcome (Stage 1) has been provided by the GPhC. The final stage is assessment of whether or not that outcome has been achieved. The second and third steps are "selecting teaching and/or learning activities likely to lead to achieving the outcomes" and "assessing students' learning outcomes to see if and/or how well they match what was intended," respectively.

Learning, Teaching, and Assessing Skills

So what methods are available to students to help learn taking a patients history as a skill and how can it be assessed? It can be helpful to refer back to Miller's pyramid and identify the four stages, with "does" at the top of the pyramid. We would need to assess that a pre-registration pharmacist can routinely, in a clinical environment with patients, obtain and record a relevant history. That is, they can demonstrate this particular outcome. So how might we assess this skill? There are a variety of assessment methods and these include essays, written reports, multiple choice questions (MCQs), modified-essay questions (MEQs), oral examinations, portfolio assessments, and OSCEs (Objective Structured Clinical Examinations). OSCEs are undertaken within a simulated environment and usually use standardized (trained) "patients", which can be staff or actors. Workplace-based assessments may use simulated or actual patients. So, of the many assessment methods, which would be appropriate to assess the "does," which requires repeated, safe, and effective demonstrating of this outcome in the performance standards? That is, using a constructively aligned approach.

Direct observation, which is repeated, and in the clinical environment is required using a validated tool. Examples of observation include the mini-CEX (mini-clinical evaluation exercise) which is a supervised learning event (SLE) involving direct observation of a clinical encounter with a patient by a trainer for teaching purposes. DOPS is another example of an SLE, and stands for the direct observation of a procedural skill. If we are evaluating at the "does" level then a series of SLEs need to be undertaken.

So how might we teach this skill? Or more importantly, how could the student learn how to perform this skill, accurately, repeatedly, and effectively and in the clinical environment with patients?

Lectures, Workshops, and Tutorials

Three well-known examples of teaching methods are the lecture, workshop, and tutorial. Brief descriptions of each, within the context of a cohort size of 160 students, follow.

Traditional didactic lectures with no or little interaction between students or between students and the facilitator. The teacher typically stands at the front of a large group of students and talks to or at them. The teacher may remain stationary or move around.

Lectures often, but not always, take place in a tiered lecture theatre or auditorium for a cohort size of 160 students. Such a format is not conducive to meaningful student learning as you may be able to recall from your experience as a student. Activities can also be introduced into lectures to make them interactive and hence more appropriate for learning in the environment of the lecture theatre/auditorium as outlined in workshops below.

Workshops are teaching sessions where tasks and discussion take place, that is, students are actively learning together. There is interaction between students, and between students and the facilitator. There is increasing use of a "flipped classroom" approach (Higher Education Academy, 2018) where students are required to undertake tasks and/or reading prior to a session and then use that preparation within the classroom. Providing the lecture notes in advance of a teaching session is one example, but it is not the only example. Unlike being in didactic lectures students are undertaking learning prior to the class rather than learning about something for the first time in the class. That is, when learning activities take place within the classroom, students learn by constructing their own learning (see constructivism as a learning theory below) through appropriate learning activities within an environment created by the teacher that has been designed to facilitate student learning (Biggs and Tang, 2011). Another benefit is that the students in the tutorial group learn with, from, and about each other, and from the facilitator. Facilitators would move between the groups and so there are times when students are working together without any facilitator input. Often, there would be time at the end to discuss and share the learning that has taken place within groups with the whole class. Typically there are groups within groups working together on activities so for a workshop with 40 students you may have eight groups each consisting of 5 students meaning these workshops are run four times (and not necessarily with the same facilitator/s).

Tutorials allow in-depth discussions with small groups of learners allowing greater opportunity to test individual student knowledge and understanding and to provide timely feedback "in the moment" to all participants within the tutorial. Compare the workshop where facilitators move around the groups spending time with each. There is opportunity to stretch the more able students in a tutorial. In a tutorial, the facilitator is part of the discussion group with all students present for all of the discussion. As with workshops students within each group learn with, from, and about each other and from the facilitator. Tutorials typically require pre-reading and/or activities to have been undertaken prior to the session. For a cohort size of 160 students, and a tutorial group size of 4 students, this would require scheduling 40 tutorials.

So when we are considering the choice of teaching method and the intended learning outcomes, there are other factors to consider in terms of resources, human and space, and scheduling. If we are looking at a 2 h teaching session for each student with one facilitator per session for a cohort of 160, then the total facilitator time will vary as outlined below.

Lecture	2 h
Workshop	8 h (2 h × 4 groups)
Tutorial	80 h (2 h × 40 groups)

This is a somewhat extreme example but serves to illustrate the continuing need to compromise ensuring meaningful student learning and effective use of limited, finite resources. If each student had 2 h of one-to-one time with a facilitator, and remember this is just for a single element of very many elements of a program, we would be looking at 320 h of facilitator time.

Other Methods of Learning and Teaching

The learning and teaching methods should be aligned with the assessment methods. Some examples of methods of assessing clinical skills include

DOPS—directly observed procedural skills
EPA tool—entrustable professional activity
ISCE—integrated structured clinical examination
Mini-CEX—clinical evaluation exercise
Mini-PAT—peer assessment tool
OSCE—objective structured clinical examination
OSATS—objective structured assessment of technical skills
Portfolio assessment.

In addition to didactic and interactive lectures, workshops and tutorials, there are other examples of a range of different teaching and learning methods and approaches. Not all will be appropriate for teaching clinical skills per se, but may be considered in developing underpinning knowledge and/or understanding.

- Demonstrations, e.g., of how to use a metered dose inhaler
- Practical classes, e.g., using placebo devices to learn how to administer epinephrine/adrenaline in an emergency
- Role-play, with or without expert patients of actors, e.g., patient request for a medicine from a community pharmacy
- Peer learning, e.g., 360° assessment, multisource feedback
- Self-directed learning—(resource-based learning)—including multimedia
- Directed study (resource-based learning)—including multimedia

- Seminar—a term used to describe different things by different individuals, for example, a workshop or a didactic lecture with question and answer component at the end.
- Tutoring, mentoring, and coaching approaches. Tutoring may involve imparting or facilitating acquisition of knowledge and skills to the learner. Coaching skills help the learner to reach their full potential and when using mentoring skills the facilitator can share specific personal and professional experiences to assist the learner to grow as an individual personally and professionally.
- Discussion groups (online) synchronous—working together at the same time enabling a real-time discourse
- Discussion groups (online) asynchronous—with a time lag, e.g., discussion forums and email
- Activity-based learning, problem-solving, and case-based learning, e.g., using patient notes, are examples of active learning
- Interprofessional learning (IPL) or interprofessional education (IPE) where members (or students) of two or more professions learn with, from, and about each other.
- Work shadowing, e.g., observation of others in a clinical or other work setting
- Workplace learning/experiential education
- Online-learning, e.g., MOOCs (Massive Open Online Courses)
- Blended learning, e.g., a combination of face-to-face and online learning
- Self-assessment, e.g., against certain criteria
- Observation, e.g., mini-CEX, DOPS
- Simulation, e.g., use of an orange, an injection pad, a high fidelity patient simulator injection arm to develop injection skills. This is a useful way of preparing individuals for clinical practice. It provides a safe, controlled environment in which new skills can be developed and competences assured. The type of simulation should be informed by the nature of the skills being developed, the level of expertise required and the learning outcomes (Lloyd et al., 2018).

They are not all mutually exclusive, for example, role-play could be used in a workshop or tutorial. Problem-solving could be used in various contexts, for example, the workplace, within a workshop, or as independent study. The mini-PAT is a peer assessment tool (PAT) consisting of an element self-assessment by the learner together with assessments from a number of the trainee's colleagues.

These are all appropriate substitutes for the clinical environment and should help build confidence to achieve the ultimate fidelity, where the individual is required to interact directly with patients under supervision. Formative assessments with feedback provided by faculty, clinical supervisors and senior students and, as appropriate, from peers help the learner develop skills in a safe environment, whatever the method used to develop clinical skills. [For more information on formative assessment and feedback, see Wood (2014)].

In addition to knowledge, understanding, and skills, demonstration of appropriate attitudes, values, and behaviors may be required and these may be incorporated into appropriate assessments. The reader is referred to Chapter 126 for further information on professionalism in pharmacy.

Reflection

Reflective learning, when learners take a step back from their learning (including feedback and/or assessment), helps them improve on future performance by, for example, critically analyzing their experience, and from using feedback, especially when formative assessment (Wood, 2014). Reflection is increasingly being used in healthcare and other settings as one component of revalidation of registered practitioners. Learners need to be prepared and so reflection is also increasingly found within initial education and training pharmacy programs for a variety of cadres. Reflection can be assessed, for example, via a portfolio and/or orally and can be incorporated as an element into formative as well as summative assessments (Driessen and van Tartwijk, 2014).

There are many different models of reflection. The learner can be informed to choose a model that they are most comfortable with or they can be given a choice of a small number of models. Alternatively, they can be told which model to use for a specific reflective writing assignment. For beginners the latter approach may be appropriate although for experienced practitioners requiring the use of a specific model would not usually be the approach used. Reflection is often associated with practice and so, for example, thinking of an incident that went well or did not go so well or when encountering something new. However, reflection can also be useful in the early stages of pharmacy education, even if they have had no real pharmacy experience. For example, learners may be asked to reflect on an assessment and its grade, their performance and the feedback they received. This should help students to incorporate the feedback received into improved performance in the future. Reflection can also be used following an interaction with a peer or faculty member that went well or did not go so well. It is important that students are facilitated to be able to reflect and develop into reflective lifelong learners. This requires formal evaluation of, and feedback on, reflective technique (Driessen and van Tartwijk, 2014).

Returning to Our Example

Let us return to the example of the outcome "Obtain and record relevant patient medical, social and family history" required of a pre-registration pharmacist prior to registration by the GPhC in Great Britain at the "does" level. We have established that direct observation would be an appropriate assessment method. Considering the principles of constructive alignment, which of the

teaching methods may be appropriate and which would be inappropriate? A didactic lecture on how to obtain patient history is highly unlikely to prepare an individual so that they are able to demonstrate that they are competent at this skill.

So when deciding on a method, or methods, we may wish to consider the following as possible options. The principles of curriculum design including identifying resources available, intended learning outcomes, and assessment methods will influence the choice of approach(es): demonstrations, observation, e.g., in a clinical setting, role play, peer assessment, self-assessment of video recording of the learner and reflection.

Directed study (resource-based learning), for example, using videos, may be selected as one element to assist learning. Although if students are required to identify videos themselves, for example, from the internet, the teacher has no influence on which videos the students use and there may be limitations or indeed errors within them. Direction to specific resources may be more appropriate, especially for novice learners as examples of good and bad practice can be highlighted.

The GPhC also requires MPharm graduates to show how they "Obtain and record relevant patient medical, social and family history." This is helpful for those training pre-registration pharmacists in that the trainers know they have a platform upon which to build and that the student has already been able to demonstrate they have, in a simulated environment, "shown how." This is an appropriate point to mention the concept of a spiral curriculum (Harden and Stamper, 1999). A spiral curriculum is one that is progressive and deals with issues in an increasingly more complex way, while revisiting previously learned material, until an appropriate level is reached. Integration with other knowledge, understanding, and skills is associated with this increasing level of complexity and facilitates clinical decision-making.

Students in the early stages of the MPharm would be informed of knowledge about the skill of history taking (the "knows") and would be expected to "know how" to take a history. The methods of assessment at this point might include examinations or coursework to assess knowledge and/or its application. The knowledge forms the platform upon which history taking can be learned, practiced, and assessed at the appropriate level. It is widespread practice in the UK that students are required to demonstrate history taking at the "shows how" level, at an OSCE station. The complexity of patients would increase year on year, aligning with the principles of a spiral curriculum so at graduation a student would be expected to be able to "show how" they obtain and record a history of more complex simulated patients, including those with co-morbidities, integrating knowledge and skills from across the MPharm curriculum. This should equate to the expected performance level of a newly graduated pharmacist in clinical practice.

So if we are going to select methods for teaching and learning of history taking in the early years of the MPharm degree we may wish to use something along the lines of the following:

An introduction to history taking as an interactive session at the beginning of a course (so at this point they have no knowledge upon which to build). This may well be a session on day 1 of the program. The session can still be made interactive though. Interactive introductory workshop/s following directed study (appropriate resources, e.g., written and video). That is, there is an element of a "flipped-classroom." Videos may include examples of pharmacists or pharmacy students or others taking a history from patients (simulated or otherwise). Discussion and application occurs within the group, so that there is interactivity, which lends itself to construction of learning by the students, with appropriate facilitation. One may wish to ask students about positive aspects of particular videos and areas for improvement. For a constructively aligned approach, the assessment tool/criteria that would be used for the final, summative assessment would be used for self, peer, and/or instructor assessment. There could be an opportunity to role-play with/without (audio or video) recording. Importantly constructive feedback and time for reflection by students would also be required. After one or more sessions a formative assessment would be appropriate. So if there is to be an OSCE as a summative assessment to assess learning, then a formative OSCE to help prepare the student would be appropriate, in addition to feedback provided "in the moment". It would also provide an opportunity for feedback to the student so they are able to use that feedback as feed-forward for subsequent learning, whether that occurs within an education/training or in a practice setting. All of these approaches benefit from supplementary early clinical exposure in the workplace ensuring that the learner is able to visualise expected future performance.

Choice of Methods and/or Approaches to Learning, Teaching, and Assessment

Choice of teaching and learning methods should be constructively aligned with the assessment whether or not as part of formal credit bearing course, for credentialing, certification, or for other reasons. Learners should be supported and if there is an associated assessment they need to be prepared for that assessment, including feedback as feed-forward in the form of a formative attempt at the planned summative assessment. It is important that teaching and learning methods, together with associated assessments are considered as part of the whole curriculum, module, unit of study, or as a stand-alone course. The principles apply whether there is face-to-face, online, or blended learning. The principles of curriculum development (or design) should be considered carefully, including the context of the learner (e.g., starting point in terms of knowledge and skills), for a student pharmacy technician or a foundation pharmacist or an experienced, expert specialist pharmacist practitioner with prescribing rights. The principles should also be applied to stand-alone courses or units of study especially so that learning methods are constructively aligned with the assessment of the intended learning outcomes/competencies.

So being clear about what students are expected to be able to do at the end of the learning is critical and then the teaching and learning methods can be selected based on their appropriateness (for a learning outcome or competency statement). This also facilitates effective course evaluation by comparing expected and achieved performance of the learners following the course closure.

How do Students Learn? Signposting to Learning Theory

Knowles, proponent of the "adult learner," defined theory as "a comprehensive, coherent and internally consistent system of ideas about a phenomenon" (Knowles, 1973, p. 5 in Kaufman and Mann, 2014, p. 7). Many theories exist that help us understand how learners learn. Eight such theories, including their implications for education practice have been outlined by Kaufman and Mann (2014) within the context of medical education and these are as follows.

Adult learning principles
Communities of practice
Experiential learning
Social cognitive theory (behaviorist)
Reflection and reflective practice
Self-directed learning
Situated learning (constructivist)
Transformative learning

An understanding of education theories can enhance learning from a student perspective as well as from that of the trainer or teacher. This applies equally to developing clinical as well as other skills and attributes, and to knowledge and understanding. Engagement with, and understanding of, learning theories helps us as educators to understand the different ways in students learn and how that learning can be facilitated or enhanced.

Constructivism as a Theory

The theory is used in the context of "constructive alignment" (see above). Others have used the terms "curriculum alignment" or "curriculum coherence" when referring to the same broad philosophical approach. Learners construct knowledge from activities, these may be undertaken alone or with others and these activities are often, but not always, selected by, or in partnership with the teacher. It is not the learning itself that brings about change but how the information is structured and applied that does. A number of constructivist models of learning exist. A model focusing on learners as independent individuals (e.g., what some refer to as psychological constructivism) and the social constructivist model which focuses on the social interactions between individuals with those who may have more expertise and assist individuals to learn. For more information on the various models please see Fosnot (2005) and Rockmore (2005). It is important to note that constructivism is a perspective on learning that is focused on how students actively construct or create knowledge out of experiences/activities.

Active Learning

Active learning can help to develop higher order intellectual capabilities such as analysis, synthesis, and evaluation, unlike the didactic lecture. However, group size and the number of facilitators each affect the quality of the learning, interaction, and feedback. Some curricula are based on problem-based or team-based learning, each of which is described below.

Problem-Based Learning (PBL)

This is a student-centered pedagogy where students use "triggers" from a scenario to identify their own learning objectives. Students undertake independent, self-directed study and then discuss their learning as a group. PBL uses well designed scenarios/cases and so requires significant resource from facilitators in the design of the cases and the step-wise process required to tackle the problem (different variations of PBL exist). It is also important that the groups are facilitated well. Problem-solving and PBL are not synonymous. The former can be used independently in any pedagogy and context and includes, for example, identifying an approach analgesic for a specific patient presenting with a tension headache.

Team-Based Learning (TBL)

TBL is an educational approach where students are more autonomous and have greater responsibility for their learning. Unlike group work, a critical component of TBL is that the groups (teams) are permanent so are able to develop into and function as effective teams of learners. The approach requires significant investment in preparing facilitators and students so this should be seen as allowing students to get on with their learning. TBL is more akin to directed or self-directed study in the form of a group. Significant time and thought is also required to develop the assignments/learning activities so that collective working and learning in a collaborative manner can be achieved.

Motivation for Learning

Motivation is having the willingness and/or desire to do something. Many theories exist that seek to explain motivation for learning, for example, expectancy-value theory, attribution theory, social cognitive theory, goal-orientation theory, and self-determination theory (Cook and Artino, 2016). Self-determination theory (SDT) is an established framework based on intrinsic motivation, extrinsic motivation, and amotivation and focuses on the human need for competence (ability to undertake a task), relatedness (a sense of belonging within the learning community), and autonomy (an element of choice and control over their learning). Intrinsic motivation is motivation relating to interest and/or enjoyment and promotes deeper learning, improved academic performance and overall wellbeing when compared with extrinsically motivating influences (Ryan and Deci, 2000a, 2000b; Niemiec and Ryan, 2009). Examples of extrinsic motivation include reward and recognition, by self or others and fear of failure/avoiding punitive measures. Kusurkar et al. (2011) identified a number of ways to stimulate intrinsic motivation in students through autonomy-supportive teaching derived from SDT and these can be applied to across a number of settings/contexts. Here are their 12 tips:

1. Identify and nurture what students need and want
2. Have students' internal states guide their behavior
3. Encourage active participation
4. Encourage students to accept more responsibility for their learning
5. Provide structured guidance
6. Provide optimal challenges
7. Give positive and constructive feedback
8. Give emotional support
9. Acknowledge students' expressions of negative effect
10. Communicate value in uninteresting activities
11. Give choices
12. Direct with "can, may, could" instead of "must, need, should"

Feedback and Feed-Forward

"Arguably the most powerful enhancement to learning is feedback during learning" (Biggs and Tang, 2011, p. 64). Formative feedback is that which is provided during learning, prior to any summative assessment. It helps the learner understand what they need to do and should be given in a timely manner so the feedback is meaningful, helps them with future learning and should be constructive, including a combination of reinforcing the positive elements and those in need of improvement (and if appropriate, sign-posting and/or support for the learner to improve). When feedback is helpful to future learning and/or assessment the term feed-forward is often used (Biggs and Tang, 2011).

Principles of Curriculum Development

The curriculum includes the syllabus but is more, much more than the content. It includes, but is not restricted to the following, in no particular order:

- learning, teaching, and assessment methods
- quality assurance and standards including criteria, e.g., what is a "pass"?
- sequencing and timing, including space and time to assimilate learning prior to any assessment
- the learners, including qualifications, experience, and numbers
- the learning environments, including online, plus within class and out of class support
- the teachers and facilitators of learning (including patients and practitioners) plus support staff, their attributes, experiences, and numbers
- finances

Input into development of a curriculum should be sought from a variety of stakeholder groups, for example, employers, prospective learners, patients and the public, other professions, professional bodies, regulators, and/or health and social care policy makers at local or other levels. That is, a needs-based approach should be used (see Chapter 123). How each element links with all other elements also needs to be planned, so horizontal and vertical integration and constructive alignment are considered. A final draft curriculum needs be communicated to stakeholder groups. It should be capable of being contested and must be responsive to change; indeed anticipate changes in practice. This is an opportunity to review the course or program and at this point further enhancements are usually made in response to stakeholders.

If the course is accredited, certified or credentialed, then compliance with the education provider's requirements (e.g., universities) and/or other bodies such as the appropriate pharmacy or other regulator, national or regional/state government and/or professional body must be adhered to. Such requirements include credits, course length, entry requirements, study hours, and

outcomes. There are additional complexities when accreditation or recognition for one course is required by two or more regulators, for example, by nursing, medicine, and pharmacy regulators and also when courses are designed for, and require accreditation in, two or more countries or other jurisdictions, for example, United States.

Importantly, the principles of curriculum design can also be applied to short courses or units of learning, as well as to a program curriculum, such as for a bachelor, masters, or doctorate level degree. So the principles can, and indeed, should be used when designing teaching/learning of clinical skills at all levels including CPD (continuing professional development) for practitioners. Please do not underestimate the time needed to communicate and meaningfully engage with colleagues and other stakeholders (and feedback) throughout the development, encouraging and listening to alternative views through the consultation. This will help result in a shared curriculum, that has ownership or "buy in" from its stakeholders.

Evaluating Courses

Once the course starts evaluation is important, and not only with the first cohort and provides valuable quality assurance for the stated aims of the course. Feedback from learners, teachers, employers, and patients of those who are developing/have developed knowledge and skills during a program should be sought in a number of ways (e.g., surveys, face-to-face review discussion groups, telephone interviews) and at various points. Curriculum review is an iterative process not an event. Adequate resource, including human, for evaluation also needs to be factored in, including, where possible evaluation by those who are independent of the course. Other forms of evaluation include review of student performance relating to any assessments, of the individual learner and also, cohort data. As further cohorts pass through, between cohort data should also be reviewed seeking to identify enhancements and reassure stakeholders, including regulators, of expected learner outcomes. (For further information on evaluation of courses and teachers see Kember and Ginns, 2012.)

Summary

In summary, seven elements of good learning contexts have been identified by others (Hattie, 2009; Biggs and Tang, 2011) namely

1. reflective learning
2. relevant learning activity
3. formative feedback
4. appropriate motivation
5. appropriate integrated/interconnected knowledge base
6. social learning
7. quality of the teaching/learning facilitation (teaching methods, attributes, and environment)

Each of these should be considered carefully when designing learning and teaching clinical skills, ensuring there is constructive alignment with the assessment(s). When used appropriately they will support independent and deeper learning, helping the individual to become a reflective, life-long learner who is able to use and apply new knowledge and develop new skills in an ever changing context.

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Needs-Based Education in Pharmacy

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The Foundation of Needs-Based Considerations in Pharmacy Education

In the contemporary world, the profession of pharmacy constitutes a wide-array of roles, scopes of practice and responsibilities. These roles range from a direct patient care provider who assures safe and effective therapeutic outcomes in patients to scientific experts engaged in all facets of drug discovery and development. Other roles focus on regulatory sciences and practices while yet other roles center on the manufacturing of drugs, biologicals, vaccines and other substances for human and animal consumption. Each of these areas of practice have a common core of competencies but then differ significantly as the expert skills are demanded by the scope of work (International Pharmaceutical Federation, 2017; Lutz et al., 2009).

Thus, a direct patient care role demands a different set of skills than the role of inspector for a national regulatory authority. A role in manufacturing technology, differs dramatically from that of a role as a dispenser of medicines in a community pharmacy (FIP, 2018; Lutz et al., 2009). While on the one hand, the variety of roles that can be taken up by an individual who is educated in a school of pharmacy and achieving a first degree in that discipline is a major advantage to new graduates, but on the other hand, the "jack of all trades but master of none" phenomena is a reality in the marketplace for employment. This dilemma is pressing on national pharmacy organizations, institutions of higher learning and on the wide array of employers who hire and utilize pharmacists.

Through the advocacy work of national organizations representing pharmacists around the globe, the issue of workforce development of pharmacists has gained some attention. In these cases, the pharmacy workforce is being described as ranging from pharmacy technicians/assistants, to generalist pharmacists, to pharmacy specialists at the highest scientific and professional levels. Along with such description of the workforce, comes the focus on length of training, content of the required educational program and ultimately, the title of the final degree that is conferred. Another critical element is the legal and regulatory infrastructure which grants practice privilege and determines the scope of practice of pharmacists in a given country (International Pharmaceutical Federation, 2017).

The majority of individuals pursuing formal higher education in pharmacy in most countries do so to become practitioners of the profession of pharmacy. That is, to prepare themselves for pharmacy practice roles that focus on patient care. Such roles typically comprise dispensing of medicines, counseling patients on their appropriate use, interfacing with prescribers to assure therapeutic rationality and various functions relating to managing the drug, vaccine and biological drug supply (FIP, 2018; WHO, 1993). In some countries where the pharmaceutical manufacturing industry secures a large portion of the national economy, the majority of graduates will gravitate to working in that industry (Lutz et al., 2009). In that case, graduates will work in areas from product manufacturing, quality assurance and control, to regulatory and marketing and sales.

Determining Needs

Given the complexity of the pharmaceutical armamentarium from both a clinical and scientific perspective, the education and training of individuals to be pharmacists is offered in institutions of higher learning (e.g. universities). The need for such high level educational programs is clearly established by the knowledge, skills, and behaviors that are necessary to assure safe, effective, and efficient use of medicines in patient populations as well as producing, distributing and utilizing pharmaceuticals, vaccines, biologicals, and contrast media (WHO, 1993, 2011). The skill set necessary for fitness for practice in any of these areas requires lengthy education and training from a faculty of pharmacy which is composed of a wide array of content experts. Such experts typically range from those who are engaged in drug discovery, drug formulation, pharmaceutical technology, analytical and quality assurance testing, and several of the medical sciences including pharmacology, microbiology, immunology, genetics, pathology, and physiology (Al-Wazaify et al., 2006; Knoer et al., 2016). More recently schools/colleges of pharmacy have added pharmacy

clinicians with specialization in specific areas of drug therapeutics and drug dosing using principles of pharmacokinetics and pharmacodynamics as well as genetic prediction of effectiveness (Knoer et al., 2016). Behavioral scientists from sociology, psychology, management, public health, and economics have also been added to some schools/colleges along with those trained in pharmacoeconomics, pharmacoepidemiology, and population-based health (AACP, 2018) (AACP colleges and schools of pharmacy). This great diversity of faculty skills and areas of expertise has come to define the scope, mission, and objectives of the curricula in schools of pharmacy.

Even though faculties of pharmacy have attempted to constitute their programs with capable and skilled content experts, the fundamental question of faculty is, "*What needs do we aspire to meet in our respective societies insofar as the pharmacist workforce is concerned?*" is often elusive. Many factors that are intrinsic to the university and the pharmacy profession contribute to the capacity to answer this policy question. Moreover, forces extrinsic to the pharmacy profession and its related university teaching program play an important part. The latter has been the focus of the World Health Organization (WHO) and leaders in the area of health professions workforce planning, through various initiatives under the banner of "social accountability in health professions education" (Boelen and Heck, 1995). The perspective embodied in these efforts seeks to construct a relationship between the nature, essence, and curricular objectives of the health professions educational program and the evident and real health care services needs of the population in a given country (Boelen and Heck, 1995).

Careful consideration of the phenomena described above might be examined from the perspective of the Millennial Development Goals (MDGs) of the United Nations (UN, 2015). These population-based goals include targets associated with acute health needs, chronic illnesses, neonatal and maternal deaths, nutrition, and environment. Clearly, pharmaceutical agents, vaccines and biological agents play a most serious role in the mitigation, cure and/or amelioration of infectious disease, other acute diseases, and chronic disease areas included in the MDGs (UN, 2015). Hence, pharmacists and pharmaceutical scientists should play a crucial role in addressing the MDGs in their respective countries. This would be reflective of acting in a socially accountable fashion and would address top priority health needs of a nation and across the world.

To assist Universities and professional pharmacy organizations in both understanding and implementing such a planning paradigm, the International Pharmaceutical Federation (FIP) has introduced a Needs-Based Educational Model depicted in **Fig. 1** (FIP, 2017a).

Key drivers in this model are VISION, LOCAL DETERMINATION, SOCIAL ACCOUNTABILITY, GLOBAL CONNECTION, and QUALITY ASSURED. The paradigm then assumes that these enumerated drivers will in turn create the competencies, educational programs and curricula, and skilled services provided by pharmacists and pharmaceutical scientists to meet the local, regional, national and global needs of the people for quality medicines, therapeutic rationality, and services (FIP, 2017a). While this idealized paradigm has witnessed broad study and discussion among educators and professionals in pharmacy, it is far from being universally adopted and utilized as an authoritative guidance for rational curricular planning (Olivera et al., 2018).

From among many challenges associated with aligning national needs related to its pharmacy workforce to an appropriately constructed pharmacy curriculum, one must focus especially on the depth, breadth and level of intensity (with respect to knowledge and skill acquisition) of the curricular program. That is, at what level and expectation do courses and instructional exercises have to be aimed, given the available human, physical and operational resources for the pharmacy program. It is not unusual when one considers all of the pharmacy curricular programs around the world, that there is also great variation in the resource levels allocated

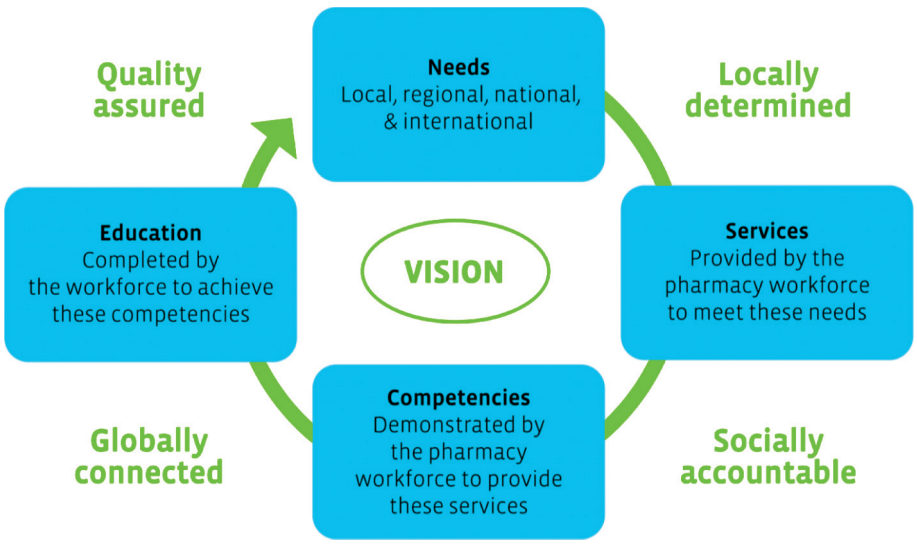

Figure 1 International Pharmaceutical Federation (FIP) needs-based educational model. *Source: Used with permission from International Pharmaceutical Federation (FIP), 2017. Research, Development and Evaluation Strategies for Pharmaceutical Education and the Workforce: A Global Report. The Hague: International Pharmaceutical Federation. Retrieved from:* http://fip.org/files/fip/publications/FIPEd_RDES.pdf (FIP, 2017a).

to the schools of pharmacy (Anderson and Futter, 2009; FIP, 2017b). Most notable are variations in facilities, numbers and types of faculty skill levels, coherent curricular pathways and support options such as financial assistance to students, library facilities, and career guidance (International Pharmaceutical Federation, 2017; FIP, 2017b; Anderson and Futter, 2009).

The Reality of Pharmacy Education Around the World and Barriers

The WHO currently boasts almost 200 countries in its membership. Among these 200 countries, it is estimated that there are over 3000 schools/colleges of pharmacy (FIP, 2017b). Careful examination of these programs demonstrates a wide-variation in content and scope of the curriculum, length of study to achieve the first degree of credential for completion, title of the degree or completion certification, numbers and skills of the faculty including areas of expertise and linkage of the program to the health care services system of the country (FIP, 2017b). Some programs produce individuals with strong skills in pharmaceutical sciences and pharmaceutical technology geared to employment in the pharmaceutical industry or national regulatory bodies. Other programs produce individuals capable of being drug experts in terms of the science and clinical aspects of comparative drug therapeutics (Anderson and Futter, 2009; FIP, 2017b; Lutz et al., 2009). Graduates from such programs find employment in hospitals, physician offices and clinics or community pharmacies (FIP, 2018). However, this great divergence in "types" of faculties of pharmacy and "types" of skill levels inherent in program graduates poses an important national and global policy problem, "*Whose needs are being met or not met?*" The corollary policy question that can be raised is, "*Can individual faculties of pharmacy produce individuals with sufficient skill and competence to carry out accountable functions in pharmaceutical industry as well as clinical management of patients?*". Additionally, "*Should the educational community continue to produce individuals called pharmacists for the pharmaceutical industry and regulatory arena at the expense of not producing pharmacists who can assure safe, effective and efficient use of medicines in the patient population and vice versa?*". These are crucial policy questions not only for the profession of pharmacy and its educators, but they are also important policy questions for ministers of health, ministers of education, consumer organizations, and patients themselves (Anderson and Futter, 2009; International Pharmaceutical Federation, 2017).

To highlight how the needs of a country shape the curriculum and focus of a pharmacy school, the comparison of Thailand to the United States reveals different approaches. In Thailand, the bachelors of science (BS) programs focus more on product-oriented topics, which is traditionally where pharmacists have been needed (Kapol et al., 2008). Of the colleges of pharmacy that offer a 6-year doctorate of pharmacy (PharmD) program, there are 4 tracks—pharmaceutical care, industrial pharmacy, specialized tracks, and an international program. This differs from the United States, whose colleges of pharmacy are more direct patient-care oriented with one track offered—pharmaceutical care. However, based on the local changing healthcare system, there is a growing need in Thailand for highly educated, practice-based pharmacists; correlating is the need for instructors who are qualified for teaching patient care (Chanakit et al., 2014; Kapol et al., 2008). Based on this, the country has several colleges planning to develop postgraduate residency programs to improve the number of pharmacists who are trained and experienced in direct patient care (Chanakit et al., 2014). Additionally, all schools of pharmacy (BS and PharmD alike) now teach from a competency-based standpoint, with eight competency domains that are mostly patient-oriented (compared to product-oriented) (Kapol et al., 2008).

In Singapore, the Ministry of Health has encouraged continued dialog regarding education, postgraduate training, and advanced practice credentialing for pharmacy-related personnel in order to address the growing need unique to their culture: combining westernized medicine with native customs. They aim to develop pharmacy into a practice that will reach their citizens in a meaningful way; "otherwise, optimization of the benefit of medications will not be within the reach of any Singaporean" (Parrish and Chew, 2018). Indeed, at National University of Singapore, Natural Products is a required class for its graduating pharmacy students (Chui et al., 2009). This ongoing work is based on Singapore's patient needs and thus they are adapting their pharmacy education force (Parrish and Chew, 2018).

Leadership in the Universities at the Faculty and Divisional levels of Faculties of Pharmacy is a critical determinant for answering policy questions such as those raised here. From among competing priorities and interests, choices have to be made, which then drive hiring, faculty development and promotion decisions. Assuring an appropriate and sufficient budgetary allocation, having utilitarian buildings and laboratories including libraries and electronic resources, and facilitating the teaching and learning process with appropriate space are elements of a leader's responsibilities as s/he administers a faculty of pharmacy. These executive tasks are challenging even in the best of circumstances and yet few individuals in these positions have formal training for such roles.

The lack of a linkage between the theoretical/didactic aspects of a university pharmacy program and the several elements of professional pharmacy practice is also a serious barrier in many countries. The lack of practitioner–teachers in many schools/colleges of pharmacy further divides the intentions of the pharmacy curriculum with the practice needs of patients and pharmacy practitioners. The profession of pharmacy is still universally rooted to the archaic notions of apprenticeship and often times institutes legal requirements for practice-based experiential education prior to licensure or other legal basis for entering into practice (Anderson and Futter, 2009; Anderson et al., 2012).

Variation in curricular content, depth and breadth among faculties of pharmacy has been a barrier to the development and utilization of a global universal model for defining the profession of pharmacy and its social tasks and accountabilities and scopes of practice (FIP, 2017b; International Pharmaceutical Federation, 2017). Hence, the expectations of policy makers, health system decision makers, other health professions and patients are oftentimes cloudy at best. This puts the profession of pharmacy in a challenging position when seeking public resources and public support.

Professional Services

Just as there is great variation in the offering of pharmacy education degree programs, there is a similar variation in the scope, depth, breadth, and extent of pharmacy services offered to patients and colleagues in the other health professions around the world. Likewise, there is great variation in how the various types of individuals comprising the pharmacist workforce are utilized.

Perhaps the most evident and universal role of the pharmacists is focused on the drug product. From its acquisition to its routes in the supply chain to the ultimate consumer, pharmacists and pharmacy technicians/assistants play an integral role in getting medicines from the source of manufacturing and/or preparation to the patient. Assuring the integrity of the supply chain is paramount since product integrity is key to therapeutic integrity in the patient. Since drugs, vaccines, and biologicals are high-tech products they require dedicated vigilance in movement, storage, and distribution. To the extent that a sufficient supply of pharmacists and pharmacy technicians are involved in all aspects of the pharmaceutical supply chain, in general it can be said and assumed that the system works effectively (WHO, 1993, 2011).

The challenge from a global perspective, is that pharmacists are not always present in the entirety of the supply chain. Many countries do not have pharmacists in hospitals (Anderson and Futter, 2009; FIP, 2018). Likewise, many countries do not have nor do they require pharmacists in local community shops where medicines are sold (Lutz et al., 2009). A number of countries have drug sellers—individuals neither educated nor controlled—who sell medicines to whomever is willing to pay under the credo "let they buyer beware" (Lutz et al., 2009). It is not known in such situations, what the incidence and prevalence of injury or death attributable to drug misadventures might be.

In the case of hospitals in a number of countries, they have left it to nurses to compound sterile admixtures on the patient floors, raising issues of scientific accuracy, sterility and chemical compatibility. They have also left the procurement task to individuals without knowledge of therapeutic appropriateness, duplication, or cost insensitivity (Anderson and Futter, 2009; Lutz et al., 2009).

Since the late 1940s, there has been contemplation and discussion of a more clinical role for pharmacists given their general knowledge of drugs and how these drugs behave in human systems (WHO, 1993, 2011). With the advent of the discipline of pharmacology and its drift into faculties of pharmacy as well as the development of knowledge in pharmacokinetics and pharmacodynamics, there have been growing pockets of practice around the world with a distinct clinical focus. In such practices, properly educated pharmacists work in tandem with prescribers to assure the most clinically effective and cost–beneficial drug therapy in patients. While early models of such a practice orientation occurred in hospitals, more recently these models have been instituted in ambulatory care environments including physician practices and freestanding clinics (Anderson et al., 2018). Several studies have demonstrated that pharmacists in such clinical roles improve patient outcomes and are economically effective and efficient (Chisholm-Burns et al., 2010). In countries with abundant resources, such as Canada and the United States, there exists advanced training for pharmacists to the level of autonomous and "full scope" practitioner. Pharmacists with sufficient training are expected to be involved in medication prescribing, disease management, ordering and interpreting of relevant tests, and vaccinations (Tsuyuki et al., 2018; Walton and Manasse, 2018).

The clinical role of the pharmacist is being advanced by a growing commitment to practice-based research (WHO, 1993). Most of these findings point to the utilization of pharmacists in assuring patient outcomes in chronic disease management, disease prevention initiatives through immunization and assuring patient adherence to prescribed therapies. Several countries have oriented their pharmacist services reimbursement systems to financially support such clinical efforts (Lutz et al., 2009). In its 2012 Declaration, the pharmacist member organizations of the FIP pledged to take on responsibility and accountability for patient outcomes that center on drug therapy throughout the world (FIP, 2012).

Moving the entire profession of pharmacy in this direction will be a significant challenge to both the profession and the educational institutions that educate pharmacists. These organizations will need to assure that a pharmacist workforce that is of sufficient size and competence will be available to all patients. Assumed in this evolution is the fact that university faculties will need to be constituted in such a way that they have sufficient and qualified faculty members that can teach and model clinical drug therapy management in real and simulated patients. It is also assumed that such faculty members have sufficient grounding in the basic, medical, and pharmaceutical sciences that roots their clinical skills in scientific evidence and clinical experience. Moreover, it will mean that faculties of pharmacy will need to align with university hospitals and medical centers as well as freestanding health care services facilities such as clinics and medical outposts for the purposes of education, training, and research.

As an example of such an undertaking, Saudi Arabia is currently expanding its number of pharmacy schools to supply the demand for pharmacists (according to a WHO report in 2006, there are only 20 pharmacists per 100,000 population in Saudi Arabia, compared to 88 in the US) (AlRuthia et al., 2018). This is a challenge for the developing country due to limited number and low quality of pharmacist–student training sites, lack of training assessments, and variety of practice models amongst sites (Aljadhey, 2012). The college of pharmacy at King Saud University, the country's oldest pharmacy school, underwent a curriculum renovation in the 2010s in order to incorporate more pharmacy practice experiences for accreditation purposes. The school increased the required number of contact hours in pharmacy practice from one semester to 500 h over two summer experiences. To support this influx of students, they created an experiential training unit that developed a preceptor training program, accredited training sites, and constructed training manuals and an assessment system (Aljadhey, 2012). In 2017, Saudi Arabia increased its number of pharmacy schools to 27 (compared to only one in 2000) (AlRuthia et al., 2018). While the country does not have its own pharmacy-specific accrediting body, three institutions are currently certified by the Accreditation Council of Pharmacy Education (ACPE) (including King Saud University) and three additional institutions are accredited by the Canadian Council for Accreditation of Pharmacy Programs (CCAPP) (ACPE, 2018; CCAPP, 2018). Additionally, increasing specialized roles for pharmacists in

hospitals, such as educating doctors and nurses on safe and appropriate use of medications, will increase the opportunities for postgraduate training (AlRuthia et al., 2018; Ministry of Health, 2017). With increasing numbers of schools and accreditation by international organizations to align global standards in pharmacy education, Saudi Arabia is working to meet the patient need for well-trained pharmacists.

As the scientific areas of discovery expand knowledge in precision medicine, genetics and population health, these findings will also find opportunity for a clinically educated and focused work force. Several practice models that focus on these areas of special expertise are already being established (Oji et al., 2013; Owusu-Obeng et al., 2014). And it is not outside of the realm of possibility that such practices will find welcome home around the world, especially where pharmacists, physicians, and clinical scientists work together effectively (WHO, 1993).

Health systems around the world are continuously confirming that the need for health care services at all levels far outpaces the financial and human resources available. Hence, these systems are constantly finding new ways to reduce budgets, create new ways of doing work, challenging the scope of benefits and implementing creative cost-cutting schemes. Pharmacy practice has not been immune to these efforts. It is incumbent on the pharmacy profession to determine cost-effective and efficient ways by which it can offer clinical services, assure the integrity of the drug supply and distribution system and keep patients satisfied with their efforts. Embracing appropriate responsibility and accountability will be the hallmark of socially-meaningful professional services.

Competencies

The wide variety of pharmacy services provided and academic pathways around the world for those positions calls into question how pharmacists and their support staff (technicians, interns, etc.) are educated and trained. Historically, a time-based model was utilized, where students who satisfactorily completed a specified course hour requirement were conferred at graduation with their degrees and eligibility for licensure (Medina, 2017). As the needs of pharmacy practice have evolved over time, so too has this education model, away from this traditional time-based requirement toward a demonstration of competency in practice by pharmacy learners for graduation (McGaghie et al., 1978). By focusing on competencies needed in practice, pharmacy education becomes up-to-date, relevant, and useful.

Outcomes-based education, also known as competency-based education, centers on a learner mastering functions necessary for practice within a practice setting (McGaghie et al., 1978). This unique curricular focus shifts pharmacy education and its accompanying assessment from merely a knowledge-based educational model, toward a knowledge, skills, and attitudes-based educational system where students are not only educated about medication products but also have the ability to function in patient care within multiple patient care settings. Under an outcomes-based educational model, the pharmacy student output is a competent practitioner ready for practice (McGaghie et al., 1978).

Outcomes-based education has been the standard of education in the United States since the early 1990s. The Center for Advancement of Pharmaceutical Education (CAPE) initially saw the need for an educational transition to outcomes-based mechanisms in an effort to support pharmacy curricular transformation toward producing practice-ready pharmacists with the growing pursuit of students for the Doctor of Pharmacy (PharmD) degree (AACP, 2004). These CAPE outcomes have been revised and updated significantly over the decades to help guide curricular change to meet the local and national pharmaceutical care needs. The Accreditation Council on Pharmacy Education (ACPE) now incorporates the CAPE outcomes as a part of their accreditation standards for colleges/schools of pharmacy (ACPE, 2015). This inclusion of outcomes-based education within the accreditation standards, forces colleges/schools of pharmacy to consider the evolving direction of pharmaceutical care provisions and the educational mechanisms to get there.

The Pharmacist Patient Care Process (PPCP) and Entrustable Professional Activities (EPAs) are additional forms of outcomes-based education and assessment that describe the pharmacist's professional competence outcomes in easy to understand language. The PPCP was devised by the Joint Commission of Pharmacy Practitioners (JCPP) to clearly describe and provide consistency to the patient care process that each pharmacist performs when providing direct pharmaceutical care (JCPP, 2014). The PPCP specifically incorporates evidence-based, best practices for the incorporation and utilization of pharmacists in direct patient care (JCPP, 2014). EPAs go beyond just the activities of pharmacists within the direct patient care settings. EPAs are tasks or descriptors of work that can be fully entrusted to a professional (Haines et al., 2017). EPAs use layman's language to describe the full scope of a pharmacists' practice, including patient care, administrative tasks and interprofessional team member related tasks (Haines et al., 2017). The PPCP and EPAs are useful resources that make outcomes-based education understandable for larger stakeholder groups, like patients and other healthcare workers, in order to communicate what a pharmacist can do, and how they perform that task in patient care settings.

There is a growing global utilization of outcomes-based education as core competencies, EPAs and ACPE's certification initiatives for pharmacy learners. The Pharmaceutical Society of Ireland has delineated a competency framework in practice for community pharmacists to elevate their education and training of pharmacy learners for practice and continuing development for practicing pharmacists (The Pharmaceutical Society of Ireland, 2013). Innovatively, The Royal Dutch Pharmacists Association has educational programming for advanced community pharmacist practice with outcomes-based education in a unique framework that incorporates both competencies from an educational level linked to EPAs within unique task areas (Royal Dutch Pharmacists Association, 2012). For global standardization of pharmacy education, ACPE and the Council for Higher Education

Accreditation (CHEA) International Quality Group (CIQG) joined forces to demonstrate their commitment to quality principles in pharmacy education that incorporate many outcomes-based educational initiatives (MOA, 2017).

Outcomes-based education is not only limited to undergraduate pharmacy education, but is also a cornerstone of postgraduate pharmacy training (Saseen et al., 2017). Pharmacy learners have postgraduate training opportunities within residency, fellowship or postdoctoral positions. While pharmacy residencies typically train pharmacists for clinical positions with further direct patient care responsibilities, fellowships and postdoctoral positions traditionally focus on intensive research training (Anon., 1987). Fellowships and postdoctoral positions for pharmacists are directed by the type of research performed by the program and have a bimodal distribution between academic institutions and pharmaceutical industry (Larochelle et al., 2009). These specialized postgraduate training opportunities are based on institution affiliation and collaborator experience and thus, do not have a listing of outcomes for the experience.

Pharmacy residency programs are wide-spread across the United States, and thus, outcomes-based education standards are critical for the support of standardization of learning and higher level pharmacy practice (e.g. beyond entry-level skills). The pharmacy residency accreditation body, the American Society of Health-System Pharmacy (ASHP), provides outcomes-based standards for residents according to the residency they are completing, postgraduate year 1 (PGY1) or postgraduate year 2 (PGY2) specialty residency. Through the formation of task forces of stakeholder groups, including the profession's leaders, residency program directors and preceptors, outcomes-based accreditation standards are devised for each type of residency program and utilized for accreditation purposes (ASHP, 2017a). Competency areas for PGY2 residency programs differ from PGY1 competency areas through specialty focus, such as infectious disease, critical care, or ambulatory care, as well as higher level clinical, administrative and/or educational functioning (ASHP, 2017b). As an element to elevate pharmacy practice across the globe, multiple international institutions have instituted pharmacy residencies and are accredited based on these same standards. International pharmacy residencies can be found in Singapore, Saudi Arabia, and the United Arab Emirates (ASHP, 2018). Nonaccredited pharmacy residency programs can be found in Spain and Argentina, as well as other countries. These programs mimic accreditation standards from the US, but are regulated by their national professional associations (ASHP, 2018).

Beyond pharmacy education and training, outcomes-based continuing education and practice are important for maintaining an acceptable level of pharmacy practice. Clinical pharmacist competencies are defined by the American College of Clinical Pharmacy (ACCP) for those postgraduate trained pharmacists who practice comprehensive medication management in direct patient care settings (Saseen et al., 2017). Uniquely, these competencies denote similarities to providers' domains by correlating the pharmacists' competencies to physician competencies in practice. Additional credentialing and privileging can occur for pharmacists at local and national levels. Each health system (e.g. individual hospital or group of hospitals) typically has their own requirements regarding credentialing at their institution or within their state jurisdictions. For example, the state of North Carolina has additional credentialing availability for qualified pharmacists to become a Clinical Pharmacist Practitioner or CPP. With this additional credentialing through the state board of pharmacy, CPPs are able to prescribe medications during the usual course of drug therapy management under the supervision of physician (North Carolina Board of Pharmacy, 2017). On a national level within the United States, pharmacists may become board certified by the Board of Pharmaceutical Specialties (BPS). Nuclear pharmacy was the first specialty to be certified in 1978; however, now there are eight recognized specialty areas including, pharmacotherapy, critical care, and ambulatory care (Board of Pharmacy Specialties, 2017). Board certified pharmacists are recognized and practicing globally.

Assessment strategies for outcomes-based education have evolved over time to match the pharmacist output. Historically, lectures were the mainstay in delivery of education in pharmacy schools (Medina, 2017). With the update of outcomes-based education models, didactic sessions are moving toward active learning models, such as case-based problem activities or lecture-discussions. These active learning models require students to prepare outside of the classroom through reading or listening to a lecture, and actively participate utilizing that information during the classroom time individually or in groups. These daily assessments of knowledge of the student prepare students for more active engagement in the patient care process, where they must take their knowledge and readily apply it to patient situations (Gleason et al., 2011; Stewart et al., 2011).

Outcomes-based education for clinical professions shifts assessment from the classroom into the clinical learning environment. In order for learners to demonstrate not only their knowledge, but also their skills and attitudes, experiential practice and assessment is important. Direct observation is the cornerstone for this type of practice-based assessment. Faculty members or trained preceptors in practice provide graded levels of supervision for learners in direct patient care activities, where novice learners are given low level tasks or are able to shadow mentors while higher level learners, such as residents, are able to perform a complete clinical task with only reactive or distant supervision. The EPA assessment framework, in conjunction with a shift to outcomes-based education, formalized this level of supervision scale to direct faculty and preceptors in their evaluations of learners. By increasing the amount of direct observation of the learner, there are increased opportunities for feedback for the learners, shifting the evaluation and feedback scheme from a summative evaluation to a progressive feedback and entrustment model (Haines et al., 2016, 2017).

A progressive, formative feedback model has multiple benefits within outcomes-based education (Downing and Yudkowsky, 2009). For the learner, this frequent feedback model can build transparency regarding the expectations of their performance through specific describing of their performance successes and areas of improvement for each activity. Additionally, learners can begin to validate the abstract outcomes into tangible healthcare scenarios building purpose into their work. For teachers, the progressive nature of this evaluation model is useful for objectifying learner performance. Previously, student evaluation required teacher gestalt and experience. With increased direct observations and documentation of learner performance, teachers can more objectively identify the level of the learner based on prescribed outcomes to provide objective summative evaluations as well as objectively compare learners within the same learning experience. Summative evaluations in this model become more useful

for learners and institutions to identify troubled learners and building of remediation plans as well as provide a scaffold for learners to self-reflect on their progress (Downing and Yudkowsky, 2009).

Education

As previously discussed within this chapter, the needs and services of pharmacy practice vary vastly across the world. And thus, pharmacy educational pathways and requirements are different across the world to meet those needs. Currently there are no accreditation standards for pharmacy education recognized internationally. This chapter will address the different pathways to pharmacy practice for pharmacists and pharmacy technicians.

The role of pharmacy is evolving rapidly around the world. A reconstructive or a reflective higher education adjustment approach can be utilized to transform curricula for the new practice models. Reconstructive approaches to higher education utilize educational innovation and visions of a desired future by implementing novel pathways initially in place of a standard (Duit et al., 2018). Reflective approaches tend to look back at current curricula, making minor adjustments over time to the education and activities to impart change (Lemberger, 1983). Reconstructive approaches rapidly shift educational mechanisms, while reflective approaches can be slow and minimal. However, reconstructive models have more risk by incorporating educational models or tools that may not be tested, while reflective approaches may be too slow and limited to adequately prepare students for practice.

The FIP most recently provided a statement to guide good pharmacy education practice. Within this statement, there are no recommendations regarding degree pathways for pharmacist practice. Instead, it recommends "*basic (first degree) education programs should provide pharmacy students and graduates with a sound and balanced grounding in the natural, pharmaceutical and healthcare sciences that provide the essential foundation for pharmacy practice in a multi-professional healthcare delivery environment*" (FIP, 2000). This recommendation and the overall standard document presents the notion that there is no one correct degree pathway for pharmacy practice. Yet, there are general principles and knowledge that every pharmacist must maintain and be tested on for practice across pharmacy settings, such as the community, hospital, and industry. At minimum, pharmacist should be exposed to: biological systems and their interaction with medications, dosage form design and development, medication actions and uses, pharmacy practice law, appropriate ethical conduct in practice, safety and risk management, pharmacoepidemiology and health economics, introduction to pharmacy practice across practice areas, introduction to effective management, and introduction to manufacturing good practices (FIP, 2000). These are broad recommendations that satisfy a cohesive pharmacy practice internationally.

Multiple degree types are available for pharmacists: a bachelor's degree, master's degree and doctor of pharmacy degree. The university requirements of these degrees vary by institution and country (Anderson and Futter, 2009). However, there are some typical themes to the type of practice allowed based on the degree awarded. A bachelor of science (BS) degree in pharmacy or pharmaceutical sciences is the typical entry level degree for pharmacist in staffing type positions, such as community pharmacy, where the main pharmacist function is distributive. A master's degree (MS) in pharmacy or pharmaceutical sciences prepares pharmacists with additive skills, typically management or research skills. Typical positions for those pharmacists with a master's degree are in industry, hospital or potentially in an administrative management position. The Doctor of Pharmacy (PharmD) degree is the highest level degree obtained by a pharmacist. This degree incorporates the basic elements of both the bachelor's and master's degree program but also has a clinical experiential component to the educational requirements. This additional experience is completed as supervised and structured rotations across different pharmacy practice sites, including community, hospital, industry, and academia. The PharmD curriculum provides the ability of pharmacists to practice across the spectrum of pharmacy, in distributive roles, managerial roles, and clinical positions (Anderson and Futter, 2009; Chanakit et al., 2014; FIP, 2018; International Pharmaceutical Federation, 2017; Knoer et al., 2016; Lutz et al., 2009).

Faculty and preceptors who enact these degree pathways differ widely across the world. Because the bachelor degree has a limited clinical focus, unfortunately, the faculty of these programs can be disjointed from actual pharmacy practice, where their understanding of educational need is different than the healthcare needs (Chanakit et al., 2014; Kapol et al., 2008; Lutz et al., 2009; Parrish and Chew, 2018). Additionally, faculty within the master's programs may be differently focused in their teaching and research skills and thus have limitations of education linking to patient care (Anderson and Futter, 2009). PharmD trained faculty have the potential for grounding their education in the clinical healthcare needs of patients and the health system because of their role in both clinical practice and education.

Skills training for pharmacists go beyond the university pathways of degrees for training in specialized areas. Pharmacy residency and pharmacy fellowship programs are skill-based training programs pharmacists may pursue after they receive their PharmD degree to prepare them for unique, higher-level practice. Pharmacist can choose to complete 1- or 2-years of pharmacy residency (ASHP, 2017a, 2017b). Pharmacy residency training focuses on additional clinical experience within a health system or practice site to prepare pharmacists for roles with direct patient care in a hospital or outpatient clinics (Anon., 1987). An 1-year pharmacy residency focuses on general knowledge, while a fellowship focuses on training pharmacists for research. These programs can be academic-based or industry-based and specialized based on the institution affiliation or industry sponsor (Larochelle et al., 2009). The diverse degree and training options for pharmacists leaves the question as to what the most optimal education for pharmacists should be. A needs-based and outcomes-based approach to education and training is critical.

Quality assurance of the educational pathways and the roles they provide for are necessary to ensure an adequate and appropriate workforce (FIP, 2009). Continuing education requirements, as mandated by pharmacy licensures, are a potential mechanism for regulating bodies to ensure the maintenance of knowledge of pharmacists in practice. However, there is a significant divergence

from the level of education required by higher education and a pharmacist licensure. While higher education models and degree pathways instill a reconstructive approach, where innovation is implemented swiftly, licensure bodies follow reflective models that are slower to adjust to the needs of practice. The disconnect between pharmacy education and licensure may cause pharmacists in practice to become outdated with time even though they are maintaining their continuing education hours. It may be warranted for pharmacy licensure regulations to implement novel approaches to keep practicing pharmacists at the highest level of knowledge and practice for the safety and efficacy of the patients they care for (Adams et al., 2018).

The FIP recognized the discordance between education and quality assurance in practice and released the *FIP Statement of Policy: Quality Assurance of Pharmacy Education* (FIP, 2009). This international statement identified key stakeholders: national governments and their regulating bodies, pharmacy member organizations and higher education institutions. A framework is provided through this statement for how each of these stakeholder groups can work together to meet the quality assurance needs of the healthcare system for pharmacy practice with innovative educational approaches in mind. While the recommendations are not explicit or prescriptive, the framework provides guidance and adaptability for application across local, regional and national systems (FIP, 2009).

While great strides have been made internationally to bring equity for pharmacist education pathways, pharmacy technician education, and training remains diverse. In many industrialized countries, pharmacy technicians tend to be more highly educated and trained based on the adequate number of practicing pharmacists. However, pharmacy technicians are commonly utilized for common pharmacy services when pharmacists are not available in underserved or less developed countries (Lemberger, 1983). Pharmacy support staff is crucial for provision of pharmaceutical needs and should be provided with the necessary education and training for safe and effective care of patients. A specific set of recommendations for education of pharmacy support staff would be useful, particularly with a focus on those skills needed for practice in underdeveloped environments where pharmacy support staff have lower levels of supervision by a pharmacist and thus, higher levels of practice (Koehler and Brown, 2017; Parrish and Chew, 2018).

Conclusion

This chapter has examined several policy questions and challenges related to national needs-based pharmacy education and how that relates to the outcomes of pharmacy education in terms of fitness for practice and preparation for roles outside of the patient care domain such as industry and regulation. Policy makers at various levels, ranging from members of a pharmacy Faculty through those whose work is at the ministerial level in education and public health are challenged to consider national needs for the pharmacist workforce.

This workforce needs to be prepared at high levels of competence to protect public safety regardless of place of employment since the focus of the workforce centers on consumption of a broad spectrum of medicinal agents. As one contemplates the future, both the variation and the scope of the pharmaceutical armamentarium will be subject to advances in science and clinical developments. These evolutions require careful analytical approaches to faculty hiring, deployment and development, curricular development, instructional strategies, performance evaluation, and overall programmatic outcomes measurement and assessment.

Assuring that there is little gap between what a nation requires from its pharmacist workforce and what its university programs produce is an important element of social accountability. This accountability lies with all levels of the decision-making process related to the educational and public health system.

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Developing and Implementing Patient Safety Standards Within the Pharmacy Practice and Education Settings

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Introduction

The acknowledgment that healthcare professionals are capable of doing harm to patients is as old as the Hippocratic oath. However, it was not until the publication of two landmark reports, *To Err is Human* (1999) (Kohn et al., 2000) in the United States and *An Organisation with a Memory* (2000) (Department of Health, 2000) in the United Kingdom, that the importance of patient safety was recognized by key stakeholders in health care. The reports highlighted the alarming number of patients that have been harmed as a result of receiving health care. For example, it is estimated that between 44,000 and 98,000 people die on an annual basis as a result of a medication errors in American hospitals (Kohn et al., 2000). Importantly, through the publication of these reports, the complexity of healthcare systems was acknowledged by key stakeholders for the first time, as was the understanding that any solutions to improve safety need to address this complexity in order to be effective.

In 2002, the World Health Organization (WHO) member states recognized the need to reduce the harm and suffering that patients and their families were experiencing from healthcare errors, and agreed on a resolution to improve patient safety. In Australia, a significant number of adverse events are attributed to medicines. In the 2002 *Second National Report on Patient Safety: Improving Medication Safety* which was published by the Australian Council for Safety and Quality in Health Care, it was estimated that approximately 140,000 hospital admissions per year are associated with adverse drug events (Australian Council for Safety and Quality in Health Care, 2002; Easton et al., 2009). This equates to a cost of about 380 million Australian dollars per year to the public healthcare system. In 2007, the number of hospital admissions due to medication error had increased to approximately 180,000, suggesting an upward trend in the number of people affected by medication errors (Roughead and Semple, 2009). Furthermore, it is estimated that 17% of all medication-related hospital admissions in Australia have resulted in permanent disability and that 3% of admissions have resulted in death (Wilson et al., 1995). Of particular concern is that 50% of such admissions are considered to be preventable, highlighting scope to improve patient safety (Easton et al., 2009).

Considering their training in medicines and evolving clinical care roles, pharmacists can play a key role in mitigating patient and medication safety incidents.

Concept of Patient Safety

Traditional Approach to Patient Safety

In 1994, medical practitioner and patient safety researcher Lucian Leape stated that "the professional cultures of medicine and nursing typically use blame to encourage proper performance . . . errors are caused by a lack of sufficient attention or, worse, lack of caring enough to make sure you are correct" (Leape, 1994). Prior to the publication of *To Err is Human* (Kohn et al., 2000) and *An Organisation with a Memory* (Department of Health, 2000), healthcare institutions and professional bodies took a relatively reactionary approach to patient safety (Leape, 1997). Traditionally, this encompassed isolating the healthcare professionals involved in an incident and blaming them for their forgetfulness, inattention, or moral weakness (Leape, 1994). In 1997, Leape went on to say that the "public preferred to believe that errors in medical practice were rare, and the professions sought to perpetuate that misconception both for medico-legal reasons and because of the difficulty physicians have in dealing with errors" (Leape, 1997). Following an error, based on the outcome to the patient, media coverage, and the public outcry, the healthcare professionals involved would be forced by their employer or regulatory bodies to undergo remediation or may even be deemed unfit to practice and lose their registration as a healthcare professional. Psychologist James Reason defined this as the "individual approach" to error, which has been colloquially described as the "shame, blame, and retrain" approach (Reason, 2000). Although this approach is emotionally satisfying for patients and is fostered by the punitive legal system, it only provides a quick fix for healthcare institutions and regulatory bodies, whereas the actual underlying issues remain unaddressed (Reason, 2000).

Changing the Safety Paradigm

Following the publication of the two seminal reports previously described (Department of Health, 2000; Kohn et al., 2000), a dynamic shift in the patient safety paradigm occurred. For the first time, healthcare stakeholders began to acknowledge the complexity of healthcare systems and proposed solutions that were needed to address this complexity in order to be effective (Helmreich, 2000; Vincent, 2011). In particular, stakeholders began to examine the approaches taken by other high reliability organizations (HROs) to mitigate safety issues. HROs are organizations or industries that have been able to significantly minimize serious adverse events or catastrophic failures despite operating in highly complex and risk-prone environments. The aviation and nuclear science industries are two highly cited examples of HROs. Four key characteristics have been identified across HROs:

1. preoccupation with failure, where the organization acknowledges and plans for the possibility of failure;
2. a commitment to resilience, where the organization proactively seeks out unexpected threats and develops mechanisms to contain them;
3. a sensitivity to operations, where the organization places attention on the issues experienced by frontline staff; and
4. an open culture of safety, where individuals feel comfortable drawing attention to potential hazards to the organization (Vincent, 2011).

In recognition of the practices employed by HROs to improve safety, healthcare stakeholders engaged safety science experts from HROs, in particular, psychologists, human factors engineers, and resilience engineering experts, to undertake evaluations and work toward improving the safety paradigm in health care. As a result, a systems approach to errors has evolved in health care.

A systems approach acknowledges human fallibility and that error is to be expected, even in the best environments (Fox, 1995). This approach views an error as a consequence of upstream systems failures rather than being caused by an individual. In this approach, defenses and safeguards are put in place to prevent incidents from occurring, and when incidents do occur, they are seen as a failure of the implemented defenses and safeguards (Reason, 2000). This approach is best illustrated by James Reason in the Swiss Cheese Model which was previously developed for complex industrial settings, primarily aviation. The model states that "in an ideal world each defensive layer would be intact. In reality, however, they are more like slices of Swiss cheese, having many holes although unlike in the cheese, these holes are continually opening, shutting, and shifting their location." In Reason's model, when an alignment of holes occurs, all the defenses have failed and subsequently an error or incident occurs (Reason, 2000). The Swiss Cheese Model allowed healthcare institutions and stakeholders to develop an understanding of the different factors that result in errors or patient safety incidents occurring. Charles Vincent, another psychologist, later developed an adaption of Reason's model that was more specific to health care (Vincent, 2011). Vincent's model (**Fig. 1**) takes a "human factors approach" to the Swiss Cheese Model and focuses on the human elements of the sociotechnical system that is used to describe health care. The model begins on the left side of the diagram, where latent failures relating to poor organizational processes set the accident sequence of events in motion. In the model, organizational processes relate to the planning, scheduling, maintenance, strategy, and policy of the healthcare organization or institution. When these latent conditions transfer from an organizational level to a department level, they become

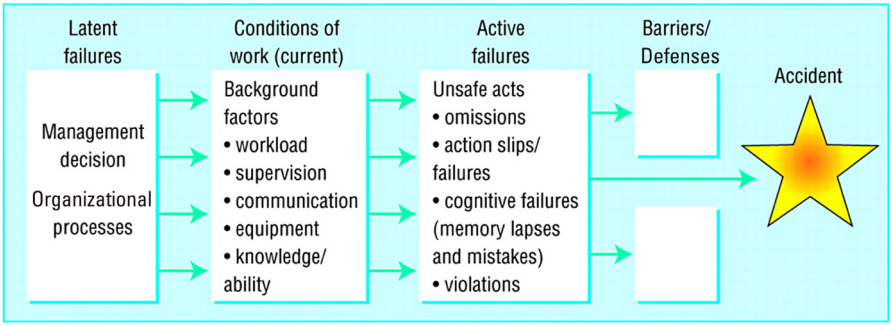

Figure 1 Vincent's Organisational Accident Model adapted from Reason's Swiss Cheese Model (Vincent et al., 1998).

Table 1 Vincent's framework of contributory factors influencing clinical practice (Vincent et al., 1998)

Factor types	*Contributory influencing factor*
Organizational and management factors	• Financial resources and constraints • Organizational structure • Policy standards and goals • Safety culture and priorities
Work environment	• Staffing levels and skills mix • Workload and shift patterns • Design, availability, and maintenance of equipment • Administrative and managerial support
Team factors	• Verbal communication • Written communication • Supervision and seeking help • Team structure
Individual (staff) factors	• Knowledge and skills • Motivation to undertake tasks • Physical and mental health
Task factors	• Task design and clarity of structure • Availability and use of protocols • Availability and accuracy of test results
Patient characteristics	• Condition (complexity and seriousness) • Language and communication • Personality and social factors

local-level conditions, which, in turn, promote the possibility of active failures to occur (Vincent, 2011). Examples of local-level conditions that can lead to failures include excessive workloads, stressful environments, inadequate supervision, inadequate communication systems, and departments lacking the equipment or resources they require. Active failures are defined by Vincent as "unsafe acts or omissions committed by those whose actions can have immediate adverse consequences" (Vincent, 1997), and include slips (e.g., being distracted while following a protocol) and failures (e.g., picking the wrong medicine from the shelf), cognitive failures (e.g., memory lapses or misreading a medicine name), and violations (e.g., deviating from standard operating procedures or best practices). This model hypothesizes that although many unsafe acts are likely to be committed, there are also a number of barriers and defenses that have been put in place to prevent a poor outcome, such as the use of alarms during the dispensing of medicines with similar names or packaging, product scanners during the dispensing of medicines, and having a dispensing protocol in place.

Vincent also identified that there are a number of contributing factors that affect the clinical practice of a healthcare professional (Vincent et al., 1998). **Table 1**, adapted from Vincent, presents a summary of common factors that affect healthcare professionals, which range from patient and individual practitioner factors to factors which arise from higher up in the health system, such as organizational and management factors. In the table, the contributory factors are listed in order of increasing effect on practitioners' behaviors and practices and in order of decreasing effect on the final outcome, that is, a patient's condition is more likely to affect how a practitioner treats a patient; however, staffing and resources available will be more likely to affect whether a patient is treated in the best possible way.

Clinical Example Demonstrating Impact of Latent Failures

Consider an elderly male patient who has been admitted to hospital and subsequently diagnosed with stage 4 pancreatic cancer. He has been scheduled to undergo a palliative stenting procedure and in preparation for the procedure, the patient is deemed to be nil by mouth. The procedure is subsequently delayed numerous times over the course of a 2-week period. The patient then reaches a critical state as he has been unable to eat properly while waiting for the procedure to occur. The procedure was delayed due to the surgeon's excessive workload and a decision was made by the hospital administration to reduce the number of operating theaters in use. In this example, the two factors that had the greatest impact on delaying the procedure were organizational and management factors (due to budget restrictions, fewer staff were available and less operating theaters were in use) and the work environment (due to reduced staffing levels). It is only at the point when the patient's condition becomes more critical, that is, a patient characteristic, that the problem is escalated and the patient is able to receive his palliative procedure.

The Need for Patient Safety Standards

One of the key findings that came out of the publication of the seminal reports was the need for a healthcare organization to prioritize patient safety. In doing so, it was acknowledged that one mechanism to force a shift toward safety-focused practices was through the use of standards. In *To Err is Human* (Kohn et al., 2000), the seventh recommendation made by Kohn et al. was to set performance standards, the concept of which could "either establish minimum levels of performance or can establish consistency or uniformity across multiple individuals and organizations" (Kohn et al., 2000). Kohn et al. described that these standards could be used for setting expectations of practitioners by the profession as well what the public should expect from their practitioners. Although, at the time the report was released, the "individual approach" to patient safety problems prevailed, both the recommendations made in this report in addition to the recording of harmful patient safety incidents have driven professional organizations to take actions (Kohn et al., 2000). Over the last 20 years, a "common law" approach has been adopted by professional organizations to develop practice standards. There has also been a shift to move away from the "individual approach," whereby individuals were penalized for harm, and for a systems focus to be adopted. When reviewing the standards that exist today it can be seen on a global scale that standards do not necessarily specify that they are specific to patient safety, the principles of patient safety are held at the core of each professional practice standard. Although this approach has had success in many developed nations, developing nations still struggle to develop standards that are adopted nationwide (World Health Organization Regional Office for Africa, 2014).

Developing Standards

A standard can be defined as " a voluntary document that sets out specifications, procedures and guidelines that aim to ensure products, services, and systems are safe, consistent, and reliable" (Standards Australia, 2018). Standards are developed as part of the introduction of a new service or practice; however, the many standards in health care have been developed as a result of reviewing practices, analysis of reports of patient safety incidents, or near-misses. As healthcare institutions and organizations transitioned from the personal approach to errors to a systems approach, methods were developed to understand the factors that were involved in the causation of errors or incidents, with the standards written to address these contributing factors. In order to undertake these analyses, data must be collected and aggregated (Leape, 1997). The five main methods of data collection that have been commonly used in safety analyses are direct observation, chart review, computer screening, focus groups, and spontaneous reporting.

Data Collection Methods

Direct Observation

Direct observation is the most labor-intensive method but advantageous as it generates the greatest amount of data. This method requires an individual to observe the practices of an individual or a group with activities ranging from simple behavioral observations to auditing (Leape, 1997). Although this method has been shown to be the best method for detecting errors, it also has a number of biases (Grote and Künzler, 2000). First, there is an inherent observation bias as even though a trained observer is required to conduct the process, the observer may be external to the system and may also misinterpret the actions or behaviors of practitioners. Second, this process is subject to the Hawthorne effect, by which those being observed change their behaviors based on whether they are being observed or not (Sacks et al., 2015).

Patient Chart Review

Patient chart review is a method whereby investigators review patient charts that are a part of the intended study group. This method involves looking through charts to identify any notes that describe an incident or a potential incident, and subsequently collating these notes in order to identify the key factors that resulted in the actual or potential incident from occurring (Leape, 1997). Although this is also a high yield method, it is limited by the quality of the patients' notes and the level of detail that is provided.

Furthermore, incidents that have caused harm are more likely to be recorded in a patient's notes as opposed to problems that have not noticeably affected a patient (Vincent, 2011; Vincent et al., 1998).

Computer Screening

Computer screening is a method that is both time efficient and cost-effective in detecting errors (Leape, 1997). This method uses computer algorithms to analyze potential and actual errors, and has been predicted to have an increasing level of uptake as health systems begin using integrated electronic patient records and medication charting. Although this method can generate a large amount of data in a small amount of time, it does have limitations in what can be detected particularly when data integrity failures occur; however, this will change as electronic record systems are advanced (Barber et al., 2007; Odukoya and Chui, 2013).

Focus Groups and Structured Interviews

Although focus groups and structured interviews cannot quantify a problem, they can provide a large amount of qualitative data to understand factors that may affect a phenomenon (Leape, 1997). The information-rich data from focus groups have been shown to be very effective in understanding the conditions faced by staff at the frontline and the underlying factors that may not be able to be measured in quantitative forms of analysis (Phipps et al., 2009). In particular, this can help identify potential or near-miss incidents that are not reported or documented. Multilevel ethnographic studies have been used by HROs to evaluate workplace culture and are increasingly being used in patient safety studies. They can also be combined with other forms of quantitative data to provide a more comprehensive analysis (Vincent, 2011).

Spontaneous Reporting

Incident reporting is one of the most common forms of quality improvement activities in health care (Leape, 1997). It is a legal requirement of many care facilities and hospitals for there to be a procedure to both report and review incidents in a timely manner (Vincent, 2011). For example, under the Quality Care Pharmacy Accreditation Program (QCPP) which is implemented in community pharmacies across Australia, it is first mandatory that incidents be recorded and reviewed, and second, that changes to practices or systems be implemented in order to prevent further incidents. The process of incident reporting involves completion of a paper or electronic version of a structured incident report form. Incident report forms aim to collect data to answer three essential questions: "what happened?"; "what were the contributing factors?"; and "how could the incident be prevented?". From this, incident data are then pooled and collectively analyzed (Mitchell et al., 2015). Although this method obtains the richest data about an incident or problem that has occurred due to the collection of both quantitative and qualitative data, the punitive methods in which incidents can be managed may discourage reporting, resulting in either poor quality of reports or a small percentage of incidents being reported (Boyle et al., 2011; Evans et al., 2007; Waring, 2005).

Investigation Methods

Following the collection of data, the two main analytical approaches that can be used to evaluate incidents are root cause analysis (RCA) and failure mode and effects analysis (FMEA), both of which have been adapted from HROs.

Root Cause Analysis

RCA was the first method used to evaluate incidents and is still one of the most common methods to be used in the healthcare industry today (Vincent, 2011). The RCA process follows a number of fundamental principles. First, this method is a retrospective method that analyzes the error or incident. The method views the incident or error as a result of a linear chain of events, which may or may not have a number of contributory factors. Ultimately, the RCA process aims to answer three questions: "what happened?"; "how did it happen?"; and "why did it happen?". At the conclusion of the RCA process, a single root cause or a small number of root causes are identified. The identified root causes are then subject to improvement strategies in order to prevent them from causing the same problem in the future (Iedema et al., 2006).

The London protocol

Although the RCA process is fundamentally good in theory, it originates from industries that are highly mechanical and, consequently, are not as effective in preventing errors or incidents from reoccurring in health care. In 2001, Vincent developed the London Protocol which is a method to perform RCA within the healthcare industry and is based on using a systems approach. This process is a multistep approach and is summarized in **Fig. 2** (Taylor-Adams and Vincent, 2004; Vincent, 2011). The process combines a number of quantitative data collection techniques as well as structured interviews or focus groups with key staff. The investigation team, which comprises practitioners ranging in experience, administrators, and experts, uses the data that they have obtained to answer the key questions of an RCA: "what happened?" (incident chronology); "how did it happen?" (care delivery problems, e.g., slips or lapses in a particular process); and "why did it happen?" (contributory factors). After this information has been ascertained, the contributory problems need to be classified into whether they are isolated to a single profession, unit, or department, or whether they are more general in nature so that an appropriate action plan can be put in place.

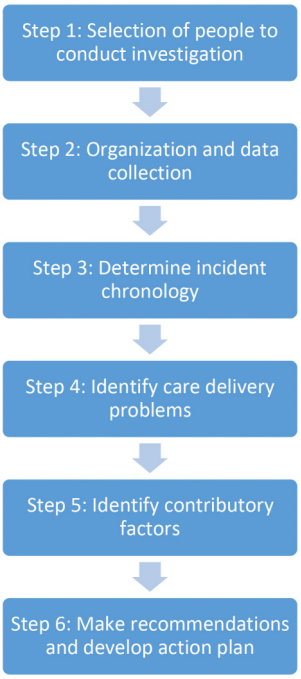

Figure 2 Summary of the London Protocol process (Taylor-Adams and Vincent, 2004).

Failure Mode and Effects Analysis

Failure mode and effects analysis (FMEA) is a prospective analytical method which has been used by HROs and adapted for the healthcare setting (Chiozza and Ponzetti, 2009). This method allows healthcare institutions and organizations to predict problems prior to their occurrence. The process of FMEA consists of five steps. First, the scope within the topic of interest is defined. Safety organizations recommend having a very specific aspect of a topic to investigate to ensure a beneficial outcome. The second step involves assembling a multidisciplinary team of experts who are involved in the specific topic being investigated. The third step involves creating high-level flow diagrams to map out each process. Within this step, subprocesses need to be identified and included within the flow diagram. The fourth step is to perform a hazard analysis. Initially, the potential failure modes for each of the processes are identified, along with their causes and the potential effects on patients. These are then rated for their severity, probability of occurrence, and likelihood of detection. During this process it is important to identify whether the particular failure mode requires further attention. The final step of the process involves determining the actions required to reduce the failure mode and prioritize the actions to be taken (Chiozza and Ponzetti, 2009; Woodhouse et al., 2003).

Investigation Method Limitations

Despite the high uptake of these two methods, they both have limitations. RCA and the London Protocol are both easily understood and adaptable methods that are useful in incident investigation (Taylor-Adams and Vincent, 2004). However, they do not allow for prospective analyses to be performed. FMEA provides a more comprehensive review of a process and can be performed in both a prospective or retrospective fashion. However, due to the costs involved in performing an FMEA, it is usually reserved for high priority or high-risk processes (Vincent, 2011; Woodhouse et al., 2003). A limitation of both RCA and FMEA is that they look at each of the factors that result in errors in isolation and do not account for the interrelationships between factors.

Standard Development Process

Following the analysis of either patient safety incidents or the observation of practitioners, there are a number of interventions that can be developed to prevent similar identified issues happening again. The implementation of standards is one such process and the development of which involves a number of steps, as summarized in **Fig. 3**. The process would usually commence with a demand from the industry, whether it be from a macrolevel organization such as a health department or professional bodies to a microlevel organization such as a pharmacy department. The standard would be drafted by an expert reference group, consisting of expert practitioners and managers and would include the scope and content of the standard as well as the adoption of key definitions. The drafted standard would then be reviewed by stakeholders from the relevant professional organizations, academics, and consumer organizations, prior to be being sent out for public comment by the targeted audience. Once the final draft of the standard has been composed, it must be formally adopted by the organization or institution, usually performed through a

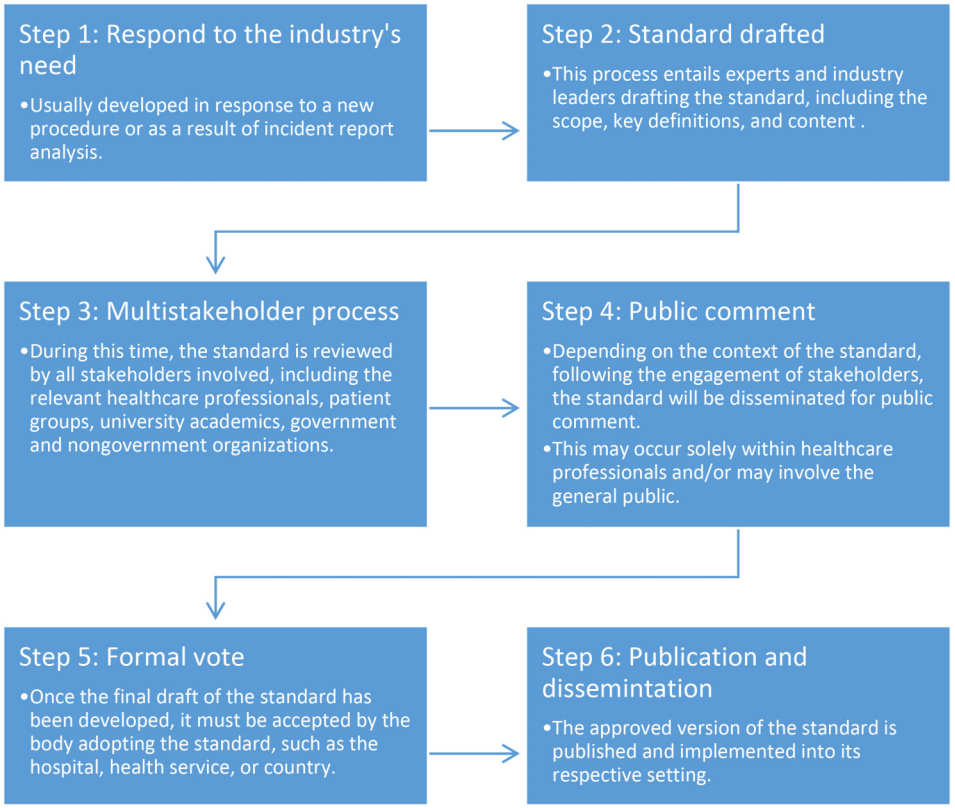

Figure 3 Summary of the Standard Development Process developed from the International Standardization Organization Standard Development Flowchart (International Organization for Standardization, 2018).

voting process. Finally, after the standard has been adopted, the standard must be disseminated to the affected practitioners and health system management.

Medication Safety Standards

Medication safety can be considered as the freedom from medicine-related harm, damage, or loss (Runciman, 2006). Medication safety standards are considered an integral part of the medication safety process. The development of many medication safety standards exists as a preventative strategy following the analysis of medication safety incidents, usually where harm has occurred. As a result standards have been implemented on a number of levels ranging from standards applied on a facility level to standards that are applied on a more global level such as throughout a health service to national and international levels.

Medicine Nomenclature

When medicines are developed, there are usually three names given to a new medicine: a chemical name (e.g., 4-chloro-*N*-furfuryl-*S*-sulphamoylanthranilic acid), a nonproprietary or generic drug name (e.g., Frusemide), and a brand name (e.g., Lasix). Although a new medicine will only have one chemical and nonproprietary name, it may have a number of brand names which can result in confusion. A strategy to mitigate this is through the standard use of nonproprietary or generic drug names. The WHO has also recommended the use of nonproprietary names for medicines in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature, prescribing and dispensing of medicines (World Health Organization, 2017). In 1953, it developed a standardized global nomenclature register for nonpropriatory names of medicines (INN). Although a number of countries have their own register of medicine names. including British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN), and United States Accepted Names (USAN), the vast majority of medicines have adopted the international nonproprietary nomenclature.

Although this standardization process can reduce confusion between different medicines, it still can cause problems. Look alike and sound alike medicine names have been the cause of a number of medication safety incidents, particularly when the products have very similar packaging. Typographical strategies have been one solution suggested to prevent this issue. Tall man lettering has been a typographical strategy that has been implemented by a number of health services. This strategy uses capitalization of the

letters of a drug name that make it different to other similar named products, for example, fluVOXAMine and fluOXETine. Although this strategy has had some success in preventing medication errors (Zhong et al., 2015), recent evidence has shown that this strategy has been ineffective in preventing errors (Lambert et al., 2016) as well as anecdotal evidence of it affecting readability of drug names by patients. Therefore, further work in this area is required (Lambert et al., 2016).

Safe Medication Practices

Standardization of medication practices has been another strategy that has been utilized to improve medication safety. The majority of safe medication practice standards and policies have been developed because of incidents occurring with regard to the use of medicines. Typically, national organizations such as the Institute for Safe Medication Practices and the Joint Commission in the United States or the Australian Commission for Quality and Safety in Health Care have developed a series of standards against which health institutions, such as hospitals, are assessed and accredited. Standards and standardizations are considered a moderately effective method of improving safety. However, some standards incorporate other types of interventions such as checklists, which are effective on a personal level as well as the highest level of intervention—a forcing function, a preventative strategy by which that would ensure an incident would not possibly occur. A classic example of this is potassium chloride ampules on hospital wards. These ampules looked very similar to sodium chloride and water for injection and sometimes were selected in error when reconstituting medicines for injection on the ward. In order to prevent this incident happening, a standard was implemented that potassium chloride was to be only available in large volume bags so as the confusion would not occur (Reeve and Allinson, 2005).

The Need for Global Standards

Although there are currently a number of standards that exist with regard to medication safety, as seen above, there are currently no standards that are applied to health systems on a global level. This issue was recognized by a number of patient and medication safety organizations. In 2017, the WHO launched its third challenge for patient safety—to improve medication safety. One of the key objectives of this global challenge was to develop a set of standards which could be implemented in health systems across the globe. The topic areas covered in these new standards had not been released at the time of writing.

Education Standards

Education has been recognized as one of the key strategies to improve healthcare professional and student knowledge and opinions on patient and medication safety. Globally, public health and patient and medication safety organizations have tried to fill the gap in patient and medication safety education for both students and health professionals. One such organization was the Institute for Healthcare Improvement (IHI), an American not-for-profit organization based in Cambridge, MA, that focuses on patient safety and quality improvement. In 2008, IHI released an online learning platform called the IHI Open School, with the intention of addressing the lack of training in patient safety and quality improvement provided to healthcare students. This platform allows students and healthcare professionals from around the globe to voluntarily develop their quality improvement and patient safety knowledge and skills using interactive web-based courses (Ward et al., 2013). Although these courses have been implemented in many health discipline curricula in North America, there is a need for a global set of standards of patient safety education for all healthcare students.

The World Health Organization Patient Safety Curriculum

The WHO recognized the need to develop an essential set of education standards for health professions in order to improve patient safety. In 2009, the WHO developed a *Patient Safety Curriculum Guide for Medical Students*, based around the *Australian National Patient Safety Education Framework* (Walton et al., 2010). This was later rereleased in 2011 as a multiprofessional edition (World Health Organization, 2011), to provide a framework for all health disciplines to deliver patient safety education to their students. The current framework consists of 11 topics, which can be incorporated at different levels into health students' curricula and include recommendations for the implementation of educational activities (**Table 2**).

Education as a Strategy to Improve Safety

Although education has long been considered one of the key strategies to improve patient safety (Oates et al., 2013), changing already full curricula, combined with capacity and capability issues within institutions, has provided a challenging environment for implementing patient safety specific education (Ahmed et al., 2013). Furthermore, it has been shown that despite the implementation of specific patient safety education, the pharmacy workforce has a bigger impact on the practice of junior practitioners (Walpola et al., 2017). If one considers the hierarchy of interventions, education is a very human-focused intervention and is considered to have limited efficacy on either the health system at large or the individual organization (i.e., hospital or community pharmacy). This has been demonstrated in the literature with pharmacy graduates' attitudes to

Table 2 Summary of WHO patient safety curriculum topics

Topic	*Title*	*Summary*
1	What is patient safety?	This topic introduces the concept of patient safety and the importance of understanding the factors that can affect patient safety.
2	Why applying human factors is important for patient safety?	This topic introduces the concepts of human factors, which traditionally were applied to engineering and psychology disciplines, and how the principles of human factors can be applied to improving patient safety.
3	Understanding systems and the effect of complexity on patient care	This topic introduces the conceptualization of the health system as a complex system consisting of a number of complex and integrating relationships, such as between departments, services, practices, and staff.
4	Being an effective team player	This topic covers a number of concepts that are critical to teamwork. A core focus for this topic is communication skills and in particular understanding the effects of miscommunication.
5	Learning from errors	This topic focuses on developing a positive safety culture through examining errors and understanding the factors that affect why things go wrong.
6	Understanding and managing clinical risk	This topic introduces the concept of clinical risk and the importance of managing clinical risk to ensure safe systems of care. The topic introduces concepts around managing complaints and making improvements to health systems.
7	Using quality improvement methods to improve patient care	This topic discusses the process for analyzing patient safety problems and frameworks to test improvements to combat the problems identified.
8	Engaging with patients and carers	This topic introduces concepts around the inclusion of patients and carers as part of the patients' own healthcare team. It also addresses how errors can be prevented through this process.
9	Infection prevention and control	This topic discusses the importance of managing infection prevention and controlling the spread of infection.
10	Patient safety and invasive procedures	This topic explores a number of safety issues associated with surgical procedures as well as discussion of safe surgical practices including the WHO Surgical Safety Checklist.
11	Improving medication safety	This topic provides a focused exploration of the factors that affect medication safety at the different points of the medicine use cycle. The topic also discusses strategies to improve medication safety.

patient safety being affected more greatly by other factors such as workplace culture on a longer term basis than whether they received education (Walpola et al., 2017). Therefore, education and educational standards are only one part of the overall strategy to improve patient safety.

Future Directions

As the core values of HROs are implemented into the health industry, the number of safety standards to improve patient safety is likely to increase. At the time of the writing of this article, there were no internationally adopted standards related to patient safety practices by healthcare professionals. Although the WHO has acknowledged the difficulty in achieving this, an objective of the WHO Third Patient Safety Challenge is to develop a set of standards that can be applied on a global scale. Although it is anticipated that the new standards will be developed, they only comprise one part of the solution to improve patient safety on a global scale. Future work should consider the principles of resilience engineering to evaluate the effectiveness of standards that have been developed and implemented.

Glossary

An error—unintentionally being wrong in conduct or judgment (Runciman, 2006).
An incident—an event or circumstance which could have resulted, or did result, in unintended or unnecessary harm to a person (Runciman, 2006).

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Pharmacy Professional Standards Defining Quality of Services

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Historical Development of Professional Standards

Since the middle of the 20th century the role of pharmacists in the healthcare system was continuously growing and changing from the traditional drug-focused pharmaceutical services toward patient-oriented care, where pharmacist was not only dispensing the drug, but also overtook the responsibility on its rational use. New area of pharmaceutical practice was first defined in the USA as pharmaceutical care in the mid-1970s (Mikael et al., 1975). The first official international definition of pharmaceutical care followed later in early 19th century by Hepler and Strand, as "Responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Strand, 1990).

Meantime, World Health Organization (WHO) as international standard setting entity in healthcare followed the recent developments in pharmacist profession and put it high on its agenda. For the first time the new role of pharmacists as one of the key elements in the rational drug use was discussed in 1986 during 39th World Health Assembly when a revised drug strategy was adopted by the member states (WHO, 1986). A series of meetings on this topic took place during the next decade (New Delhi, 1988; Tokyo, 1993, Vancouver, 1997 and Hague, 1998) under the aegis of WHO. This was followed by the adoption of two resolutions: WHA47.12 (WHO, 1988) on the role of the pharmacist and the WHO/DAP/98.13 (WHO, 1998) on the role of the pharmacist in self-care and self-medication.

New professional roles required new professional standards to define quality and safety of pharmacists' activities (WHO, 2000). Professional organizations are the key stakeholder in the process of developing professional standards. WHO and International Pharmaceutical Federation (FIP) worked together to define the full range of roles of pharmacists, as well as type and quality of pharmacy services. The first version of international professional standards was published by FIP in 1992 as "Good pharmacy practice in community and hospital pharmacy settings." In 1997 followed FIP/WHO joint document on good pharmacy practice (GPP). The practical handbook on implementation of services was published in 2006 (Wiedenmayer et al., 2006).

A pilot project on the implementation of GPP standards was conducted by technical assistance of FIP together with National Member Organizations in Cambodia, Moldova, Mongolia, Paraguay, Thailand, Uruguay, and Viet Nam (2005–07). The updated version of GPP standards was published in 2009 after several meetings (Bangkok, 2007; Basel, 2008) and an extensive review of existing national standards on GPP in at least 37 countries.

The most recent version of the Joint FIP/WHO guidelines on GPP: standards for quality of pharmacy services was adopted and published in 2011 (WHO&FIP, 2011). The guidelines provide the framework for the excellence in implementation of GPP. It needs to be adjusted and adopted by the national organizations of countries considering historic, political, economic, and social background.

Table 1 Roles and functions of pharmacists

Function	*Role*			
	Prepare, obtain, store, secure, distribute, administer, dispense, and dispose of medical products	*Provide effective medication therapy management*	*Maintain and improve professional performance*	*Contribute to improve effectiveness of the healthcare system and public health*
A	Prepare extemporaneous medicine preparations and medical products	Assess patient health status and needs	Plan and implement continuing professional development strategies to improve current and future performance	Disseminate evaluated information about medicines and various aspects of self-care
B	Obtain, store, and secure medicine preparations and medical products	Manage patient medication therapy		Engage in preventive care activities and services
C	Distribute medicine preparations and medical products	Monitor patient progress and outcomes		Comply with national professional obligations, guidelines, and legislations
D	Administration of medicines, vaccines, and other injectable medications	Provide information about medicines and health-related issues		Advocate and support national policies that promote improved health outcomes
E	Dispensing of medical products			
F	Dispose of medicine preparations and medical products			

(Based on Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services, 2011)

According to the guidelines, there are four main roles where pharmacists' involvement or supervision is expected by society and the individuals they serve:

1. Prepare, obtain, store, secure, distribute, administer, dispense, and dispose of medical products.
2. Provide effective medication therapy management.
3. Maintain and improve professional performance.
4. Contribute to improve effectiveness of the healthcare system and public health.

Every role requires different functions and activities, which may vary for each individual pharmacist depending on their practice responsibilities (Table 1).

Specific standards of GPP can be developed only within a national pharmacy professional organization framework.

During the last 4 decades, the philosophy of pharmaceutical care and standards of GPP were continuously spreading and disseminating, providing a wide range of national professional standards and initiatives. Professional pharmacy practice standards are developed and adopted both by regulators (e.g., pharmacy councils, chambers, boards, etc.) and professional organizations (e.g., pharmaceutical associations, society, etc.). In this regard these norms are either mandatory, or recommended depending on country.

Concept of Quality of Pharmaceutical Care Services

The quality of pharmaceutical services can be defined, assessed, and evaluated in different ways (Curtiss, 2004; Bruchet, 2011; Rotta, 2015). Nevertheless, measurement and analysis of service quality is a key milestone in developing quality in services (Edvardsen, 1994; Cochrane, 2007; Francke, 2008).

The starting point is to state the perspective from which it will be assessed: patient, pharmacy professionals, or other stakeholders; public.

From the patient perspective, quality of service can be defined as an extent to which service meets customer's need or expectation. With other words, quality of service is a difference between customer's expectations of service and perceived service. If expectations are greater than performance, then perceived quality is less than satisfactory and the service provider has to deal with customer dissatisfaction (Wisniewski, 1996; Shiyanbola, 2015). One of the most popular methodologies for the quantification of patient's satisfaction is SERVQUAL model (Wisniewski, 2001). For the pharmacy settings there is also specific tools for the evaluation of patients' satisfaction available—PC Satisfaction (Patient satisfaction with pharmaceutical care questionnaire, US) (Larson, 2002), CPPQ (Community Pharmacy Patient Questionnaire, UK) (Pharmaceutical Services Negotiation Committee, 2013).

From the professional perspective, high-quality services ensure provision of the most effective and safe care. For the quality assessment it is important to define the aspect of care being measured. The classical approach proposed by A. Donabedian differentiates between structure, process, and outcome of care (Donabedian, 1988, 1980; Rupp, 2018). A wide range of instruments can be used for evaluation of quality of care in the community pharmacy: Community Pharmacy Contractual Framework (UK)

(Pharmaceutical Services Negotiation Committee, 2017), Maturity Matrix for Community Pharmacy (UK) (Morris, 2004), Manchester Patient Safety Assessment Framework (UK) (Ashcroft, 2005), Medication Safety Self-Assessment (US) (Institute for Safe Medication Practices, 2017), Medication Safety Self-Assessment for Community/Ambulatory Pharmacy Canadian Version (Canada) (Institute of Safe Medication Practices Canada, 2015), Pharmacy Safety Climate Questionnaire (UK) (Denham and Phipps, 2012), Internal (I-Val) and External Validation (E-Val) Instruments for Community Pharmacy (Malta) (Azzopardi, 2000), and Pharmaceutical Care Self Assessment Tool (EDQM). Most of the tools presume self-assessment of the practice by the pharmacy team (except Pharmaceutical Services Negotiation Committee (2017) and partly Azzopardi (2000)).

From both professional and public perspective, for quality assessment in community pharmacy is possible to evaluate the adherence to national guidelines for GPP or use quality indicators. National initiatives on the quality standards as described further focus on one or several of these possibilities. International initiatives focus to a greater extent on the public instruments that can be used across the countries.

National Initiatives

Australia

Pharmaceutical Society of Australia adopted already 5th version of professional practice standards (PPS) (PSA, 2017), that articulate the values of the pharmacy profession and expected standards of professional behavior of pharmacists toward other healthcare stakeholders and patients. The 16 individual standards in the PPS are grouped into streams—Foundations of Practice, Providing Therapeutic Goods, Providing Health Information, and Delivering Professional Services. The streams in the document are hierarchical. The two standards in the Foundations of Practice stream—Fundamental Pharmacy Practice and Leading and Managing Pharmacy Practice—are overarching, and apply to all pharmacists, regardless of setting or scope of practice. The standards in the Providing Therapeutic Goods and Providing Health Information streams detail key functions of pharmacists relevant to the provision of activities and services covered by the standards in the Delivering Professional Services stream. There are following professional services described: collaborative care, screening and risk assessment, vaccination service, minor alignments service, disease state management, medication review, dose administration aid service, and harm minimization service. The criteria and actions required are described for each standard. Two further tools support the quality improvement of the practice—a self-assessment tool for the pharmacists and an implementation tool with useful practical questions.

USA

American Pharmacist Association is providing a range of professional standards and practical tools for the delivery of treatment options (American Pharmacists Association). The pharmacy services include appointment-based model (ABM) which is a patient care service designed to improve patients' adherence to medications and build efficiencies in pharmacy operations, immunization services, pain management service, medication therapy management (MTM), and medication administration of various products beyond vaccines. Professional standards capture all services and describe in detail provision of service, required qualification of pharmacist, resources, processes, and collaborative care.

For the evaluation of individual pharmacists who are coordinating, developing, and/or actively providing MTM and other clinical services there is a fitted tool available—Pharmacist Clinical Services Performance Evaluation (American Pharmacists Association, 2009). In the tool are clinical core competencies in patient care, practice management, patient care projects/programs as well as mentorship/perception, professional/community outreach. After the evaluation new professional goals and objectives for professional development should be set. The performance is rated from 1 to 5; a total performance rating is evaluated in terms of achieving expectations.

Canada

The Canadian Pharmacy Services Framework (CPSF) is an implementation project, developed in collaboration between Canadian Pharmacists Association, Canadian Association of Chain Drug Stores and provincial pharmacy associations. It outlines the ways to deliver patient-centered pharmacy services that are based on the needs of population, are cost-effective and valuable for the healthcare system (Canadian Pharmacists Association, 2011).

In the standards the core dispensing services are separated from the technically focused, non-clinical dispensing services and include, i.e., assessment for adverse drug events, interactions, allergies; assessment for accessibility (e.g., formulary coverage, affordability); patient dialogue and callback (Canadian Pharmacists Association, 2011). These services are focused on the pharmacist's therapeutic role in core dispensing services, to ensure safe, appropriate and effective medication therapy. Another areas are specific pharmacy services, including adapting a prescription; therapeutic substitution; prescribing in an emergency; refusal to refill; administration of a medication by injection and immunization; comprehensive medication management; interpreting and ordering laboratory tests; minor ailments assessment and management; medication reconciliation; chronic disease management. For each specific service CPSF includes a range of standard operating procedures and workflows

that will help to ensure that professional services are delivered and measured consistently across the country (Canadian Pharmacists Association, 2016; Winslade, 2011). A template for the implementation of service is provided as a standardized tool for description of the service requirements, eligibilities and other considerations specific to a particular jurisdiction (Canadian Pharmacists Association, 2018).

The Framework also provides a guidance on financial viability of services. The standards are adopted to fit the health needs in particular provinces (Canadian Pharmacists Association, 2011, 2016).

UK

In United Kingdom, General Pharmaceutical Council supported by the Royal Pharmaceutical Society is the main regulatory body responsible for professional standards in pharmacy practice (General Pharmaceutical Council, 2018a).

There are two types of standards: standards for pharmacy professionals (General Pharmaceutical Council, 2017) and standards for registered pharmacies (General Pharmaceutical Council, 2018b).

The standards for pharmacy professionals reflect the requirements set based on patients' expectations and specialists' perspective on the profession. These standards include professional principles (provide patient-centered care, collaborate, maintain and develop professional knowledge and skills, use professional judgment), behavioral principles (show leadership, communicate effectively), and ethical principles (behave in professional manner, respect person's confidentiality and privacy). The basic principles for the operation are applicable for all services (General Pharmaceutical Council, 2017).

The standards for registered pharmacies set out the requirements for the provision of pharmacy services at or from a registered pharmacy. National Health Service (NHS) and Pharmaceutical Services Negotiation Committee (PSNC) provide the description and quality standards for essential and advanced services. The essential services are provided by all pharmacies and include dispensing of medicines, appliances, repeat dispensing; clinical governance; public health activities; disposal of medicines; signposting; self-care services. To provide advanced pharmaceutical services pharmacy should meet structure and staff requirements (including special training). The quality standards for the advanced services are available on PSNH website and include: medication use review, flu vaccination, new medicine service, appliance use review, stoma appliance customization as well as NHS urgent medicine supply advance service (Pharmaceutical Services Negotiation Committee, 2017).

Royal Pharmaceutical Society took over the conceptual work, providing the certified process for guidelines development, nursing homes, ambulance settings, etc.

Bermuda

Standards of practice for pharmacists were developed and adopted by Bermuda Pharmacy Council in 2013 and are effective since January 1, 2014 (Pharmacy Council, 2013). The Standards of practice are a statement of professional conduct that describes a pharmacist's responsibilities including the skills and judgment required in practice. They set out the principles upon which GPP is based and promote a consistent quality of professional performance. The Standards were developed during 2013 in collaboration with the Bermuda Health Council. A broad consultative process included input from practicing pharmacists and pharmacy owners as well as comparison with standards in Australia, Canada, United States, and United Kingdom.

Singapore

Good Pharmacy Practice Guide (Pharmaceutical Society of Singapore, 2017) was developed by Pharmaceutical Society of Singapore includes recommendation for suitable premise, equipment and storage of medications, good dispensing practices, inventory practice, review of medication orders, counseling points, recommendations to mitigate dispensing errors, role of pharmacists in health promotion, training and competency, code of ethics, disposal of medications, and hand carried export sales of medications.

South Africa

National GPP guidelines were published by the South African Pharmacy Council in 2010. They describe the underlying philosophy, the scope of practice as well as professional standards for premises of the pharmacy. For the minimum standards of pharmaceutical services there are five categories of pharmacies are defined: manufacturing pharmacy, wholesale pharmacy, consultant pharmacy, community pharmacy, and institutional pharmacy. The services which may be provided in the different categories of pharmacy are stated in the act Regulations relating to the practice of pharmacy (GNR. 1158 of November 20, 2000). Information relating to compliance with GPP standards should be submitted in support of an application for a license for a pharmacy premises.

National professional standards focusing on quality of services vary a lot between countries. Great examples of service excellence can be further found in Netherlands, Republic of Ireland, and New Zealand (see "Further Reading" section).

International Initiatives Focusing on Quality of Services

Pharmaceutical Group of the European Union

The Pharmaceutical Group of the European Union (PGEU) is the European association representing community pharmacists. PGEU's members are the national associations and professional bodies of community pharmacists in 33 European countries including EU Member States, EU candidate countries, and EEA/EFTA countries. PGEU's Ordinary Members are associations from EU Member States, while PGEU's Observer Members are organizations from non-EU European countries. The PGEU's main objective is to advance the contribution of community pharmacists to European health systems, society, and individual patients.

In 2012, a joint European Community Pharmacy vision, namely European Community Pharmacy Blueprint was unanimously supported by the PGEU General Assembly. In order to embrace current and future challenges, European Community Pharmacy Blueprint paves the way for a future where services offered at European community pharmacies, at the heart of the communities by highly qualified and independent healthcare professionals' community pharmacists—further support individual patients, public health, and the healthcare system (Pharmaceutical Group of European Union, 2012). European governments are seeking to optimize the use of medicines, achieve better value from pharmacotherapy of patients, and reduce the overall cost of healthcare. Making better use of the competences of European pharmacists can help them achieve these goals. To enhance the contribution of community pharmacies to the effectiveness and efficiency of health systems, community pharmacists are ready to play an active role in the primary healthcare team, therefore use of eHealth solutions in the community pharmacy should be supported, and national medicine management strategies need to be developed. The unique asset that is the community pharmacy network needs to be better exploited to improve access and safety of medicines, improve treatment outcomes of individual patients and public health as well as contribute to quality and efficiency of the health sector.

Forum of Americas

Forum of Americas (est. 2000) is one of the regional pharmaceutical forums established by the initiative of FIP in collaboration with the WHO in order to bring together national pharmaceutical organizations. Following the strategy of FIP for GPP implementation, the General Assembly of Forum of Americas adopted in 2008 a Declaration setting as one of the objectives: "To establish, apply and update pharmacotherapeutic quality criteria and to raise the quality standards of pharmaceutical services, for the health improvement of the population of the countries in the region" (Pharmaceutical Forum of Americas, 2008).

The adoption of the declaration by the member countries of Forum of Americas in 2008 was followed by the conference "Promotion of Change in Pharmaceutical Services in the Americas, From the new conceptual framework to reality" (Montevideo, Uruguay, October, 2011). The resolutions stated the need to create/strengthen National Technical Groups with the participation of professional associations, the academy, the Pan American Health Organization (PAHO), the Ministry of Health, and other relevant partners for the design, implementation and follow-up of a national strategy for improvement of the quality of Pharmaceutical Services based on Renewed Primary Health Care (PHC) and Good Practices in Pharmacy (GPP). The decisions were endorsed by the General Assembly of the Pharmaceutical Forum of the Americas in October, 2011 (Pharmaceutical Forum of Americas, 2011). The core document on pharmaceutical services in the primary care was published as a position paper in 2011 and in 2013 as guideline by the PAHO and includes definition of the services, requirement for resources, integration process, implementation, and quality assurance (PAHO, 2013). For the dissemination of the quality standards in the Americas region since 2012 a Virtual Course of Pharmaceutical Services based on Primary Health Care for Managers is offered in collaboration with PAHO and FIP (Emmerick, 2014). The activities and annual reports on the quality of the services in the member countries are available on the official website (see "Further Reading" section).

European Directorate for the Quality of Medicines and Healthcare (EDQM), Council of Europe

Recognizing the role of pharmacists in the provision of the rational drug use, EDQM contribute to the improvement of pharmaceutical care and pharmaceutical practices through public health oriented policies and practical programs. According to the EDQM program of activities in this area, the Committee of Experts CD-P-PH/PC commissioned a survey in 2008 on the key concepts in pharmaceutical care and the performance indicators used to evaluate the quality of pharmaceutical care and pharmaceutical services in the Council of Europe member states. The aim of the project was to find the indicators that would be equally applicable to a wide range of countries, and their development, testing, and validation had to involve the cooperation between countries with different background of pharmaceutical care, medical traditions, and healthcare systems.

The areas of PC relevant to be evaluated by indicators were defined in scoping studies and discussed with member states' experts and stakeholder associations at the expert workshops "Assessing the quality of patient-centred pharmaceutical care in Europe—where do we stand, where should we go?" (Strasbourg, 2009) (EDQM, 2009). The scientific rationale of model indicators was further explored on the basis of published literature and the experiences of the scientific collaborators involved, and discussed at the expert workshop "Indicators of the quality of pharmaceutical care" (Strasbourg, 2010) (EDQM, 2010). Based on these developments five sets of indicators were piloted in 2011–12 in 17 countries in Europe, followed by multinational validation study of four of the above five sets in 2013–14 in different countries in Europe (in and beyond EU member states), under real-life conditions, and in different healthcare settings (community, ambulatory, and hospital settings) covering four key areas of the pharmaceutical care process. Namely:

- Adherence to nationally agreed clinical practice guidelines (TG1);
- Monitoring of therapeutic plans and medication safety by pharmacists through data linking and exchange of information about therapy and patient's medical condition in anticoagulant and antibiotic therapy (TG2);
- Structured patient-pharmacist consultations (chronic therapy; polypharmacy; polymorbidity) via "My CheckList" (TG3);
- Pharmaceutical care: special needs in certain regions (developing countries in Europe) (TG4).

The aim of Topic Group 1 was to develop, pilot, and validate a quality indicator focusing on the impact of inter-professional collaboration on adherence to antimicrobial prescribing guidelines in ambulatory care settings. An international working group, consisting of representatives of Germany, Ukraine, Poland, and Georgia, defined the indicator.

The calculation formula is: TG1 = $(A - B)/B \times 100$, where A = patients prescribed in compliance with clinical practice guidelines after pharmacist's intervention (%). B = patients prescribed in compliance with clinical practice guidelines before pharmacist's intervention (%). A pharmacist's intervention included meeting with GP, discussion of the current clinical guidelines for antibiotic prescribing in three indications. For the piloting and validation a study protocol was prepared and agreed on one EDQM meeting in 2012 (Strasbourg, France). A pilot and validation studies were conducted in Ukraine, Poland, and Georgia, the data will be published soon. The results of the studies showed 25.6% ($P < 0.001$) increase in adherence to guidelines after the pharmacist intervention, the indicator was proofed to be specific, acceptable, and feasible. The indicator can be adopted for quality assurance of pharmaceutical services such as clinical governance, medication review, as well as some aspects of collaborative care.

Topic Group 2 focused on the development and validation of two quality indicators focused on the access to individual patient's medical and prescription data (patient health record) at hospital pharmacists' level. Health data availability would allow hospital pharmacists to play an active role in the development, implementation, and follow-up of the therapeutic plan (structure indicators).

Indicator 1: Number of patients who were prescribed an anticoagulant and suffered from a bleeding event where hospital pharmacists had information about this latter/Number of patients who were prescribed an anticoagulant and suffered from a bleeding event (%).

Indicator 2: Number of patients with a culture and sensitivity test (antibiogram) performed and available to hospital pharmacists/Number of patients with a culture and sensitivity test (antibiogram) performed (%).

Four countries participated in the study—Georgia, Hungary, Ireland, and Poland. The results showed that the evaluation of following indicators is rational only if electronic patient records are available. Both indicators could be used to monitor health data availability in hospital pharmacies and could play a role in promoting good and safe use of medications. In particular, in the case of high-risk medications, health information exchange between healthcare professionals could facilitate the availability of patient-specific health information, which, in turn, could be used to provide high-quality pharmaceutical services such as medication review or medication reconciliation at discharge.

Topic Group 3 aimed to measure the level of patient involvement and, hence, the quality of pharmaceutical care by evaluating the following items:

1. Documented counseling provided by a pharmacist during a patient–pharmacist consultation based on the so-called "My CheckList" at the start of a new chronic treatment;
2. Provision of documented medication reviews following the needs that arose during the so-called "My CheckList" consultations, in the case of elderly patients who are suffering from multi-morbidity and receiving polypharmacy.

The international working group to achieve the goals elaborated following indicators:

Indicator 1: Documented counseling during "My CheckList" consultation/Total number of patients receiving "My CheckList" (%).

Indicator 2: Documented medication review in patients having attended a "My CheckList" consultation/Total number of patients who attended a "My CheckList" consultation (%).

"My CheckList" is a form developed for the study purposes, representing a short checklist where patients can include the medications they are using, their experience with the new medication (indicator 1) or usefulness of their chronic treatment (indicator 2), and questions to be discussed with the pharmacists. Pharmacists were provided with additional education, the consultation lists were also peer-reviewed after the interventions to provide pharmacists with a feedback.

The limited number of countries participated in the validation did not give the possibility to make conclusions regarding validity of the indicators. But the feedback from pharmacists was positive in most of the cases (90%), highlighting the need for policy makers and professional bodies to consider that provision of education, mentoring, and peer review of consultations will help pharmacists improve their consultation and communication skills to engage more effectively with patients. These indicators also have a potential to evaluate processes of provision of pharmaceutical services such as new medicines service and medication use review.

A working group with focus on specific needs of certain areas in Europe (TG4) was established within this initiative. The working group consisted of members of the Committee of Experts of Council of Europe and scientific collaborators from different European regions developed a self-evaluation tool (PharmSAT) for pharmacists to assess their progress in pharmaceutical care implementation in daily practice. In particular, the working group decided to elaborate a checklist focusing on background information, pharmaceutical care initiatives, documentation/monitoring, qualification/training, communication, and involvement of further health professionals and patient's perspective, based on the so-called "easy pharmaceutical care concept" that was developed during

project. This concept is based on the principle that implementing pharmaceutical care is a continuous process which adds the quality of care principles to a given (one point of time) pharmaceutical service (e.g., medicines dispensing, blood pressure measurement, etc.). The pharmaceutical care process includes but is not limited to patient counseling and education, documentation of interaction (medication decision), follow-up of medication decisions (to stop, to go on, modify medication), inter-professional collaboration, and patient involvement with a view to meeting the patient's needs and expectations.

The PharmSAT was pre-tested and piloted in 10 countries of European region. The results of the studies demonstrated that the PharmSAT has a relevance to community pharmacy practice in most of the participating countries, but its applicability is limited in countries with a longer history of pharmaceutical care (e.g., Denmark and the Netherlands).

The results of the EDQM project and proposed quality indicators are published (EDQM, 2017). These indicators can be used by health authorities and healthcare professionals to evaluate pharmaceutical care practices and policies, and to promote the efficient and safe use of medicines, leading to the best possible medication outcome for the patient.

Pharmaceutical Care Network Europe

Pharmaceutical Care Network Europe (PCNE) is one of leading research groups on quality of services. The working group of PCNE conducted the extensive investigation of provision of pharmaceutical services in two large multinational studies in Europe in 2006 (Hughes, 2010) and 2012/2013 (Costa, 2017). The results showed that implementation of pharmaceutical care in Europe varies between countries and efforts are needed to minimize difference between developed and developing countries in the future. In the 2013 PCNE researchers reviewed all published definitions of pharmaceutical care and redefined the core term stating that "Pharmaceutical Care is the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes" (Allermann, 2014).

Summary

Since the middle of the 20th century the role of pharmacists in the healthcare system was continuously growing and changing, where pharmacist overtook the responsibility on medicines rational use. New professional roles required new professional standards to define quality and safety of pharmacists' activities. Professional organizations are the key stakeholders in the process of developing professional standards. World Health Organization and International Pharmaceutical Federation are working together to define the full range of roles of pharmacists, as well as type and quality of pharmacy services. The most recent version of the Joint FIP/WHO guidelines on GPP: standards for quality of pharmacy services was adopted and published in 2011. The guidelines provide the framework for the excellence in implementation of GPP and needs to be adjusted and adopted by the national organizations of countries considering historic, political, economic, and social background.

The quality of pharmaceutical services can be defined, assessed, and evaluated in different ways, but starting point is to state the perspective from which it will be assessed: patient, pharmacy professionals, or other stakeholders; public, as well as the aspect of care being measured. From the professional perspective, high-quality services ensure provision of the most effective and safe care. Many tools for professional evaluation of services in community pharmacy were developed and implemented in the UK, US, Canada, and Malta. From both professional and public perspective, for quality assessment in community pharmacy is possible to evaluate the adherence to national guidelines for GPP or use quality indicators.

National initiatives on the quality standards as described further focus on one or several of these possibilities (Australia, USA, Canada, UK, Bermuda, Singapore, and South Africa). National professional standards focusing on quality of services vary a lot between countries. Great examples of service excellence can be further found in Netherlands, Republic of Ireland, and New Zealand.

International initiatives reflect primarily professional and public perspective and offer guidance on provision of pharmacy services and their quality assessment in Europe (Blueprint, Pharmaceutical Group of the European Union), Americas (Forum of Americas), as well as on the transregional level (European Directorate for the Quality of Medicines and Healthcare, Council of Europe, Pharmaceutical Care Network Europe).

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Professionalism as the Core Competency in Pharmacy

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Consensus on the Importance of Professionalism

Professionalism has long been an expectation for pharmacists. As in other medical fields, pharmacy organizations have insisted on the need for practitioners to follow professional principles and guidelines that have been embedded in codes of conduct, oaths pledged by pharmacists, and statements or white papers disseminated by professional organizations.

Although there are many similarities in the identified traits of professionalism, there is also some divergence. For instance, in the United States a white paper on student professionalism endorsed by the American Pharmaceutical Association Academy of Student Pharmacists (APhA-ASP), American Association of Colleges of Pharmacy (AACP), and American Society of Health-System Pharmacists (ASHP) identified professional traits as: knowledge and skills of a profession, commitment to self-improvement of skills and knowledge, service orientation, pride in the profession, covenantal relationship with client, creativity and innovation, conscience and trustworthiness, accountability for his/her work, ethically sound decision-making and leadership (APhA-ASP, 2000). The American College of Clinical Pharmacy (ACCP) white paper on student professionalism listed as traits: commitment to excellence, respect for others, honesty and integrity, caring and compassion, accountability, responsibility (Roth and Zlatic, 2009). All agree on the importance of professionalism but not all identify it in the same way.

To promote global agreement on essentials of professionalism, the International Federation of Pharmacy (FIP) in 2004 encouraged all nations to create a code of conduct for pharmacists and recommended 14 "obligations" that undergird the evolving roles and responsibilities of pharmacists (International Federation of Pharmacy, 2004). Ten years later, in an effort to identify essential traits of professionalism that pertain to all nations of the world, the FIP Council adopted an Oath for Pharmacists which could be adapted according to the various countries' situations for use in events such as graduation ceremonies and conferences (International Federation of Pharmacy, 2014).

Around the world, nations have developed statements on professionalism and codes of ethics, which differ according to local historical, socioeconomic, cultural, and religious factors. For instance, the Saudis include such traits as "avoidance of trivialities and pettiness" and "passion and love" as ethical values, and in South Africa ubuntu (the bond that connect all humanity) is an important professional value (Pharmaceutical Society of Australia, 2017; Pharmaceutical Society of Ireland, 2009; Pharmacy Board Malaysia, 2009; Pharmacy Council Malta, 2008; Saudi Commission for Health Specialties, 2014; Singapore Pharmacy Council, 2015). In addition, the statements differ according to the people to which the codes apply, the level and scope of practice in that country, the degree of legality and institutional policy that is referenced, and other such factors.

However, although there is near universal agreement on the value of professionalism for pharmacy, there is not always consensus regarding what it is and what it entails.

Less Commonality on What Professionalism Entails

Abilities, Competencies, Objectives

As the assessment movement has increasingly permeated higher education over the last 21 years, organizations have established more detailed, criteria-referenced lists of outcomes that graduates must demonstrate. These include the requisite knowledge, skills, and attitudes/values required for professionalism. Although researchers from Great Britain and Australia in 2010 concluded, "to date, very few Schools of Pharmacy appear to formally teach it let alone assess students' acquisition of professionalism" (Rutter and Duncan, 2010). Currently, there is renewed interest in teaching and assessing profession, particularly in the United States but also extending to other countries (Schafheutle et al., 2010).

The American Association of Colleges of Pharmacy (AACP), Center for Advancement of Pharmacy (CAPE) Outcomes, formulated in 1994, 1998, 2004, and 2013 were attempts to describe educational outcomes for American pharmacy school graduates, some of which were adapted by the American Accreditation Council for Pharmacy Education (ACPE) to serve as accreditation standards (Accreditation Council, 2015). The first three iterations of CAPE Outcomes framed outcomes in terms of abilities, that is, as integrations of knowledge, skills, and attitudes/values—what a student must know, what the student must do, and the appropriate values that the student must demonstrate. In earlier iterations, professionalism was not listed as a distinct ability but was a component of valuing and ethical decision-making. CAPE 13 identified outcomes as competencies, that is, as more discrete, atomistic, measurable descriptions of knowledge, skills, or attitudes/values. Professionalism in that document is approached as a "domain": "Exhibit behaviors and values that are consistent with the trust given to the profession by patients, other healthcare providers, and society" (CAPE, 2013).

Entrustable Practice Activities (EPAs)

Another recent attempt at defining pharmacy educational outcomes is the entrustable practice activities (EPAs). According to an AACP special report, these "core EPAs for New Pharmacy Graduates are discrete, essential activities and tasks that all new pharmacy graduates must be able to perform without direct supervision upon entering practice or postgraduate training.... [they are] independently executable, observable, and measurable in their process and outcome." The EPA report further notes: "The first assumption is that professionalism must permeate every EPA statement. Without professionalism none of these tasks would be possible. Also, it was deemed that no single task can comprise the entire construct of professionalism" (Haines et al., 2017, p. 1). The implication is that professionalism may not be a "what," an activity, but a "how,"—that is, not a thing but a way of acting or being.

Some Components of Professionalism

Within college programs, thoughtful statements on student professionalism have included virtues, such as compassion, accountability, excellence, respect, duty, altruism (Brown et al., 2009; Kelley et al., 2011), but understandably in practice college definitions frequently focus on civility, academic honesty, and appropriate appearance, demeanor, and behaviors. Common among the latter are traits, such as promptness, attendance, grooming, and appropriate use of electronic devices. At the class level, professionalism is translated into the specific and concrete: address all medical professionals and patients by title, avoid clothing too short/long or too revealing, do not use strong perfumes, do not wear open-toed shoes, turn off your cell phone. Unprofessionalism is exemplified by terms such as complaining, being a nonteam player, uncaring, having a negative attitude, being obnoxious, being a know-it-all, and being disrespectful (Hammer, 2000; Hammer et al., 2003; Masters, 2005; Schafheutle et al., 2010). It may not be immediately obvious to some students how their choice of hairstyles is related to loftier goals of professionalism such as "selflessly serving humanity."

These attempts to identify the elements of professionalism also raise questions about the nature of professionalism itself (Brincat, 2006; Huddle, 2005; Kuczewski, 2006). Outcomes for professionalism are variously labeled as abilities, competencies, objectives, concepts, and domains. Sometimes these terms are used interchangeably; sometimes they denote distinct entities. It is appropriate to begin with an analysis of the quiddity or "whatness" of professionalism, for how professionalism is defined determines how it is taught and assessed. It is also important to establish what it means to be the "core" competency of pharmacy education.

The terms "objectives" and "competencies" imply that we can dissect professionalism into 40–50 or more traits that students must demonstrate in isolation of one another, and we can even create professional "report cards" to evaluate whether a student is a professional at the C+ or A-level. Such an atomistic approach ignores that a whole is not equal to the sum of its parts; the relationships between the parts create new components. Such an atomistic approach can blur the distinction between the unprofessionalism exhibited by unshined shoes and the illegal dispensing of drugs. Life, private or professional, is not compartmentalized that way. Professionalism intersects in many intricate ways with most of everything else in a professional degree program.

Our language reveals that neither is professionalism exactly the same as abilities such as thinking, communicating, collaborating. We think, communicate, collaborate but we do not "professoriate." Like self-awareness, professionalism is not something that we do but something that we are, as is indicated by the wording of many outcome statements: "be professional," "be self-aware." In short, though professionalism can be classified as an ability, objective, or competency, there are advantages to interpret it as an orientation. It is this orientation that justifies professionalism's designation as *the* core outcome.

"Presentation Professionalism" Versus "Existential Professionalism"

Our definitions are influenced by the models, paradigms, and metaphors that shape our worldviews. Often such paradigms are invisible to us, which enhances the power they have in influencing our perceptions and conceptualizations. The well-known cliché, "I would have to see it to believe it," is often unknowingly reversed: "I would have to believe it to see it." Similarly with professionalism, what we see as professionalism often is based upon unexamined concepts, principles, and values. Certainly, for example, professionalism can and must be assessed (Brown et al., 2009; Chisholm. et al., 2006; Hammer et al., 2000; Kelley et al., 2011; Rutter and Duncan, 2010), but the limitations of our assessment methods should not define professionalism for us (Brincat, 2006; Huddle, 2005; Kuczewski, 2006). Though professionalism emanates out of dimensions not easily observable or measurable, a demand for exclusively empirical assessment alone can circumscribe what professionalism encompasses and proscribe what is taught and how it is taught.

The meaning of professionalism depends upon the context and the purpose for its use. For example, Castellani and Hafferty observed seven different professional stances in the contemporary medical world, for instance, the "nostalgic" noncommercial autonomous professional who despises entrepreneurialism but revels in control and prestige, the "academic" who shares lofty values but puts less emphasis on autonomy and dominance, and the "activist" dedicated to social justice (Castellani and Hafferty, 2006). Each of these professional models would require different educational preparation and assessment.

Recent attempts to define and measure student engagement and professional engagement also provide evidence that the concept of professionalism cannot be exhausted by one definition, perspective, or methodology. A Delphi approach designed to uncover the cognitive, affective, and behavioral attributes of an engaged pharmacy professional resulted in 12 beliefs and 9 behaviors, with a major difference being, "the professionally engaged pharmacist thinks and behaves in ways that positively affect patients' health and advance the profession's values and societal mission." Although professionalism and professional engagement overlap in many aspects, "individuals who are engaged exhibit vigor, dedication, and absorption" (Aronson and Janke, 2018; Miklich et al., 2016, p. 406). The questions remains, what is the motivation and in fact the imperative for a person in any profession to exhibit the cognitive, behavioral, and affective traits that comprise professionalism.

Professionalism as a competency focuses on professionalism as "what," but professionalism can also be defined in relation to identity, with a focus on "who" (Hafferty, 2006a,b). For our purposes here—to justify the claim that professionalism is the core outcome of pharmacy education—we will distinguish two complementary conceptualizations of professionalism: a marketing or "presentation professionalism" and an interiorized "existential professionalism." That is, professionalism can be defined as something we have or something we are. Personalist philosophers and psychotherapists have noted a trend toward commodification that is subtly reflected in the increasing use of the word "have" in contemporary society (Marcel, 1935; Fromm, 1997). The difference between a "having" and "being" orientation can be illustrated by the answer to the question, is there a difference between having an education and being educated? The student who is at all costs intent upon maintaining a high GPA and getting a diploma with highest honors, and who thereby avoids challenging courses, does not engage in controversial discussions in class, writes on tests what he or she believes what the instructor wants to hear—this student is in a "having" mode. On the other hand, the student who is curious, wants to figure things out, makes learning rather than grades a primary goal, who challenges the instructor when he or she does not agree, and is working toward a personally constructed world view—this student is in a "being" mode. He or she does not want to "have" an education but "be" educated. Similarly, there is a difference in orientation when one says, "I have a guilt complex" versus "I am guilty." In the former, guilt is something I have; it is external to me. I can go to a psychotherapist to get it removed, like a wart—I do not need to change. To admit "I am guilty" requires a more interior response.

In the same way, professionalism can be seen from within the orientations of "having" or "being." There is an inner and outer face of professionalism. It is something that I can have and it is something that I can be. The American 19th century writer, Henry David Thoreau, observed: "A man [or woman] who has at length found something to do will not need to get a new suit to do it in.... I say, beware of all enterprises that require new clothes, and not rather a new wearer of clothes. All men [and women] want, not something to do with, but something to do, or rather something to be" (Thoreau, 1854; 2004). Professionalism requires neither simply an approved style of appearance nor merely a proscribed set of behaviors, but a transformation of self. Putting on a white coat does not make a student a professional; rather, the white coat is symbolic of an internal transformation that is beginning—the student is *becoming* a professional. Professionalism, in a deep existential sense, is rooted in being.

Again, definitions depend upon context and purpose, and thus two people using the same words may be talking about two different things. "Professionalism" is an honorific term that can be applied to athletes (who get paid for playing) and to plumbers or roofers who produce high-quality services reliably and efficiently, as opposed to a fly-by-night, uninsured, minimally-skilled worker in a tee-shirt and torn blue jeans who knocks on doors after a severe storm.

"Presentation professionalism" is not a pejorative term. Appearance is very important for a professional. Although not accurate or fair, the general public tends to place more trust in a well-dressed, well-groomed, well-spoken, polite individual than in the person with unconventional hair coloring, extravagant piercing, sloppy attire, and a sour attitude. Trust gets to the center of professionalism (Hall, 2005). In fact, one study suggested that "restoring public trust, particularly in medicine, is really what lies at the heart of attempts to define, describe, measure, and assess professionalism in the healthcare professions" (Schafheutle et al., 2010, p. 14). Of course the more important issue is not simply restoring trust but ensuring that such trust is warranted. In other words, presentation professionalism is necessary but not sufficient attribute for a professional health practitioner. Existential professionalism extends deeper, to the core of the professional.

Fiducial Relationships: The Essence of Professionalism

Occupations and Professions

The differences between an occupation and a profession are crucial for identifying professionalism as pharmacy's core competency. We sometimes do refer to a carpenter, receptionist, hairstylist, chef, soldier, and so on as "professional", that is, as a person who gets paid for rendering high-quality services in a business-like way in a reliable, conscientious, and pleasant manner. We can and do refer to such fields as professions, but more technically, they are classified as jobs or occupations. Traditionally-defined, elements of a profession have included such traits as extensive, esoteric knowledge; autonomy in practice; a code of ethics; self-governing and self-policing privileges; a covenantal relationship with patients/clients. The essential difference between an occupation and a profession pivots on the nature of the relationship that the provider has with those being served.

The four fields that historically have been identified as professions are medicine, law, teaching, and religion—doctors, lawyers, teachers, and clergy/religious leaders. To speak of any of these as "jobs" sounds a bit jarring or cynical. Instead, each of these fields is referred to as a "vocation" or "calling." People in occupations certainly can be better educated than professionals, can have an ethical code and a greater sense of integrity, can make considerably more money, and can have more control over their work environment—these are not the essential distinguishing traits of a profession. Similarly, occupational workers can exhibit altruism, integrity, respect; and they can be "engaged"—exhibiting "vigor, dedication, and absorption" in their work. While these traits are important for professionalism, they do not distinguish professionals from people with jobs.

An essential difference between a profession and an occupation is embedded in the language that surrounds the professions, specifically in the names applied to the persons whom the professionals serve (Ong, 1978). A doctor/medical professional/pharmacist serves patients, a lawyer serves clients, a teacher serves students, and clergy serve a flock/congregation/worshippers. The carpenter, barber, manicurist, cable operator interact with *customers*. If doctors or religious leaders begin referring to those they serve as customers, it may be time to get a referral or convert to another religion.

Mercantile and Fiducial Relationships

This is not a simple issue of nomenclature or tradition. In an occupation, a businessperson has a *mercantile* relationship with customers. This is not unethical or inappropriate. The businessperson's primary loyalty is to one's company/employer. The phrase "caveat emptor," let the buyer beware, alerts us to this fact. "The customer is always right" might be an adopted slogan of a businessperson, but the motivation is to ensure future business, not to actually act in the best interest of the customer.

In a profession, the primary relationship of a provider to patient/client/student/worshipper is not a mercantile but a *fiducial* relationship. "Fiducial," from the Latin word *fides*, means faith or trust, fidelity. The professional is obligated to put first the interests of clients (Ong, 1978). Certainly, someone in an occupation can choose to put the best interest of customers first (if only because it is good business), but he or she is not obligated to do so. A professional is a professional by nature of his or her obligation and pledge to do so.

Professions exist to help others in matters of extreme importance to their well-being: their freedom, knowledge, physical lives, and for the believer even their immortal souls. These matters of extreme importance require expertise, knowledge, and skills that the person served does not have and cannot have without similar extensive training. The person served cannot even adequately evaluate the services provided by the professional. As the American Pharmacists Associations Code of Ethics, asserts, the client/patient has little choice but to give the provider the "gift of trust," and in exchange the provider promises, "you can trust me," that is, he or she accepts the fiducial obligation to act in the best interest of the client/patient (American Pharmacists Association, 1994; cf. Cruess and Cruess, 2006). As is proclaimed in many statements of professionalism, this is a covenant established between the profession and society; it is not so much a contract, which implies distrust by its very nature—requiring documents, signatures, and notaries—but a covenant, a pledge, and a word of honor. It revolves around trust. This does not mean that occupational workers cannot be trusted, or that they cannot put the interests of their customers first. Again, the difference is that in a profession there is not only an expectation but also an *obligation* to do so. There is no room in professionalism for caveat emptor.

Because of its commercial interests, its diminished autonomy, divided loyalties between patients and customers, lack of authority to control medicines, and its inability to define its own role in the health care system, pharmacy over the year has been challenged to maintain its identity as a profession, being judged an "incomplete or marginal profession" (Denzin and Mettlin, 1968), a "profession in transition" (Adamcik et al., 1986), "not a true profession" (Agomo, 2012, cited in Chaar et al., 2013). Similarly in 1996 William Zellmer suggested that pharmacy then was not a profession but an occupation on its way to becoming a profession (Zellmer, 1996). Implicit in his critique was that most pharmacists at the time did not embrace fiducial relationships with patients as an essential element of their product-dispensing activities. The change in mission from a product-centered practice to a patient-centered practice enabled and necessitated fiducial relationships, that is, obligations of trust. This fiducial relationship is the core of professionalism.

This is not a modern claim. The obligation to put the patient first extends at least to Plato:

> No physician, in so far as he is a physician, considers his own good in what he prescribes, but the good of his patient; for the true physician is also a ruler having the human body as a subject, and is not a mere money-maker.
>
> There is no one in any ruler who, in so far as he is a ruler, considers or enjoins that which is for his own interest, but always that which is for the interest of his subject and of his art; to that he looks, and that alone he considers in everything which he says and does.

Except for the paternalism implied by the metaphor of a professional as a "ruler," the American Board of Internal Medicine's 1995 publication "Project Professionalism" echoes Plato in identifying professionalism as "those attitudes and behavours that serve to maintain patient interest above physician self interest" (Stobo et al., 1995, p. 2). FIP's Centennial Declaration of October 2012 echoes the commitment "to encourage pharmacists and pharmaceutical scientists to adhere to the highest standards of professional conduct, always giving top priority to serving the best interests of patients and society at large" (Chaar et al., 2013, p. 3). It is telling that many codes of ethics in pharmacy and medicine around the world mention this obligation to recognize the primacy of the patient, often as a first principle. The Code of Ethics for the Pharmaceutical Profession created by the Pharmacy Council of Malta is explicit:

> Establish and preserve a fiduciary relationship. Members of the pharmaceutical profession must endeavour to establish and maintain a professional relationship with their patients. Members of the pharmaceutical profession must uphold the trust granted to them by patients and society and build confidence in their commitment and competence to achieve the desired objective and maintain their trust. (Pharmacy Council Malta, 2008, p. 29)

If students are taught this, they will better understand how all the other traits of professionalism are interconnected: why appearance, ethics, honesty, demeanor, caring, empathy, life-long learning, reliability, all derive from the same source: to ensure professionals have the competence, will, and fidelity to act in the best interest of clients/patients who have few alternatives other than to put their trust in them. This is why trust, an obligatory fiduciary relationship, is the "core" of a profession.

However, there is some concern that in our evolving complex technological culture "existential professionalism" may not survive.

Challenges to Professionalism in the 21st Century

Many of the perceived threats to professionalism in the 21st century are related to this core element of a profession: to trust, to the fiducial relationship between provider and client. There is a growing skepticism about professional organizations' dedication to self-interest rather than promotion of the public good (Coulehan, 2006; Zlatic, 2010a). This diminution of confidence has led to questioning of the autonomy of professionals and has led a de-emphasis of professional judgment as governments, insurance companies, and regulatory bodies exercise more oversight. A resulting litigious culture encourages defensive practice and a suspicious if not adversarial relationship between provider and client. Further, the "best interest of patients" becomes more ambiguous in light of a complex health care environment in which populations in addition to individuals are the focus.

The obligation to maintain fiducial relationships is also at the center of the tensions between professionalism and the commodification and corporatization of pharmacy (Hafferty, 2006a,b; Relman, 2007). In a profession, there is a fiducial obligation to act in the best interest of patients. In a business there is a mercantile relationship between a supplier and customers. Keeping the allegiances distinct can be difficult. In South Africa, for instance, in 2007, one scholar theorized that definitions of professionalism were not adequate for the task of inculcating professionalism: "Although defining itself as a patient-centered profession, private sector (community and private hospital) pharmacy often appears to be that of a product-for-profit centered occupation" (Williams, 2007, p. 1285). According to the FIP Working Group on Pharmacist Ethics and Professional Autonomy, "evidence shows that increased corporatization of pharmacies creates a 'duality of interest,' diminishes pharmacist professional autonomy and threatens patient safety" (Chaar et al., 2013, p. 43). Mass media advertising of professional services also evoke in audiences business models for health care in which patients are targeted as health care consumers. It can be difficult for the shrewd consumer not to weigh the glitzy pitch of the medical professional with the same suspicion as the clever jingle of the used car salesperson (Zlatic, 2010b).

That being said, nostalgia is not the solution. A complex, global, technologized environment in which medical professionals seek expanded services to greater numbers of people and continually explores scientific and medical advances to improve health care outcomes—all of this requires management, centralization, efficiency, and marketing. This hopefully can be accomplished within a professional framework for what "best interest of the patient" means in this environment is different from what it meant in the 1940s community pharmacy. It will be important, though, first to acknowledge the ongoing tensions between corporate mercantile interests and fiducial relationships; and second, to work toward minimizing those tensions. Care must be taken that presentation professionalism becomes not an extension but a substitute for existential professionalism.

Another threat to professionalism is consumerism in schools. Pharmacy faculty can experience the same tensions as pharmacy practitioners regarding the nature of the relationship they have with students, the people they serve. Higher education continues to adjust to the contemporary social-political-economic environment. The number of college administrators has increased significantly in recent times, many administrators now having graduated from business programs (Michael, 1997). Although schools may be nonprofit, today they must be run like businesses—advertising for students, retaining them, and cementing relationships with faithful alumni who will provide future support. College planners talk unapologetically about identifying a "brand" for their program. To maintain enrollment—and to act in what they believe is in the best interests of students—administration sometimes urges faculty to treat students as customers. The intentions are honorable and laudatory. Too often students are not treated as customers in a restaurant. Although pharmacy students, even those working in pharmacies in retail settings, are instructed that they do not have customers but patients, faculty are asked to treat students as customers, without regard for the irony or the implications. In the two-tiered system of higher education of faculty and administration, administrators may need to treat students to some degree as customers, but once again professionalism, of the instructor as well as the future

pharmacist, is threatened if a faculty member's fiducial obligation to students is replaced by a mercantile one, when faculty are asked to adopt the customer paradigm for students. A student as customer model might not be a problem as long as the students' goals align perfectly with the needs of the profession, but frequently the personal goals of incoming students conflict with the needs of society. For faculty whose advancement and salary are contingent upon student (customer) satisfaction, the temptation to inflate grades, lower standards, and ignore breaches of professionalism may be hard to resist. The *reductio ad absurdum* of such a mentality are online "universities" that basically sell degrees, and customer satisfaction pledges that educational content, processes, and assessment will be designed to suit individual student preferences (Holdford, 2014; Zlatic, 2014). Teaching as a profession requires faculty to treat students not as customers but better than customers. If the warning, "caveat emptor" (let the buyer beware) is extended to "caveat discipulus" (let the student beware), students will learn lessons about professionalism that will not benefit their future patients.

The essential fiducial obligation to patients also clarifies another potential threat to professionalism: professionalization itself. The paradox is resolved by noticing two different interpretations of professionalism at work here. Professionalism does entail allegiance to one's profession and its advancement. However, if loyalty to the profession entails actions and decisions that are motivated by privilege, status, or economic gain, the results can be policies and actions that are detrimental to patients. Again, ironically, in the process of attempting to socialize students, professionalization could be transformed into "jobification" (Kuczewski, 2006; McKnight, 1977).

Quantum computing, robotics, artificial intelligence, medical apps, genetic engineering, and big data certainly will revolutionize many if not most aspects of our society, including pharmacy. Predictions that our children or grandchildren may expect to live to be 125 years old no longer can be quickly dismissed as complete science fiction. This technology can be a threat to professionalism, inserting machinery between the provider and patient (Wachter, 2015), and some worry that the efficiency, accuracy, and speed of robots and artificial intelligence will lead to the replacement of humans. But there is also room for optimism and opportunity. It currently seems highly unlikely that machines will be able to establish fiducial relationships with patients, to truly empathize and care for and about a patient. Artificial intelligence most likely will reach the point that it will pass the Turing test: one will not be able to tell whether he or she is interacting with a human being. But a computer cannot think; it calculates. A computer does not remember; it stores data. A computer cannot feel pain and thus cannot be empathic. A robot can be programmed to act empathically and appear empathic but cannot be empathic—for empathy means placing yourself in the position of another person. Some would argue from a behaviorist perspective, it does not matter whether a person is a professional, as long as he or she acts like one. The future appearance and behaviors of a machine may be indistinguishable from that of a human person, but at least as we now are as a people, most of us would not be comforted in our pain and sorrow by expressions of empathy by sophisticated programming, regardless of how tenderly the words were uttered.

Preserving Professionalism as the Core Outcome in Pharmacy

Although some pessimistically predict an "end of professionalism" or assert the impossibility or irrelevance of fiducial obligations in contemporary pharmacy interactions (Broadbent et al., 1997; Haddad, 2017; Pellegrino, 2000; Sullivan, 2004), pharmacy can take steps to enable pharmacists to earn patients' trust that the pharmacist will put their best interests first. The efforts can begin with pharmacy education.

To ensure that professionalism is in fact a core outcome in pharmacy, it is necessary first to come to consensus regarding a clear conceptualization of what it is and what it entails. Then it becomes necessary to ensure that all stakeholders understand and support the effort to inculcate professionalism, and for schools to recruit and admit students who are predisposed toward a professional orientation. Faculty members need to ensure that professional outcomes are clearly identified within their courses and experiential education, and that detailed criteria make explicit what good practice entails. The next step is to review all courses in order to map a curriculum in which professionalism is treated sequentially at more complex levels throughout the program, using consistent definitions and criteria. Within courses and experiential education, pharmacy faculty needs to create opportunities for students to practice and internalize professionalism, and to provide constructive feedback on improvement. Perhaps most important, professionalism must be modeled routinely in the classroom, clinic, elevators, and hallways.

Faculty and Administration

Developing a professional orientation can be the "core" outcome in a pharmacy program only if the administration and staff make it so. That requires an institutional commitment to the development of what professionalism means in their country and institution. Faculty workshops and retreats can provide opportunities for faculty and administrators to reflect upon professionalism and to agree upon what they want to accomplish with their students. Administration must endorse and promote the efforts of the faculty, and their commitment to professionalism must be evident in school philosophies, policies, procedures, contracts, and documents. School web pages and marketing should reflect professional values. Dancing dollars signs under an advertisement to recruit students into pharmacy does not send a message conducive to fiducial responsibility. A commitment to professionalism requires administration to recruit, hire, and reward faculty predisposed to core values. Faculty modeling of professionalism, making it an inextricable element of the program, is essential. The commitment to a culture of professionalism can also be evidenced by public recognition of faculty who personify professionalism.

Students

One way to better ensure student professionalism is to admit into the program students predisposed to such values. The school can disseminate promotional literature that attracts students with a desire to place patient needs as a priority. The school can then design an application process that prioritizes professional values, and can conduct interview process that queries applicants' motives and goals. Admitting students with a propensity for professional values and behaviors can help to foster a culture of professionalism.

Outcomes/Criteria

Once educators define what professionalism means at their institution, they can ensure that it is included in the outcomes and criteria created for courses. Faculty and students cannot intuit what professionalism involves. It must be clearly stated and identified with specific criteria. For instance, in teaching simulations on the ability of educating patients, often a given criterion is "maintain eye contact," which would be better stated as "establish rapport": in some cultures it is impolite to look people in the eyes, and most people are uncomfortable by prolonged staring. "Establishing rapport" is a more difficult and meaningful task. Similarly, it is important to be precise regarding what it means to be professional. Because they are easily observable, quantifiable, and assessable, usually the criteria for what is here called presentation professionalism are clearly listed, while the link to characteristics of honesty, fiducial obligations, and integrity is not so clear. The learning objective "dress in a professional manner" would be better stated as "instill trust in patients by dressing professionally" so that the connection between presentation professionalism and fiduciary relations is clear, and so that students understand that "unprofessional" is more of a matter than trendy hairstyles, full-body tattoos, piercing, and gum chewing.

Mapping a Curriculum

Once faculty establishes course outcomes and detailed criteria for professionalism, they can map a curriculum, which provides a systematic set of outcomes, practice opportunities, criteria, and assessment feedback over the length of the curriculum. In an integrated curriculum, professionalism would be an outcome across all years. Each course syllabus would clearly identify the outcomes regarding professionalism that are appropriate for that level of student, with the outcomes becoming more complex as the student progresses through the curriculum. Earlier courses would build a foundation by covering knowledge of professionalism and ethics and providing opportunities to practice skills such as empathic listening and ethical decision-making. In an addition to an ethics of action (which asks what is the right thing for me *to do*, a question often answered by invoking theories such as deontology and utilitarianism), students can learn an ethics of character or virtue (which addresses the question of what type of person must I *be*). In simulations and later in capstone courses and experiential education, more internalized traits of professionalism—honesty, integrity, empathy, establishment of fiducial relationships—can be taught, observed, practiced, reflected upon, given feedback, and learned, if the preceptor thematizes, models, and assesses them. Unfortunately, virtues such altruism, beneficence, honesty, and integrity are more frequently cited in school documents than in course syllabi and criteria.

Teaching and Assessing Professionalism

In order to develop professionalism, one must be given many opportunities to practice and get feedback regarding the knowledge, skills, and attitudes/values that constitute professionalism. Some may argue that professionalism, like empathy, cannot be taught: either you have it or you do not. This could be true, depending upon what one means by "professionalism" and what one mean by "taught." Lecturing students and testing them on professionalism can increase their knowledge of professionalism: what it is, why it is important, how it is communicated, how it can be breached. Additionally, students can be taught behaviors and skills required by professionalism, such as empathic listening: students can be taught how to act professionally. It is unlikely, though, that didactic education can teach students to be professionals.

While there is legitimate debate whether professionalism in a deep or existential sense can be taught didactically, it is more apparent that it can be learned, when the learning is directed by instructors who create experiences that engage students' minds, senses, and emotions. Empathy, for instance, involves putting ourselves imaginatively in the place of others: thus the wider our experiences, the greater the potential for empathy. With limited experience, we often do not put ourselves in the place of others but put others in our place, interpreting them from our own limited perspectives. Students can "learn" empathy by widening their experiences.

Disparity in health resources can be taught from a textbook; one can be stimulated to act upon those disparities by participating in a medical mission trip—seeing, hearing, touching, tasting, and smelling the effects of disparity of health resources in a community that lives in a garbage dump in which bare-foot 4-year-old children scamper with adults to be the first to get to the dumping garbage truck (Sims, 2011). Listening to a lecture about the difficulties of smoking cessation can provide useful knowledge about struggles with addiction, but empathy can be deepened by serving in an advanced practice experience at a smoking cessation clinic where one interacts with struggling patients, such as the woman whose mother watched her as a young girl be abused by the mother's boyfriends, the man whose son survived fighting in Afghanistan only to die of *Neisseria meningitidis* within a month of his return, and the woman who with her son was set on fire by a man who had doused them with gasoline (Wilken, 2011).

However, experience is not only the best teacher, it can also be the worst teacher. You can die from it. Additionally, the cost and logistics of international trips and community volunteering can be prohibitive. Sometimes it is better to learn from the experience of others. Novels, film, poetry, drama, reflection essays, and nonfiction such as *The Spirit Catches You and You Fall Down* allow us to relive the experience of others and thus increase the potential for empathy in ourselves. Stories that graphically depict the lingering effects of poverty, injustice, and racism provide a context for understanding the "difficult" and perhaps abusive patient who walks into a community pharmacy. The humanities capture dimensions of human experience that are omitted or—out of a misguided quest for a circumscribed idea of "objectivity"—even, are intentionally excluded from professional education (Bumgarner et al., 2007; Spiro, 1992; Wear and Bickel, 2000).

In didactic education experiences can be simulated, as in the Geriatric Game in which students' senses of sight, sound, and touch are muffled to give them an understanding of how an older person experiences the world, thereby enhancing the students' potential for empathy. Role plays, simulations, case studies that are rich in socioeconomic, cultural, ethical, emotional issues can heighten reflection on professionalism and allow students to internalize what they have read in codes of conduct and statements of professionalism (APhA-ASP Professionalism Toolkit for Students and Faculty).

Journaling is another strategy for developing and assessing professionalism. In journaling students reflect upon their experiences, analyze them, and plan strategies to be more effective, particularly after insightful, sensitive feedback from instructors/mentors (Brody et al., 2002; Schumann et al., 2004; Zlatic and Zellmer, 2011). Such journaling can orient students to the strategies of continuing professional development (CPD), and can encourage reflective practice that leads to life-long learning (Schafheutle et al., 2010). Structured, reflective journaling encourages cognitive and affective development that enables understandings that lead to knowledge that is not additive but transformative. Some evidence suggests that journaling can be helpful in Professional Identity Formation (PIF), "'the transformative process of identifying and internalizing the ways of being and relating within a professional role' by adopting characteristics of a professional, such as altruism, respect for others, honesty and integrity, and commitment to self-improvement" (Johnson and Chauvin, 2016, p. 1). This gets to the core of professionalism, both presentational and existential. One's professional appearance is not as a masquerade but an indicator of an inner commitment to trust. Becoming professional involves identity formation.

In the classroom and clinic, instructors and preceptors can share their own stories with students and coworkers, their encounters, successes, and failures related to professionalism. But more importantly, what instructors and preceptors do is perhaps much more compelling that what they say. The "hidden curriculum" refers to the actions, behaviors, attitudes, and values that are actually displayed rather than preached from a lectern or advertised on a web page. Unfortunately, "what is 'taught' in this hidden curriculum often can be antithetical to the goals and content of those courses that are formally offered" (Hafferty, 2000; Hafferty and Franks, 1994; Schafheutle et al., 2013). Eloquent statements of college mission, systematically designed curricula, and classroom-inspiring lectures regarding professional practice have less influence on professionalization than what students observe on a daily business in the classrooms, clinics, research laboratories, faculty and staff offices, and elsewhere on and off campus. White coat ceremonies and honor codes have important symbolic value in fostering professionalism, but students become cynical if the symbols prove empty by infractions they observe on a daily basis. Students need models and mentors that they respect and want to emulate. Ideally, each institution would inspire a "culture of professionalism" (Berger et al., 2004) in which the professional responsibility of working in the best interest of the patient is concretized by instructors and preceptors who exhibit a fiducial obligation to act in the best interest of students and the patients that they serve (Popovich, 1991).

Dissenting Views

Arguments against placing covenants or fiducial obligations at the center of professionalism raise important points: a professional code should not be aspirational but actual, reflecting current environment and practice; additionally, such codes should be applicable to all segments of professional practice. It is further argued that the physical resources, organizational structures, and legal authority required to form fiducial relationships are lacking (Haddad, 2017)—a position, in effect, which echoes William Zellmer's 1996 opinion that pharmacy was an occupation still on a path to becoming a profession. An alternative to identify pharmacy as an occupation would be to create a different definition of pharmacy professionalism, one that centers on a social contract, because covenantal or fiducial relationships are too paternalistic, too idealistic, and too contaminated by the world of finance. Perhaps fiducial relationships are the foundation only for pharmacy careers that involve patient care. For other career paths, the social contract offers a clear-cut statement that identifies and limits what the professional and patient owe one another.

Every advantage has its tax, and every statement of professionalism is open to criticism. The social contract, for instance, does offer clarity and limits provider responsibility to what is defined in the contract, but it also invites lawyers, lawsuits, and protective practice into the professional/patient relationship. Although, it would seem at first that a contractual model of professionalism would not result in significantly different outcomes from a fiducial relationship model if the first article of any social contract pledged to place patient interests first—for that is the essence of the obligation of a fiducial or trust relationship. However, more subtly, the contractual model contributes to an externalization of professionalism that moves it closer to a "having" orientation, de-emphasizing professionalism as an identity. Professionalism so understood tends toward a competency, but not one that would seem to justify the designation as the core competency in pharmacy. If pharmacy has not yet reached a stage at which it can include in codes of ethics a guarantee of trust or fiducial relationships to patients, perhaps a first step is to restrict such aspirations to statements on professionalism that inform programs for professional development.

It would be better, though, to interpret the covenantal and social contract models not so much as an agreement between individuals (provider and patient) as an agreement between a profession and society. The fiducial or faith relationship, the promise of trust, operates more intimately, interpersonally, between patient and provider—as a patient I do not trust the pharmacy profession, I trust you.

Summary

In summary, the term "professionalism" covers a wide range of practices, attitudes, commitments, and values that can extend from the color of toenails to a commitment to seek justice in the distribution of health care resources. All are important. In pharmacy, however, professionalism is a core outcome when it integrates the appearance of trust (presentation professionalism) and the willingness always to put the best interests of patients first (existential professionalism). Professionalism is a core outcome because it is a component of everything that is taught in a pharmacy program—whether the teaching is intentional; whether it is presented in the classroom, practiced in the clinic, or modeled in the hallways; whether it consists of positive lessons or negative examples. Pharmacy educations require the accumulation of knowledge, the honing of skills, and the demonstration of values, but professionalism is the core outcome because it is (or should be) transformative. It is the core outcome because it touches the core of the individual; it requires the assumption of an identity, the identity of a professional, a person of integrity who can be trusted to be competent, caring, and honest. Perhaps pharmacy practitioners and educators can best influence such a transformation through modeling that can be observed in organizational policies, positions, and practices and in the daily routines of their instructors, preceptors, mentors, supervisors, employers, and professional representatives.

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Quality Assurance and Quality Advancement of Pharmacy Education

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Introduction

The global healthcare workforce is in a period of change. Increasing demands for services associated with longer population lifespans and associated chronic disease burdens are impacting both the need for and scope of healthcare workers' practice (Bates et al., 2016). The World Health Organization (WHO) estimates that currently there is a 7.2 million global healthcare workforce shortage, which, by 2035, will grow to 12.9 million (Campbell et al., 2013). To adequately address this shortage, the WHO has identified the need to transform and scale up the education and training of health professionals worldwide (World Health Organization, 2013). Simply increasing the pipeline and increasing the production of healthcare workers is not the solution. Rather, education and training must ensure that graduates possess the needed skills and competencies to effectively address the evolving needs of the world's populations.

As noted by the International Pharmaceutical Federation's (FIP) Board of Pharmaceutical Practice, today's pharmacists should have expertise in all aspects of pharmacy including the supply and use of medications, providing cost-effective access to safe medications and assuring the responsible use of medications by individual patients and healthcare systems (International Pharmacy Federation, 2018). Countries are facing a critical need to assure the infrastructure exists such that educational institutions are able to produce graduates who possess the requisite competencies necessary to provide pharmacy services that address the healthcare needs of the country. In this regard, a national quality assurance process is essential to assuring the quality of the pharmacy workforce is maintained. The quality assurance systems of individual countries vary globally, with well-developed quality assurance systems already operating in some countries compared with a complete lack of a quality assurance system or an emerging system in place in others. Ideally, all countries will operate a national system for quality assurance of pharmacy education to assure pharmacy graduates are prepared to meet the unique needs of the individual country (International Pharmacy Education, 2009).

The system for quality assurance would assist in ensuring quality pharmacy education is provided. In general terms, quality education is education that:

- Adheres to established standards;
- Addresses national needs of the profession;
- Is appropriate to the national context and socially accountable;
- Undergoes continuous quality improvement to ensure dynamic needs of the profession are met;
- Is appropriately innovative, utilizing the latest active learning methodologies and pedagogy;
- Promotes life-long learning and facilitates the development of skills and attitudes required by graduates to self-direct their own life-long learning;
- Develops in students not only knowledge, skills and abilities but attitudes and behaviors; i.e., is competency-based; and
- Achieves the intended learning outcomes of the educational process (International Pharmacy Federation, 2014; Accreditation Council for Pharmacy Education, 2018a).

Purpose of the Quality Assurance Process

Implementation of a quality assurance process provides professional judgment of the quality of the educational program at a school of pharmacy and facilitates continued quality improvement. Responsibilities of the quality assurance process include:

- To develop and update quality standards which a school of pharmacy is expected to meet and maintain.
- To create policies and procedures which are used to govern the quality assurance process.
- To evaluate, both initially and periodically, schools of pharmacy in accordance with the quality assurance standards, policies and procedures.
- To maintain a public list of pharmacy schools that have been evaluated in accordance with the quality assurance standards (Accreditation Council for Pharmacy Education, 2018a).

The quality assurance process serves multiple stakeholders including:

- the **public:** Implementation of a national quality assurance process assures that pharmacy schools have conformed to general expectations for the pharmacy profession developed and validated through a broad-based process. It facilitates the identification of schools of pharmacy that have explicitly undertaken activities directed at improving the quality of their educational programs, and are carrying them out successfully. The quality assurance process also supports improvement of the professional services available to the public in that schools of pharmacy and institutions offering pharmacy education are expected to be socially accountable by modifying and updating their requirements to reflect contemporary national and societal needs, as well as advances in knowledge, technology, and practice.
- **students and prospective students:** Implementation of a quality assurance process provides an assurance that a pharmacy school has been found to provide satisfactory educational preparation for practice.
- **institutions of higher education:** A quality assurance process provides a framework for self-assessment and improvement as well as the opportunity for external, peer review and feedback, and the exchanging of experience with other pharmacy schools. Implementation of a quality assurance process can also provide a basis for evaluation and decision-making by private and public agencies (including universities evaluating the academic qualifications of candidates applying to graduate programs), national, state and local governments (Accreditation Council for Pharmacy Education, 2018a; Institute of Medicine, 2003).

Models for Quality Assurance

Ideally, a comprehensive quality assurance system will both assure quality and promote a culture of quality improvement (International Pharmacy Federation, 2014). Historically governments have been charged with oversight of the quality assurance process for education of healthcare professionals (World Health Organization, 2003). Typically, government oversight occurs through a department or ministry or a governmental agency specifically established for assuring quality education programs (World Health Organization, 2003). Other quality assurance models involve national pharmacy organizations or other independent agencies. In some countries, more independent and autonomous bodies have been established (World Health Organization, 2003). Such accreditation bodies typically maintain a large degree of independence and autonomy in their operations and decision-making processes. The use of an independent agency represents a growing trend (World Health Organization, 2003). While many different models for quality assurance exist, each with advantages and disadvantages, the differences of each model will not be addressed in this chapter, as it is believed that the principles identified apply universally to the quality assurance process. Rather, the principles and core elements of quality assurance apply regardless of the model of quality assurance system utilized. Countries in close proximity may collaborate via a joint quality assurance system to reduce costs and conserve resources.

There are a number of steps to consider when developing or enhancing an accreditation body. These steps include: (1) conducting an environmental analysis; (2) engaging stakeholders; (3) identifying the national vision/mission for pharmacy education including the mandate for the quality assurance process; and (4) developing the accreditation body (International Pharmacy Federation, 2014).

Environmental Analysis

Individual countries will be at different stages with regard to development of a quality assurance system for pharmacy education. The extent to which quality assurance systems are in place and actively used can vary greatly. Some countries have well developed quality assurance systems, which have been in place and operating for a considerable amount of time. In other countries, the quality assurance system may have been implemented recently or is completing lacking. An analysis of quality assurance systems conducted via European faculties of pharmacy revealed that roughly half of the 28 countries responding to the survey indicated that a quality assurance process was in place and operating within the country (Guimaraes Morais et al., 2011).

Ideally, every country will have a quality assurance system with well-developed standards that are reflective of the contemporary practice of pharmacy and the healthcare needs of the country and are used to evaluate pharmacy education programs (International Pharmacy Federation, 2014). Given that the principles and core elements utilized in the quality assurance process are common, limited resource countries wishing to implement or enhance their quality assurance system may utilize FIP's Global Framework for Quality Assurance of Pharmacy Education to develop or improve their quality assurance process (International Pharmacy Federation, 2014). This chapter summarizes many elements of the Framework and the Framework may be referred to for more detail in each aspect.

Regardless of the stage of development, and whether or not a quality assurance process is already in place, each country should begin by identifying an organization or entity to be in charge of the quality assurance process. For countries with a quality assurance processes already in place, these organizations will likely lead a process of reviewing the current process. For a country that does not have an existing quality assurance process an organization must be identified to assume responsibility. Such an entity may be appointed by the government or a professional organization. Regardless, a leadership group within the pharmacy profession should ideally lead the charge for development of the quality assurance process.

Development or improvement of a quality assurance process occurs within the context of existing systems and regulations. Environmental analysis involves mapping the existing environment to establish a baseline from which new interventions are considered or existing ones are adapted. While the main focus of the environmental analysis is on the quality assurance system, it will identify connections between the regulation of the pharmacy workforce, the education sector (pharmacy schools), and the practice sector.

The initial step then is to conduct an environmental analysis of the professional regulation of pharmacy practice and pharmacy education within the country. Some elements to consider include:

- What professional organizations or governmental agencies are already involved in regulation of the practice?
- What are the different cadres of pharmaceutical professionals practicing within the country?
- What legislation already exists regarding pharmacy education requirements?
  - If legislation mandating requirements for pharmacy education does not already exist, what steps would be needed to enact legislative changes? Are such legislative changes feasible? What organizations/entities need to be involved in the process to change the legislation?
- Does a quality assurance agency for pharmacy education already exist?
  - Does it have established standards and regulations to ensure quality?
  - What aspects should be modified in an effort to improve the quality assurance process?
- What organizations are involved in the provision of pharmacy education offered in the country?

Needs-Based Education

While some healthcare needs are universal, individual needs and priorities will vary between countries, given differences in economic, educational, cultural and societal issues. The national, societal and population needs, along with regulatory mandates and educational capacity within individual countries, will influence which healthcare services are provided by pharmacists within individual countries. Consequently, competencies needed to practice pharmacy between countries will vary. Entry-level pharmacy education programs (hereafter referred to as pharmacy schools) must graduate pharmacists that have been trained with the requisite competencies to address the needs identified within the individual country. The use of a needs-based educational model (**Fig. 1**: Needs-Based Education), as recommended by the FIP's Global Quality Assurance Framework, ensures graduates are trained to address the country's pharmacy workforce needs in terms of delivery of services to the public (International Pharmacy Federation, 2014). In this regard, a critical step in the quality assurance process is the identification of competencies needed by

Figure 1 FIP's Needs-Based Education Model. *Accreditation Council for Pharmacy Education, August 2018. ACPE Self-Study Workshop. FIP, Chicago, IL.*

the pharmacy workforce. Following initial identification, competency needs should be periodically reassessed to ensure education continues to meet the contemporary needs of the country.

Stakeholders

To ensure competency needs are adequately identified, input from a comprehensive array of stakeholders should be obtained. All stakeholders should provide input during the development of the profession-wide vision of practice that clearly articulates the nature and status of pharmacy practice within the country. The process of conducting an environmental analysis will assist in the identification of stakeholders vital to the quality assurance process for pharmacy education.

Ideally, all stakeholders relevant to pharmacy education will be identified for input into the quality assurance process. A commitment to quality assurance and improvement means a commitment to change which benefits most if stakeholders are committed and engaged in the process. Stakeholders are individuals or organizations with a direct or indirect interest in the process and outcomes of the exercise or project, whether positive or negative. A stakeholder should be thought of as any individual or group that can affect or be affected by the actions, decisions, policies, practices or goals of the project. As every country differs, not every stakeholder group will be relevant for every country. It is encouraged that each country initially conduct an environmental analysis to identify stakeholders and their perspectives.

In general, stakeholders with an interest in pharmacy education encompass a wide variety of demographic groups. Fig. 2 builds upon the FIP Needs-Based Education Model and outlines those stakeholders with a stake in pharmacy education.

Regulators and policy makers, such as the government and, where applicable, other specific authorities responsible for the regulation of the education and skills development as well as the practice of pharmacy, have the responsibility of ensuring the competence of the pharmacy workforce. This requires that the government assures the public that graduates are competent to deliver the range of services permitted by the country's Practice Act(s) and regulations. Invariably, as major (or exclusive) contributors to the financing of higher education, governments have another reason to desire continued competence of practitioners. These stakeholders then will have interest in all areas of the pharmacy education quality assurance process.

Pharmacy schools provide the education and must ensure compliance with the quality assurance standards. Engagement of pharmacy administrators and academic staff is essential to the quality assurance process. Similarly, input should be sought from pharmacy students, the consumers of the education process.

Employers are another essential group to include in the development of the model for the quality assurance for pharmacy education. Employers need reassurance that graduates will be competent to practice. In this regard, employers' knowledge and support of the quality assurance process is essential.

The profession as a whole, as it seeks to advance and better serve society and its members, relies heavily on the quality assurance system to ensure the competence, professionalism, and leadership of practitioners. Input from professional organizations, if functioning within the country, can be utilized as a means to obtain input from the profession as a whole.

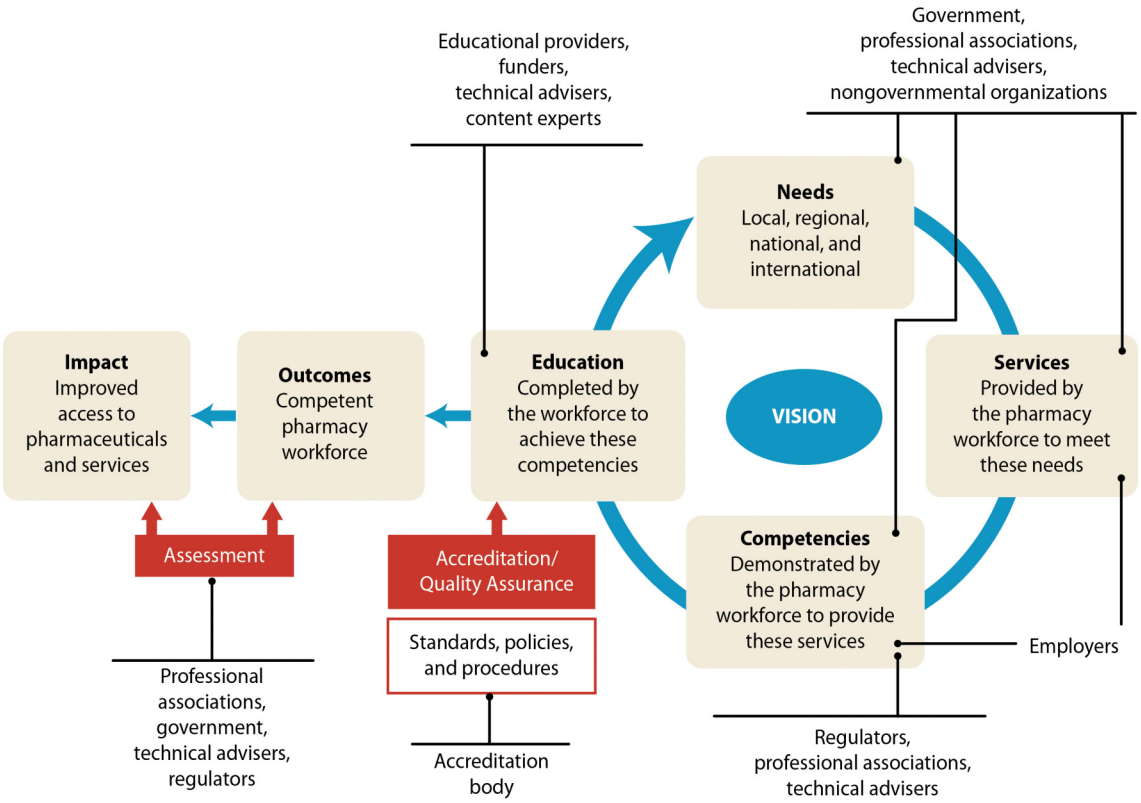

Figure 2 Involvement of stakeholders in pharmacy education. *Rouse, M.J., Vlasses, P.H., Wadelin, J.W., Zarembski, D.G., Joshi, M.P., Mabirizi, D., Saleeb, S.A. 2016. Continuing Pharmaceutical Education: Guide to Establishing Quality Assured and Accredited Programs. Submitted to the U.S. Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Management Sciences for Health (MSF), Arlington, VA. Used with permission from MSH.*

Finally, it is the public, as the ultimate "consumers" of the wide range of services provided directly and/or indirectly by the pharmacy workforce, which derives the greatest benefit from a system that assures the quality of pharmacy education. Consequently, it is increasingly becoming standard practice that members of the public are involved in the quality assurance process.

National Vision

National health care needs and priorities, and the scope of pharmacy practice vary globally. Overall, the role and contributions of pharmacists has changed in recent history with pharmacists now assuming greater responsibility for the safe and effective use of medications (International Pharmacy Federation, 2013).

Countries are at many different stages in the evolution of pharmacy practice and many factors, including culture, history and politics, can influence the rate of change in practice. Infrastructure to support the change in scope of practice has included changes to the education of pharmacists and regulation of pharmacy practice.

Given the benefits that can be achieved by expanding pharmacists' roles and responsibilities, many countries are reviewing pharmacy education (Kheir et al., 2009; Bhuyan, 2013). As practice evolves, education will need to be changed to meet the shifting needs of practitioners.

Development of standards for educational programs should occur following identification and development of the vision for pharmacy practice. Within each quality assurance system, mechanisms should be in place to ensure that input from stakeholders is sought and utilized to assure and advance the quality of pharmacy education. In this regard, stakeholder input on the periodic evaluation and revision of the standards will assist countries in ensuring the standards remain relevant to the healthcare needs of the country. Accreditation standards should typically be reviewed and updated every six to eight years in view of the dynamic nature of pharmacy education and practice.

The Quality Assurance Organization

During development of any quality assurance organization, consideration should be given to the structure, governance, policies and procedures under which the organization will operate (International Pharmacy Federation, 2014).

Mission and Vision

The quality assurance organization should have a mission and vision that clearly articulate its scope of operations. It should be noted that, in many countries, the quality assurance organization will have a broad scope of operations; currently a minority of such agencies are profession-specific. The first step in the development of a quality assurance system is to determine the structure and purpose of the entity (e.g., agency/commission/committee) charged with assuring the quality of pharmacy education. In this regard, it will be essential to determine the quality assurance organization's mission and scope of operations. Methods that will be used to communicate the mission to stakeholders should be identified. An evaluation plan that will be used to determine if the mission is being achieved should be developed and implemented. The evaluation plan should clearly identify the assessment tools that will be used and the individuals responsible for the assessment process.

Legal Status or Other Oversight Requirement

A regulatory mandate or other oversight requirement should govern the operations of the quality assurance system, including its scope of practice. Other oversight bodies should also have a clear description of their scope of authority and who has provided it (e.g., professional organization). Accountable parties should be identified, along with entities that recognize the quality assurance organization. The organization's relationship with government, professional organizations and other stakeholders should be described. Any requirements or criteria that the quality assurance organization must meet should be clearly delineated when it is established. Methods that will be utilized to assure autonomy must be carefully identified and steps must be taken to ensure that the body is not impacted by undue influences and is free from conflicts of interest.

Governance

The organizational structure of the quality assurance program should be appropriate to discharge the obligations mandated by the legislation or other authority. The quality assurance organization will typically include a staff who runs the day-to-day operations of the quality assurance process and a decision-making entity (e.g., Board of Directors). The composition of the decision-making entity or board of the organization should be established and consideration should be given to incorporating representatives from the broad array of stakeholders (e.g., pharmacy school academic staff and administrators, regulators, employers, and members of the public). Once the composition has been determined, the process that will be used to select or appoint individual members of the decision-making body and the role and selection process of officers, if used, should be determined. The identification process and duration that the officers and members of the decision-making body will serve in their various capacities should also be established. In general, it is considered as a good practice to overlap the terms of some members of the decision-making body to ensure consistency.

However the system is structured, the possibilities for "conflict of interest" should be removed, minimized or effectively managed. Members of the decision-making body are typically trusted, knowledgeable, experienced and respected members of the profession and community. In their role on the decision-making body, these individuals have responsibility to the profession and the public. Members of the quality assurance program's decision-making body (e.g. board, commission, etc.) have a fiduciary obligation to act in the best interest of the quality assurance organization. Each quality assurance organization should develop and implement a conflict of interest policy, which requires signed statements by all members of the decision-making body and which is reviewed periodically. Consistent with this policy, representatives of the quality assurance organization's decision-making group and its employees should periodically identify any pharmacy schools for which a conflict of interest exists. Conflict of interest policies should require that any representative of the quality assurance organization (defined as its decision-making body and staff) should recuse themselves from participation in discussions or the decision-making process for pharmacy schools for which a conflict of interest exists or is possible.

Finally, the funding sources to support the quality assurance organization must be identified. Funding sources can include governmental or other grants and fees for services. Regardless of the source, funding should be provided free from conflicts of interest. The fee structure for services should be established such that the ongoing needs of the quality assurance organization and the costs of operating the quality assurance process are addressed without being too punitive to the individual pharmacy schools. The quality assurance organization should independently develop and determine its own budget, without review by or consultation with any other entity or organization.

Standards

Every quality assurance system should have a well-developed set of standards or quality criteria (hereafter referred to as standards) which clearly state their purpose and expectations, and are used to evaluate and determine the quality of the pharmacy education program. Standards should be developed using a clear and cooperative process involving key stakeholder groups described above.

Stakeholder feedback should be sought and incorporated throughout development of the standards. The final standards should be endorsed by the profession and readily available to the public and the profession. Given rapid change in the pharmacy profession, standards should be periodically reassessed and revised as needed to ensure education within the country continues to address healthcare needs identified and adequately evaluate the quality of education provided by the school. The standards review process should be comprehensive and obtain input from key stakeholders, evaluating the context and relevance of individual standards as well as the standards as a whole. Following adoption of any revised standards sufficient time should be provided to allow pharmacy schools to bring their program into compliance with the new standards prior to implementation of the revisions.

Quality assurance standards should provide sufficient specificity to provide a basis for assuring that all pharmacy schools, through evaluation of structure, process and outcomes, produce graduates who have achieved the required competencies. The standards should not be overly prescriptive as to how these outcomes are achieved; however, thereby allowing individuality of programs in line with mission, as well as opportunities for innovation.

Pillars and Foundations of Quality

The FIP QA Framework utilizes five pillars and three foundations for educational quality, which should be addressed within the standards. The five pillars are *context*, *structure*, *process*, *outcomes*, and *impact*, while the three foundations are *science*, *practice* and *ethics* (see **Fig. 3**: Pillars and Foundations of Educational Quality). Each of these eight aspects is briefly described below. Greater detail can be found in the full FIP Framework found on FIP's website at: http://fip.org/files/fip/PharmacyEducation/Quality_Assurance/QA_Framework_2nd_Edition_online_version.pdf (Accreditation Council for Pharmacy Education, 2018a).

Standards related to **context** address the situation in which the school is located and the circumstances in which the education is delivered, and ensure that the educational environment is evaluated. Standards related to context should evaluate the school's mission to ensure it: 1) is specific and measurable; 2) reflects the current and intended future practice of pharmacy within the country; 3) provides the foundation for a culture of assessment and quality improvement; and 4) includes a commitment to research and scholarly activity (Accreditation Council for Pharmacy Education, 2018a).

Quality indicators for context include analysis of the school's mission, goals and values in relation to the needs for pharmacy services within the nation and its alignment with the mission of the university. The analysis should review the school's mission, provide evidence that the school is achieving its stated mission and goals, and state how the school's stakeholders are involved in the process of development, review and revision of the mission.

Standards related to **structure** outline expectations necessary to ensure the development, delivery and sustainability of the pharmacy education program. Standards for structure ensure that the pharmacy school is adequately organized, and has sufficient resources to deliver the curriculum and achieve the school's mission and goals. Structure standards describe the quality assurance organization's expectations regarding the role of the administrative leadership, organizational and governance structure, committee structure, and collaborative relationships within and external to the institution. Structure standards also address the structure and duration of the educational program, as well as the academic and staff resources, financial resources, physical facilities, practice facilities and library and educational resources needed to deliver the educational program. Quality indicators related to a school's structure involve analysis of the school's dean/director, administrative leadership team, committees, internal and external collaborative relationships, curricular content, educational activities, quantity and credentials of academic and other staff including

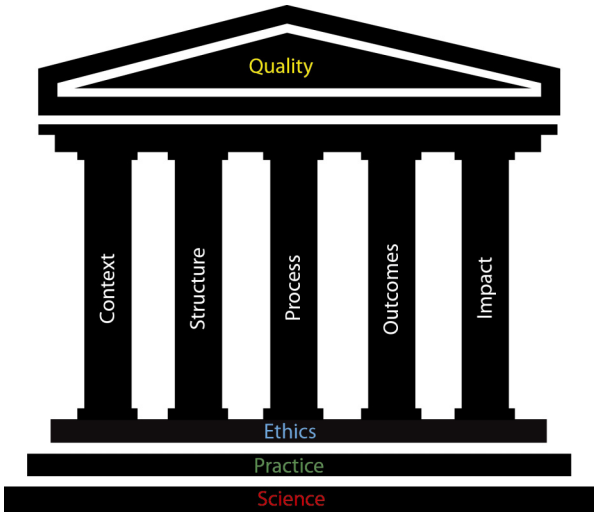

Figure 3 Pillars and foundations of educational quality.

pharmacy preceptors, number and nature of practice facilities, physical facilities including availability of simulated pharmacy practice settings, financial resources, and educational and library resources.

Standards related to **process** encompass the school's activities, policies and procedures including strategic planning, evaluation, assessment, admissions and enrollment management procedures, student services, student involvement, curricular development and improvement, and teaching and learning methods. Quality indicators related to the school's process ensure that the strategic plan is developed with broad-based input and addresses the external environment. Quality indicators also evaluate the school's enrollment against national pharmacy workforce needs and in relationship to resources available at the program to ensure an appropriate balance exists and expected quality of the school and its program(s) is achieved and maintained. Additional quality indicators for process include the adequacy of student services, incorporation of student feedback and input, the curricular development and revision process, incorporation of interprofessional education, adequacy of elective courses, adequacy of active learning strategies within the curriculum, and curricular assessment.

Standards related to **outcomes** address the short-term or immediate results of the educational program and mission-related activities. Analysis of a school's outcomes should involve review to assure that the learning outcomes and competencies are appropriate and aligned with national needs, and evaluate the extent to which they are achieved. The school's outcomes should address not only the knowledge needed for practice but the skills, attitudes and values (e.g., ethics, professionalism) of students as well. Research, scholarly, practice and service-based contributions of the school should also be assessed. Quality indicators for outcomes include that the school's programmatic learning outcomes are competency-based, specific and measurable; that the school uses validated measures to evaluate the extent to which the desired outcomes of the program are being achieved; and that through the research, publications, and other scholarly activities of its academic staff and students, the school contributes to the generation, dissemination, and application of new knowledge. It is expected that the school's outcomes will be aligned with national needs.

Standards for **impact** describe expectations regarding contributions to the advancement of education, practice and the profession. Evaluation in this regard should assess: the school's contributions to advocacy through the leadership of the school, its academic staff, and graduates; the development of graduates who are agents of change and contribute to advancements in pharmacy practice through the introduction of new activities and services; and contributions to addressing and solving national healthcare needs through research, innovation and generation of new knowledge. Quality indicators used to assess impact include evidence that demonstrates the school's contributions to changes, innovations and advancements in science, practice, professional and educational knowledge, and meeting the needs of society, thereby demonstrating social accountability.

Schools should also address the three foundations of pharmacy education, namely: *Science* (knowledge), *Practice* (skills and experience) and *Ethics* (attitudes and values) (Accreditation Council for Pharmacy Education, 2018a). Assessment of student competency should address all areas including knowledge, skills, attitudes, and values.

The school's curriculum should have a strong **science (knowledge)** foundation including adequate breadth and depth of the biomedical, pharmaceutical, social/administrative/behavioral and clinical sciences. Faculty should be adequately trained and experienced, and have the requisite credentials needed to deliver the curriculum. Knowledge and competence should develop, from introductory to mastery, as students progress through the curriculum. The curriculum should be evidence-based and relevant to the healthcare needs of the country. Graduates should be able to apply the foundational sciences to the provision of patient-centered care.

The curriculum should emphasize the relationship to **practice.** Teaching and learning activities should demonstrate clear links to practice and real-life scenarios. Simulations should be used to mimic actual and realistic pharmacy practice situations. Faculty of the school should include pharmacy practice (clinical) faculty—whether full-time, part-time or adjunct—with active, contemporary practice roles.

The school should incorporate professional **ethics** within and throughout the curriculum to ensure graduates develop competencies related to behaviors, attitudes and values necessary to demonstrate self-awareness, leadership and professionalism. Graduates should demonstrate self-awareness and be able to examine and reflect on personal knowledge, skills, abilities, beliefs, biases, motivation and emotions that may impact personal and professional growth. Graduates should demonstrate behaviors and values that are consistent with the trust given to the profession by patients, other healthcare providers, and society.

Policies and Procedures

The quality assurance process should be sufficiently rigorous. Policies and procedures should ensure consistency in the decision-making process. Decisions enacted by the quality assurance system must be fair and impartial to maintain the integrity of the evaluation process and the credibility of the organization.

Confidentiality should be assured and a policy in this regard is essential. Individuals involved at all aspects of the review process should receive adequate orientation and training to ensure correct and consistent evaluations. The criteria and process used to select and train individuals involved in evaluation needs to be developed as part of the quality assurance organization's policies and procedures.

Policies should outline the types of substantive change that would require providers to notify the quality assurance organization as well as the timing and the process that should be utilized to communicate such changes. The quality assurance organization's policies and procedures should provide for an appeals process for schools receiving an adverse accreditation decision. Similarly, the

quality assurance organization's policies and procedures should include the process through which any complaints received by the accreditation body will be addressed.

The duration that the quality assurance organization will maintain its records on each provider should be determined along with the location where the records will be maintained.

Eligibility Criteria

The requirements for eligibility and the components of the initial application for accreditation/recognition/approval (hereinafter "accreditation") will need to be established. The frequency that the quality assurance organization will review pharmacy schools and the process that will be used to periodically reevaluate pharmacy schools need to be established. The initial term of accreditation may be shorter to allow for greater oversight of the pharmacy school during this initial period.

Self-Study Process and Report

Each pharmacy school should complete an in-depth self-study, or self-assessment, of the educational program in relationship to the standards. The self-study provides the foundation for the quality assurance process. The school's self-study process should be in-depth and involve a broad base of internal and external stakeholders including the school's administrators, faculty, staff, students, alumni, and practitioners. A report produced after the conclusion of the self-study should document the school's self-assessment of compliance with each of the quality assurance standards and include relevant documentation and data as evidence to support the school's findings and conclusions along with an analysis of the school's strengths and limitations. In essence, the self-study report should answer three fundamental questions: *What? So What? What Next?* The "What" should be a factual, objective description of the school and its program against all the criteria in the standards. In line with a typical "SWOT Analysis" the self-study report should describe strengths, weaknesses, opportunities and threats of the program and school. The "So What" is more of a subjective reflection on the implications of the situation, as described, for the quality of the program and compliance with the standards. The "What Next" should describe specific, measurable plans to address deficiencies and desired quality improvements, including implementation strategies, timelines, and needed resources. Use of a self-assessment process facilitates development of a culture of assessment within the school.

On-Site Evaluation Team

An evaluation team, made up of "peer" members, conducts an on-site evaluation for purposes of validating the school's assessment findings. Peer members on the evaluation team should have the appropriate qualifications, expertise and experience commensurate with the school under evaluation. Credibility of the quality assurance process is enhanced using qualified and well-respected evaluation team members. All members of the evaluation team should receive training prior to participating in an on-site evaluation. Training should address the quality assurance standards, policies and procedures of the quality assurance organization (including confidentiality and conflict of interest), evaluation techniques, the team member's role in the on-site evaluation, and other protocols. Any credential requirements for evaluation team members, in terms of position or experience, should be well established and clearly communicated. Periodic re-training of evaluation team members should occur following any changes to the quality assurance standards or revisions to the process. A list of team members should be provided to the school under review and evaluation team members with real or potential conflicts of interest as identified by the school should be replaced with alternative individuals.

On-Site Evaluation

The duration and proposed schedule of the on-site evaluation should be clearly communicated to the school in advance to facilitate their planning. The schedule should provide sufficient time for a comprehensive evaluation of the school and the pharmacy degree program. Time should be provided to conduct interviews with the school's administrative leadership team, faculty, current students, graduates, experiential preceptors, staff from centralized university services, and institutional leadership. During the on-site visit, the evaluation team should conduct a survey of the school's physical facilities, the library and educational resources available to the school and a sampling of practice facilities, if available. Ideally, a standardized evaluation form will be utilized as a means to enhance consistency in the quality assurance process.

Accreditation Action and Term

Given the need to ensure ongoing compliance with the quality assurance standards, the quality assurance process should involve an initial term of accreditation with subsequent periodic evaluations on a regularly scheduled basis. Typically, an accreditation term is

defined for a set period. Schools demonstrating compliance with the standards can be awarded the maximum term while a shortened term may be awarded to schools with demonstrated deficiencies. Typically, at the end of the awarded term, the program is required to undergo a comprehensive evaluation for continuation of accreditation; such evaluation would include a self-study by the school and an on-site evaluation visit.

Monitoring During the Accreditation Term

Between comprehensive on-site evaluations, monitoring and reporting may be required depending on issues identified during the on-site evaluation. Annual monitoring (e.g., enrollment numbers, academic staff capacity, and graduates' performance on nationally standardized examinations) or other periodic reporting requirements may also be imposed as a means to continually monitor programmatic quality. If accreditation standards have changed in the period between comprehensive evaluations, the quality assurance organization may require the school to submit a report to indicate how it will meet the expectations of the new standards.

Adverse Actions

The consequence of noncompliance with the standards needs to be determined and stated clearly in policies and procedures. Possible consequences can include requiring additional reporting, placing the school on probation if noncompliance continues for an extended period, or withdrawal of the school's accreditation by the quality assurance organization. The method that will be used to communicate the consequence to schools should also be identified. While a letter to the school may provide sufficient communication regarding the quality assurance organization's findings of noncompliance, follow-up real-time interactions may be beneficial to provide greater depth regarding the quality assurance organization's concerns and expectations regarding resolution of the issues. Written communication to the key stakeholders should occur when the quality assurance organization has put the program on probation or withdrawn accreditation. With withdrawals, the quality assurance organization should communicate the effective date. Informing the public usually can be accomplished via the quality assurance organization's website; in addition, the accreditation organization is likely to require public disclosure by the institution, for example, via its website.

Most quality assurance organizations include in their policies and procedures the option for the institution to appeal against an adverse action.

Public Disclosure

The decisions of the quality assurance organization must be made public to increase transparency and credibility of the system. The quality assurance organization will need to make its criteria/standards, policies and procedures available to schools, stakeholders and the public. Posting such information on its website, if available, provides one means to accomplish this task. In addition, the decision-making body will need to communicate information regarding its decisions/actions. As noted above, this is especially relevant for programs on probation or whose accreditation has been withdrawn. In general, the quality assurance organization should provide the public with a list of programs accredited by the organization, along with the current term and any special requirements or conditions.

Quality Advancement of Pharmacy Education

The quality assurance process establishes minimum requirements and expectations for the evaluation of education provided at individual schools. An additional purpose of the evaluation process—both internal and external—is to advance the quality of education. This should be central to the mission of the quality assurance organization. Standards should be developed to allow programs flexibility in the manner requirements can be addressed. By allowing individual schools flexibility in meeting requirements outlined in a standard, the quality assurance process encourages and promotes innovation and quality advancement. For example, the quality assurance process will ensure that the individual school has a mission. The specific mission and how it is achieved and advanced, however, is determined by the individual school and university. Another example of a quality advancement centers on curricular delivery. The quality assurance process seeks to ensure that the teaching and learning methods used are effective in delivery of the curriculum. Quality advancement initiatives would seeks to maximize the number and nature of active learning techniques used in delivery of the curriculum to enhance student engagement within the curriculum and optimize learning. When so requested, peer review through external evaluation can provide many opportunities for schools to receive advice and quality improvement strategies from more experienced colleagues. By allowing flexibility in the quality assurance process, quality advancement is facilitated.

Quality assurance bodies can also be important drivers for change and quality advancement at a national level. Frequently, changes and advances in education that are recognized profession-wide as being necessary may be difficult and/or unpopular to

make. By setting new or higher expectations for educational institutions, accreditation standards can drive needed change. Good examples are the strengthening of clinical areas and integration of practice experiences within the curriculum, inter-professional education, promotion of the development of self-directed life-long learning skills and attitudes by students, and expanded student representation and participation in school and programmatic administration.

Quality Assurance and Advancement of Continuing Education and Continuing Professional Development Activities

Many national quality assurance organizations also have a role in the accreditation of continuing education and continuing professional development activities. Pharmacy professionals (including pharmacists and pharmacy support personnel) must maintain and advance their contemporary competence through self-directed life-long learning, which includes engagement in continuing education (CE) and continuing professional development (CPD) activities. Ensuring quality in CE/CPD involves three main groups of stakeholders: (1) the individual pharmacy professional who engages in CE/CPD to maintain competence; (2) the educational provider that offers the CE/CPD activities to the pharmacy professionals; and (3) the CE/CPD accreditation body that oversees the CE/CPD quality assurance or accreditation process. The CE/CPD process then can be considered from three different but inter-related levels:

- The **first level** involves the individual pharmacy professional who, through a CE/CPD process of reflection—which may include evaluation by a third party (such as their employer)—identifies individual educational and training gaps, needs or goals that must be addressed to maintain or enhance competence. Based on identified needs or goals, the professional develops and implements a personalized learning plan, which should involve both formal and informal learning activities and achieve desired learning outcomes. The learning should be applied in practice and its effectiveness, outcomes and impact evaluated.
- The **second level** involves the CE/CPD provider who offers activities, which must be of sufficient scope and quality to adequately address the individual pharmacy professional's educational and training needs and goals.
- The **third level** is the oversight of the overall process and involves development of a quality assurance or accreditation system.

The individual pharmacy professional forms the basis of the CE/CPD process (**Level One**). The continued competence of individuals is at the center of the CE/CPD process. Through participation in CE/CPD and training activities, the individual participates in a process of life-long learning that is designed to maintain and enhance his/her competence as a pharmacy professional. The first section of a CE/CPD quality assurance framework focuses on the process in which individual pharmacy professionals should engage to ensure life-long learning and the maintenance and enhancement of competence.

Level Two involves the quality of the individual CE/CPD and training activities in which pharmacy professionals engage. Consistently high quality CE/CPD and training activities are needed to ensure that the CE/CPD process is maximized and achieves the desired outcomes and impact. CE/CPD activities that are of poor quality in terms of structure, content and process will not optimally assist pharmacy professionals in the maintenance and enhancement of competence. The quality of individual CE/CPD and training activities can be assured via the use of quality assurance criteria/standards to which individual activities may be compared. These criteria/standards for quality should address the "Pillars of Educational Quality" (*Context*, *Structure*, *Process*, *Outcomes*, and *Impact*) as well as the "Foundations" (*Science*, *Practice*, and *Ethics*) that form the basis of the elements of quality (Mestrovic and Rouse, 2015).

In general, the CE/CPD quality criteria/standards should incorporate the following aspects:

- Educational need for the activity that is based on a pre-identified competency (knowledge, skills, attitudes and values) or practice gap
- Learning objectives that are specific, measurable, achievable, relevant and timed (SMART)
- Content and learning methods that are evidenced-based, cater to needs of diverse learners, and free of bias and conflicts of interest
- Presenters that are knowledgeable, experienced, and free of bias and conflicts of interest
- Instructional materials, including handouts, tools and resources, that can be used by the learners in the practice setting
- Use of active learning techniques that facilitate learning
- Assessment of learning to ensure the learning objectives have been achieved
- Evaluation of the CE activity

Individual organizations (e.g., employers, hospitals, professional associations) offering CE/CPD and training activities in countries that lack a process to accredit CE/CPD and training activities may use these criteria/standards during development of individual CE/CPD and training activities (e.g., a CE/CPD course). In addition, these can be used at the national level.

Level Three involves development of an oversight process that is charged with ensuring the quality of the CE/CPD and training activities. Ideally, an accreditation body would be established at the national or regional (multi-country) level and involve the review of CE/CPD activities or providers by an "external" group (i.e., evaluators not involved in the development or delivery of the CE/CPD activities). Development of an accreditation system should start with establishing the entity that will be responsible for the accreditation process. A legal mandate for the entity should be established along with the mission, scope of operations, organizational structure, and accreditation body's policies and procedures. The policies and procedures should ensure that the accreditation process is efficient, fair, transparent, credible and accountable. Disclosure of the entity's policies and procedures as well as findings and actions should be made public.

In the absence of sufficient resources to develop an accreditation body, countries, regions, professional organizations, or individual employers and health care organizations may consider adopting or adapting the quality assurance policies and procedures and standards utilized by other countries or regions. A description of these is provided in the full report (Rouse et al., 2016).

Quality Advancement in CE/CPD

Any comprehensive and robust system for quality assurance—whether it be an internal or external system—ideally should also promote and facilitate quality advancement. Accreditation bodies can and should be important drivers for change, with quality standards and expectations reviewed and revised on a regular basis. For example, the Accreditation Council for Pharmacy Education (ACPE), the U.S. national agency for accreditation of pharmacy education, sees its mission as *"assuring and advancing"* the quality of pharmacy education. In rapidly changing sectors, such as pharmacy education and practice, and in view of constantly evolving societal needs, technological innovations, and the growing base of evidence from research into successful models for teaching and learning, accreditation bodies need to communicate and collaborate with all stakeholders to identify and implement changes that are needed. Such changes, while necessary for quality improvement, may not be easy and are not always well received by those who have to make the changes. For this reason, it is important that such changes are identified through profession-wide consensus, and not arbitrarily imposed by one sector or body.

In the area of CE and CPD, new models for life-long learning and professional development are vitally important because the majority of practitioners did not receive pre-service education and training that fully prepared them with the necessary knowledge, skills, attitudes and values for contemporary—and constantly evolving—practice. Although not yet pervasively implemented on a profession-wide and global scale, in recent years, one of the most important innovations has been the transition from the more traditional, hours-based CE model to the CPD model, which is a more holistic approach to self-directed learning that focuses strongly on needed outcomes and impact of the learning. In some countries, this quality improvement has been driven by the body responsible for quality assurance of pharmacy education. In other countries, this has been by regulators, employers, and CE providers themselves.

Other notable quality improvements and innovation in CE and CPD include:

- Incorporation of inter-professional education within CE/CPD to better prepare practitioners from all health professions to work together in teams to improve the effectiveness, and outcomes of patient care and reduce cost in health care delivery. Two examples of innovations in this regard are the introduction of a joint accreditation system for providers of inter-professional CE ("education for the team, by the team") and the development of inter-professional competencies for health care professionals (Joint Accreditation Interprofessional Continuing Education, 2018; Interprofessional Education Collaborative, 2016; Canadian Interprofessional Health Collaborative, 2010).
- Greater incorporation of technology-enhanced learning (Scott et al., 2017).
- Consideration of a competency-based or outcomes-based credit versus a time/participation-based credit (Lucey, 2017; Austin et al., 2005a; Austin et al., 2005b; Pharmaceutical Society of Ireland, 2010; Pharmacy Council of New Zealand, 2018a; Pharmacy Council of New Zealand, 2018b).
- Increased focus on practice-related outcomes for CE and CPD activities. Some accreditation bodies have changed the classification of educational activities to promote awareness and encourage participation in a wider range of activities; that is, not just knowledge-based activities. In the USA, for example, ACPE categorizes activities as (i) knowledge-based, (ii) application-based, or (iii) practice-based (Accreditation Council for Pharmacy Education, 2018b).
- An emphasis on assessment and documentation of competence (performance) in the workplace and the role that CE and CPD plays in enhancing the competencies that have been identified as needing strengthening (Meštrović et al., 2011, 2012; Ontario College of Clinical Pharmacists, 2018).
- Evolution of the CE administrator from a "support person" to more of a CE professional; establishment of a certification credential for CE administrators (Alliance for Continuing Education in the Health Professions, 2018).
- Use of internet-based technologies, including smart phone applications, to improve systems to track CE activities and support learners in their CE/CPD (National Association of Boards of Pharmacy, 2018).

Conclusion

Pharmacy education must adapt to the changing needs of the profession. Implementation of appropriate policies, procedures and standards helps to assure and advance the quality of pharmacy education and provides assurances to the profession and the public. Development of a quality assurance process must consider the national context and vision for pharmacy practice and education and engage all key stakeholders. The quality of pharmacy education can be ensured through development of and adherence to quality criteria and standards that are based on the "Pillars and Foundations of Quality" model.

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Using Patients and Other Forms of Simulation in Teaching Clinical Skills

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Introduction/Background

The development of clinical skills is a necessary component of the practice of pharmacy. Experiential learning through clinical training in patient care settings has been a cornerstone in enhancing clinical skills and competence. However, due to evolving healthcare professional education models, patient safety, and availability of clinical training opportunities, other avenues for teaching clinical skills are being utilized. Healthcare simulation is one teaching methodology with growing interest and an increasing body of evidence.

Simulation has long history of use for education and training in non-healthcare related industries such as space and aviation, military, business, and law education. Simulation modeling has also been utilized for predicting changes to the economy and forecasting the weather. The past few decades have witnessed an increase in the use of simulation for health professions education, including medicine, nursing, and pharmacy.

Simulation is currently utilized used in health professional education to recreate real-world experiences that supplement other teaching and learning methods. Simulation, as defined by David Gaba, "is a technique, not a technology, to replace or amplify real experiences with guided experiences, often immersive in nature, that evoke or replicate substantial aspects of the real world in a fully interactive fashion" (Gaba, 2007). The body of literature examining simulation methodologies in pharmacy education is growing. Currently the majority of this literature primarily focuses on training student pharmacists, however, the use of simulation for

Table 1 Selected examples of simulation for pharmacy education and training

Content/skill area of focus	*Reference(s)*
Pharmacotherapy	Branch (2013), Serag-Bolos et al. (2017b), Miranda et al. (2017), Raney (2007), and Douglass et al. (2013)
Medication Errors/Patient Safety	Atayee et al. (2016), Frenzel et al. (2017), Kiersma et al. (2009), Rickles et al. (2010), and Warholak et al. (2011)
Device & Injection Technique	Basheti (2014) and Skoy et al. (2013)
Medical Emergencies	Bastin et al. (2017) and Robinson et al. (2011)
Pharmacy Compounding	Cretton-Scott et al. (2015)
Patient Assessment	Grice et al. (2013), Seybert and Barton (2007), and Tokunaga et al. (2010)
Cardiovascular Resuscitation	Bingham et al. (2015), Davis et al. (2013), Eng et al. (2014), Maxwell et al. (2016), and Mieure et al. (2010)
Communication	Gillette et al. (2017), Fejzic et al. (2016), Hasan et al. (2017), Kostoff et al. (2016), and Shrader et al. (2015)
Patient Counseling	Ragland et al. (2015), Glasier et al. (2010), and Dolovich et al. (2007)

training practitioners, including pharmacy residents, has been described. **Table 1** illustrates examples of simulation in pharmacy education.

This chapter will examine the use of simulation methodologies used for training within pharmacy education and clinical practice. Specifically, we will address how simulation is utilized to foster professional knowledge, skills, and attitudes of student pharmacists and practicing pharmacists. While a goal of training and education is to equip learners with knowledge, skills, and attitudes that are transferrable to practice and patient care, it is important to recognize there is limited data evaluating the impact of simulation on clinical pharmacy outcomes. Currently, examples of simulation education improving clinical practice are predominantly associated with medical and nursing education (Barsuk et al., 2009a, 2009b; McGaghie et al., 2014; Wayne et al., 2008; Ford et al., 2010). Due to the dynamic nature of this topic, this chapter will consider insights and applications of simulation from other health professions.

Rationale for Simulation-Based Education

"*Tell me and I forget, teach me and I may remember, involve me and I learn.*" This quote, attributed to Benjamin Franklin, resonates strongly with the principles of simulation-based education (SBE) because simulation immerses learners in the learning process and shifts the education model from teacher centric to learner centric. An essential process of health professional education is the transfer of knowledge, skills, and attitudes from the classroom to professional practice. However, this transfer and application of knowledge is not necessarily innate and may present a challenge for learners. Over the past few decades, there has been a growing body of evidence describing and evaluating the rationale for simulation learning methodologies in healthcare education. As the demand for the highly trained and practice ready healthcare professionals has increased, the need to explore new and innovative teaching methodologies and technologies has risen. The growing integration of SBE for training pharmacists and student pharmacists is multifactorial. Factors contributing to the rise in SBE in pharmacy education include: (1) alignment with principles of educational theory; (2) profession and curriculum evolution; and (3) demand for experiential education and clinical practice sites. This section will discuss these factors in more detail.

Educational Theory

The role of simulation in healthcare education draws from several educational theories. In particular, SBE aligns with concepts of (1) Malcom Knowles theory of adult learning, or andragogy; (2) David Kolb's experiential learning theory; and (3) Donald Schon's theory of reflective practice. Each of these educational theories contributes to the application of SBE for clinical and non-clinical training. A brief overview of these theories will now be discussed.

Andragogy

Knowles' theory of adult learning begins with the rationale that adults learn differently than children (Knowles et al., 2012). Principles of adult learning theory are illustrated in **Table 2**. Considering the vast majority of learners in pharmacy education are adults, simulation educators may enhance learning by developing curriculum around these core principles.

Table 2 Characteristics of andragogy

Self-directed
Experience based
Subject dependent on life or work needs
Problem solving
Internal
(Knowles et al., 2012)

Experiential Learning Theory

David Kolb's experiential learning theory emphasizes a four-stage cycle of how new knowledge is acquired and embedded. The foundation for experiential learning theory follows: (1) that learning takes place with a concrete *experience*; (2) followed by *reflection* upon the experience; (3) *analysis* and formation of abstract concepts; (4) then *experimentation* to create a new experience (Kolb, 2015).

Reflective Practice

Reflection has been described as a "rich source of continued personal and professional growth" (Killion and Todnem, 1991). Schön (1983, 1987) describes two forms of reflection, reflection-on-action and reflection-in-action. Reflection-on-action is described as thinking back on an experience to discover how or what we could change for the future experiences. Self-assessment, an example of reflection-on-action, and reflection-in-action have been identified as "missing links" in the development of higher learning in pharmacy education (Austin et al., 2008). Reflection-in-action and reflection-on-action are essential components of simulation through the scenario and debriefing, respectively. A discussion of the primary components of SBE will be discussed later in the chapter.

Profession and Curriculum Evolution

As the profession of pharmacy and scope of practice continues to expand, curricula for pharmacy education and training need to evolve. Competency-based training is a concept that has been utilized in many health-related educational programs (Carraccio et al., 2002). The Accreditation Council for Graduate Medical Education (2017) has shifted from a traditional knowledge-based model for graduate medical education to a competency-based curriculum. Other health disciplines such as pharmacy have been or are attempting to follow suit with their educational standards.

The profession of pharmacy has worked diligently to advance pharmacy practice and gain recognition of pharmacists as an essential member of the healthcare team. The implementation of new methods of defining and assessing pharmacy practice skills is an integral part of further advancing and achieving this goal (Pittenger et al., 2016). The concept of Entrustable Professional Activities (EPAs) represents a potential mechanism of defining and assessing pharmacy practice skills (Pittenger et al., 2016). EPAs are units of professional practice, defined as tasks or responsibilities to be entrusted to unsupervised performance of trainees once the trainee has attained sufficient competence. EPAs are independently executable, observable, and measureable in their process and outcome (Ten Cate, 2013a, 2013b; Haines et al., 2017).

A prime example of advancing the profession is the development of the Pharmacist's Patient Care Process (PPCP) which recognizes the need for a consistent process in the delivery of care across the profession, regardless of practice setting. The PPCP includes the following five steps: (1) collect; (2) assess; (3) plan; (4) implement; and (5) follow-up: monitor and evaluate. These steps incorporate collaboration, communication, and documentation around patient-centered care (Joint Commission of Pharmacy Practitioners, 2014). Simulation is well positioned to train and assess the ability to demonstrate this patient-care process.

In order for pharmacy education to transition to a competency-based model, innovative teaching and learning strategies must be developed. Simulation has been identified as an active learning methodology for training in a competency-based curriculum (Accreditation Council for Pharmacy Education, 2015). There has been a growing interest in the use of SBE to teach and assess cognitive (knowledge), psychomotor (skills/competency), and affective (attitudes) domains to individuals and increasingly with teams (Motola et al., 2013).

Simulation for Formative and Summative Assessments

The terms "formative" and "summative" were first formalized in the 1960s in relation to program evaluation (Scriven, 1967). Later in the same decade, Benjamin Bloom, expanded the context to include formative assessment as an integral component of the teaching and learning process (Bloom, 1968). Since then, they have become commonplace in assessment of education. The primary purpose of formative assessment is to provide feedback on student performance, specifically their strengths and weaknesses, during the course of study (Downing and Yudkowsky, 2009). Examples of formative assessments are reflective writing, student portfolios, and debriefing with simulation (DiVall et al., 2014). In contrast, summative assessments generally occur at the conclusion of a course or learning module, such as a midterm or final exam (Downing and Yudkowsky, 2009). Summative assessments may also be considered "high stakes," since they generally determine if a learner may progress to the next phase of curriculum (DiVall et al., 2014). When used in conjunction, formative assessments *for* learning and summative assessments *of* learning provide a constructive framework for assessment during the learning process and terminal data for learner progression and course modification.

If colleges and schools of pharmacy are expected to produce graduates that are both practice ready and team ready, methods for assessing preparedness must be developed. Benedict et al. (2017) designed a blended simulation progress test to assess for practice readiness. Practice readiness was measured through knowledge and performance evaluation for first- and third-year student pharmacists and first-professional year postgraduate pharmacy residents. This type of assessment stands to provide valuable insight on the progression of learners across the spectrum of their education.

Demand for Clinical Experiences

The quality and capacity of experiential education continues to be a top priority for pharmacy education (Gibson et al., 2017). Experiential education contributes to the development of clinical reasoning and problem solving skills that are essential to clinical

practice. Experiential education programs are faced with the challenge to secure clinical practice sites in areas such as ambulatory care and internal medicine (Plaza and Draugalis, 2005). Brackett et al. (2009) identified the need for quality experiential education as a significant barrier to the matriculation of the increased number of pharmacists. In the U.S. an additional burden on experiential education programs is the Accreditation Council for Pharmacy Education (ACPE) requirement to deliver at least 300 hours of Introductory Pharmacy Practice Experiences (IPPE) as a component of the pre-Advanced Pharmacy Practice Experience (pre-APPE) curriculum, of which 20% of these hours (e.g., 60 hours) may come from simulation (Accreditation Council for Pharmacy Education, 2015).

Patient safety and standardized experiences are additional challenges for experiential learning. For example, a practice site may limit student experiences for legal, ethical, or patient safety reasons. Full standardization of learning experiences in the clinical environment is not practical and generally impossible.

Early Evidence Examining the Roles in Experiential Education

SBE provides one avenue to reduce the burden on experiential education programs by creating standardized and safe learning environments (Maran and Glavin, 2003). Simulation may be particularly beneficial and appropriate for clinical experiences that are rare or inconsistently observed. It is worth noting that simulation is intended to supplement, not completely replace experiential learning in the clinical environment.

Vyas et al. (2010) developed a simulation to supplement IPPEs. Fourth year student pharmacists at a satellite campus participated in a 6-week high fidelity patient simulation series incorporating three scenarios: asthma exacerbation, acute decompensated heart failure, and infective endocarditis. Following each simulation students completed a post-simulation quiz to evaluate students' knowledge, skills, and attitudes compared to a control group on the main campus. The control group completed identical curriculum, with the exception of the simulation exercises. Long-term retention was evaluated with an identical assessment administered 3-months later. All knowledge-based quiz items at completion of series demonstrated significant improvement compared to pre-simulation quiz ($P < 0.001$). Overall, students felt more confident making clinical recommendations (76%, $P = 0.01$) and identifying the physiologic effects of medications on the human body (70%, $P = 0.01$) following the simulation experience.

Results of a 2012 survey found that 21% of hospital practice sites that responded did not allow APPE students to prepare compounded sterile preparations (CSPs) (Wuller and Kwasiborski, 2012). This finding represents a potential gap in experiential education. The incorporation of sterile compounding simulation exercises into the curriculum may bridge this gap. Cretton-Scott et al. (2015) incorporated a sterile-technique module into an IPPE for third-year student pharmacists. Students performed a modified media fill challenge test for low-risk level CSPs and prepared an antibiotic injection solution. The CSP was analyzed for accuracy by Liquid Chromatography Mass Spectrometry (LCMS) or High Pressure Liquid Chromatography (HPLC) in 2012 and 2013, respectively. CSP analysis showed that 84% in 2012 and 71% in 2013 were within 10% of the desired concentration. While additional research is needed, it can be deduced from these and similar examples that simulation may be an appropriate model to implement as a complement to clinical practice sites and reduce the burden created by expanding programs.

Implementation of SBE

Simulation Framework and Facilitation

The framework of healthcare simulation generally consists of three distinct components: (1) pre-briefing; (2) simulation scenario; and (3) debriefing. Facilitation occurs throughout the SBE exercise. This section will explore the purpose of each component in simulation education.

Pre-Briefing

Pre-briefing, or briefing, occurs prior to the simulation scenario and serves as an orientation session for participants. Components of the pre-briefing may vary, but in general should include: (1) setting ground rules; (2) defining learner expectations; (3) ensuring psychological safety; (4) establishing a fiction contract; (5) providing a technology review or orientation to the simulation environment; and (6) a case lead-in. Pre-briefing helps guide the learners by setting the stage for the simulation exercise.

Simulation Scenario

An important component of SBE is choosing appropriate scenarios. Prior to developing and implementing SBE, considerable thought must be applied to the curriculum design process. Essential elements for curriculum development include systematic and scientific approaches when constructing learning experiences (Rosen et al., 2008). Effective instructional design should also be intentional (Branch, 2009). Educational theory provides the systematic framework when developing curriculum so the effects of design may be collected and analyzed. The use of systematic approaches to curriculum design, such as Kern's six step approach (Kern et al., 1998) will enhance the curriculum including the simulation teaching and learning experience. Additional consideration for scenario development and implementation are summarized in **Table 3**.

Table 3 Considerations for simulation scenario development and implementation

Description	*Comments*
Develop learning objectives	Objectives should be SMART: specific, measureable, achievable, realistic, and timely (INACSL Standards Committee, 2016b)
Develop a script for standardization	Rigidly scripted scenarios may decrease fidelity; Minimal scripted scenarios may be difficult to control or standardize
Create a scenario flow chart	Outlines progression of scenario and aids facilitator and simulation technician
Document list of equipment and supplies	Aids in staging or resetting the scenario
Rehearse the scenario	Provides opportunity to evaluate the scenario and identify opportunities for improvement

(Alinier, 2011; INACSL Standards Committee, 2016a; Motola et al., 2013)

Table 4 Seven essential elements of debriefing in healthcare simulation

Ensuring psychological safety
Establishing basic assumptions of the learner or learners
Establishing of ground rules
Establishing a shared mental model
Addressing learning objectives
Utilizing open-ended questions
Utilizing silence

(Sawyer et al., 2016)

Debriefing

Debriefing and feedback are critical components of the learning process with healthcare simulation (Issenberg et al., 2005). These terms are often used synonymously in the healthcare simulation literature (Sawyer et al., 2016), but important distinctions exists. Feedback may be described as a passive form of learning, by providing information for, or an evaluation of performance. Debriefing has been described as an active learning methodology, where faculty and students reflect on experiences to close performance gaps and enhance the learning process (Dreifuerst, 2009; Raemer et al., 2011; Rudolph et al., 2008) and is recognized as a critical component of SBE (Cheng et al., 2015a). The value of debriefing in SBE originates from its connection to elements of experiential learning and reflective practice. It is important to recognize that reflection on one's practice is an essential component of the experiential learning process (Rudolph et al., 2008; INACSL Standards Committee, 2016c).

While debriefing is generally conducted at the end of or following a scenario debriefing may occur during a simulation scenario, in the form of a "time-out" to explore immediate actions or frames or to assist learners that may be struggling (Motola et al., 2013). Debriefing during a simulation is an example of reflection-in-action, whereas debriefing following a simulation illustrates reflection-on-action. Numerous debriefing strategies are described in the literature (Cheng et al., 2015b, 2016; Raemer et al., 2011; Sawyer et al., 2016; Rudolph et al., 2007). Sawyer et al. (2016) describes seven essential elements for debriefing in healthcare simulation. These elements are listed in **Table 4**.

Barriers to Simulation Implementation

Many barriers exist for designing and implementing SBE. Barriers include, but are not limited to: time, resources, logistics, and faculty development. As with any project, allocating an appropriate amount of time is essential to its success. Resource allocation, including competition for said resources, may present an additional barrier. Budgetary restrictions may limit the quantity or quality of simulation resources available. If simulation resources are shared with other colleges, schools, or departments then competition for those resources may be an issue.

Due to the cost of purchasing, maintaining, and running patient simulations, it is critical to determine the educational value compared to other educational methods. Ray et al. (2012) compared pharmacy students' knowledge retention and comfort level with a simulation using a patient simulator and a written patient case. Performance improved for both the simulation and written case groups compared to the pre-test and post-test results. When comparing results from the post-test and retention test, the simulation group scores remained the same and there was a small, but not significant decrease in the written case group. Participation in simulation may improve retention of knowledge by pharmacy students compared to written cases but more research is needed to draw a conclusion.

Logistical barriers can prove particularly challenging as they involve coordinating schedules for learners, faculty, and staff. Successfully navigating logistical barriers includes respectful, meaningful, and efficient use of time and resources. Additionally, faculty development is a potential barrier that should not be marginalized. The skill of blending simulation technology with clinical cases takes time and experience. Furthermore, effective facilitation of debriefing for reflective practice is a new concept for many faculties. Fortunately, debriefing is a skill that simulation educators may learn through specific training and experience (Cheng

et al., 2015a). Training programs are currently offered by manufacturers of simulators, at professional conferences, through academic institutions, and simulation centers. Debriefing assessment tools are available to evaluate debriefing practices and afford feedback, or debriefing, for the debriefer (Arora et al., 2018; DASH, 2011).

Simulation Modalities

Various types of simulation are used in health professions training. Features of the simulation methodology employed include the degree of fidelity and technology as well as which skills are to be trained or assessed. This section will discuss the relationship between fidelity, technology, and various types of simulation methods. When determining the appropriate methodology to employ, consultation with other faculty accompanied by a thorough examination and alignment of a simulator's capabilities with learning objectives is essential.

Fidelity vs. Technology

Distinguishing between fidelity and technology is an important consideration in SBE as they are often used interchangeably. In general, fidelity describes the degree to which the simulation replicates the real event and/or environment, or the level of realism of a simulation exercise (Lopreiato et al., 2016). In contrast, technology describes the equipment and devices utilized for training within a simulation (Lopreiato et al.). A high-fidelity simulation should be interpreted as more realistic compared to a low-fidelity simulation. Based on these definitions, one must realize that while fidelity and technology are essential components of a simulation, they are distinct from one another. The fidelity of a simulation scenario depends not only on the technology utilized, but the environment, equipment, and supplies as well. It is essential to consider both simulation technology and fidelity when developing a simulation exercise and specifically consider how technology will impact fidelity.

Skoy et al. (2013) compared the impact of low-fidelity and high-fidelity simulation on student pharmacists' injection technique using a cross-over study design. The described low-fidelity and high-fidelity simulations incorporated an injection pad and a partial task trainer injection arm, respectively. The primary outcome was to ensure the ability to properly administer both intramuscular and subcutaneous injections to a peer. All students demonstrated competency with the injection administration. The results of this study indicated that students' ability to administer injections through either route of administration was not significantly impacted by one level of simulator fidelity over the other.

Standardized Patients

Standardized patients (SPs) are individuals trained to portray a patient with a specific condition in a realistic, standardized, and repeatable way. SPs may be referred to as a simulated patient, simulated participant, confederate, or embedded participant. SPs portray many roles within SBE, including patients, caregivers, family members, and healthcare providers (Meakim et al., 2013; Lopreiato et al., 2016). Standardized patients are advantageous when teaching communication and interpersonal skills (Maran and Glavin, 2003). Disadvantages of SPs include time and resource allocation for training as well as limitations on training procedures that may harm the SP.

Patient Simulators

Patient simulators afford learners the opportunity to practice skills from basic assessment to advanced clinical skills. The technology of patient simulators (a.k.a. human patient simulator, manikin, or mannequin) continues to grow (Maran and Glavin, 2003). Today, features of high technology simulators are advanced and include breathing (normal and complicated), ophthalmic changes (pupillary dilation and constriction, eyelid opening and closing), cardiovascular (heart and Korotkoff sounds, pulses with variable intensity, and electrocardiogram rhythm monitoring), intravenous (IV) access, seizures, moving limbs, and bowel sounds. Communication through the patient simulator is often possible via pre-recorded or instructor narrated options. Some patient simulators may be paired with a compatible computer program to control these features (Laerdal, 2018).

For the purpose of this chapter, the term "patient simulator" will designate a full-body human patient simulator. Partial-body patient simulators will be referred to as "partial-task trainers." A description of partial-task trainers is provided below.

Partial-Task Trainers

Partial-task trainers, or task trainers, are a type of patient simulator, but rather than represent a whole patient, they are generally intended to represent a specific part of a human body for training a distinct task. Partial-task trainers include limbs, body parts, or other structures. These models may be integrated into training to facilitate learning of technical, procedural, or psychomotor skills (Bradley, 2006). Task trainers are available for teaching skills such as (1) injection technique; (2) assessment of vital signs; and (3) auscultation of body sounds. Partial-task trainers are not inherently low-technology. For instance, partial-task trainers for educating and assessment of cardiopulmonary resuscitation (CPR) may incorporate high-technology to measure rate and depth of chest compressions as well as accuracy of breaths administered during a Basic Life Saving (BLS) simulation. While generally considered

low-fidelity due to their nature and function, these simulation models are useful for high-volume simulation training, such as basic assessment skills involving vital signs. Partial-task trainers may be paired with other simulation methods such as standardized patients in hybrid simulations.

Computerized Models

Computerized simulation models include virtual reality and augmented reality. Virtual reality refers to the recreation of environments or objects as a complex, computer-generated image (Bradley, 2006). Virtual reality simulations require the use of a computer or computerized technology such as wearable goggles. Computerized models have recently grown to include: (1) virtual cleanrooms (Patel et al., 2011); (2) virtual patients for communication, patient assessment, and documentation training (Hussainy et al., 2012; Taglieri et al., 2017); and (3) electronic health records (Kirwin et al., 2013).

Hybrid Simulations

Hybrid simulations incorporate two or more simulation modalities. Hybrid simulations may be beneficial when more than one skill is being trained or assessed. An example of a hybrid simulation would include pairing an SP with a partial task trainer for assessing communication skills and accuracy of blood pressure measurement. Assessment of both skills would be difficult if employing only one of these modalities.

Simulated Learning Environment

A simulated learning environment is the physical area or location where simulation-based education and learning exercises occur. Development and utilization of a realistic environment may enhance the fidelity of simulation. A high-fidelity simulated environment allows for both profession specific and interprofessional education (IPE). Simulated environments will generally contain another form of simulation, such as SPs or patient simulators, and equipment and supplies appropriate for the fidelity of the simulation.

Current Uses of Simulation-Based Education for Teaching Clinical Skills

This chapter has alluded to significant changes to the practice and profession of pharmacy over the past few decades. The progression of pharmacy practice incorporates new skills beyond the traditional dispensing role of a pharmacist to the provision of clinical services. This section will describe examples of simulation training for a variety of skills for student pharmacists and practicing pharmacists, including: (1) clinical skills; (2) professional attitudes; (3) patient counseling and communication; (4) patient safety; and (5) IPE.

Clinical Skills

The emergence of pharmacist-delivered patient-centered care has generated new expectations of pharmacists in ensuring continuity of care as members of an interprofessional team. Accompanying roles of the pharmacist have progressed into more clinical services from medication reconciliation to disease state management. With this expanding role, student pharmacists should become more familiar with the different needs and expectations in both inpatient and outpatient settings. Serag-Bolos et al. (2017a) incorporated simulation to assess the knowledge and attitudes of third-year student pharmacists toward institutional pharmacy practice, specifically transitions of care. Students learned concepts of medication reconciliation, medication errors, and communication in an interprofessional team while using electronic medication records as the basis of their patient cases. Students reviewed their cases prior to the simulation and participated in an open discussion afterwards. By the end of the simulation, student pharmacists showed an increased ability of doing hospital pharmacy practice and felt more prepared for their fourth year rotations.

One of the earliest examples of SBE in pharmacy education was for teaching blood pressure assessment. Seybert and Barton (2007) assessed students' skills to accurately assess blood pressure on a patient simulator. Student satisfaction with the teaching method was also measured. Didactic lectures were used in conjunction with patient simulators for the training. Students practiced on the patient simulator at two time points prior to the final skills assessment. The ability of the students to measure blood pressure accurately, as assessed by a rubric, increased with each session. Vital sign assessment using simulation was also described by Tokunaga et al. (2010).

Pharmacy simulations focused on cardiovascular life support and resuscitation have been described in several studies. Mieure et al. (2010) described the design and implementation of an Advanced Cardiovascular Life Support (ACLS) workshop incorporating a patient simulator with didactic lecture and a calculation exercise. Participants reported an enhanced learning experience with the simulation exercise, but mean score on knowledge-based questions was only 25%. Bingham et al. (2015) assessed the long-term retention of knowledge and skills following prior ACLS training with a patient simulator. Teams were evaluated within 120 days of previous training. In this study, teams that included participants with prior simulation training demonstrated numerical, but not

significant, superiority in ACLS knowledge and skill retention compared to those without previous training. Maxwell et al. (2016) evaluated the impact of an ACLS simulation on pharmacy student knowledge and confidence. Both knowledge and confidence scores improved significantly post-simulation, but scores were not significantly correlated. In a related study, Davis et al. (2013) compared the improvement in ACLS knowledge, confidence, and satisfaction between high-fidelity simulation and lecture. This was a parallel, cross-over study between two groups. The sequencing of teaching and learning methods, lecture vs. simulation, differentiated the groups. The greatest improvement in test scores from baseline was observed in the group where lecture preceded the simulation. Overall, there was not a significant difference in improving knowledge of ACLS. Simulation participation was associated with higher self-confidence in ACLS skills and learning satisfaction. While these studies incorporated student pharmacists in their design, Eng et al. (2014) assessed the impact of high-fidelity simulation on pharmacy residents. A review of their institutions cardiopulmonary arrest algorithm, applicable medications, and calculations preceded participation in three simulated scenarios with patient simulators. Six-months after the initial training and three-weeks prior to the high-fidelity patient simulator enhanced training, pharmacy residents completed pre-simulation knowledge, competency, and confidence assessments. Post-assessments were completed three weeks following the simulation training with high-fidelity patient simulation. Post-simulation knowledge scores, competency evaluations, and confidences scores improved significantly.

Professional Attitudes and Behaviors

Simulation has also been used in healthcare education to assess attitudes and behaviors such as empathy and professionalism. Perdue et al. (2017) measured the effects of a simulation on medical, nursing, and pharmacy students' beliefs about adherence and concordance following a polypharmacy simulation. During the simulation portion of the curriculum, participants were provided a seven-day regimen of four simulated medications. Following the simulation, the majority of participants found it harder to take the medications than they expected, a decreased confidence in their ability to take their medications correctly, and an increase attitude toward the importance of concordance.

Blaszczyk et al. (2017) assessed the effects of a simulation exercise on student empathy toward polypharmacy. Participants were provided a one-week supply of eight prescriptions simulated with jellybeans and instructions for administration. Students completed a pre-and post-questionnaire to assess difficulty managing the medication regimen. Statistical analysis indicated a significant increase in empathy ($P < 0.001$) from pre- to post-simulation questionnaire responses. There was also a statistically significant change in students' perception that the simulated medication regimen was difficult post-simulation.

Simulation has also been utilized to assess attitudes and empathy of student pharmacists toward geriatric patients. Chen et al. (2011, 2015) incorporated an aging and geriatric medication game where students role-played older adults during simulated scenarios. They implemented a game, which encompassed the disabilities, limitations, and barriers in healthcare of the senior population. The simulation incorporated different workstations, including two physician's offices, a pharmacy, a laboratory testing area, and specific activities to reflect real-life settings of the older population. Students completed surveys on cognitive and affective qualities and empathy. Overall, the results from the instruments showed an increase in student empathy as well as attitudes toward geriatric patients and the challenges they face.

Zagar and Baggarly (2010) evaluated student perceptions about medication management difficulties in patients with low-vision. Students wore low-vision simulation goggles and engaged in medication management tasks such as reading prescription labels and patient information leaflets, distinguishing physical characteristics of medications, and measuring doses of liquid and injectable medications. These exercises created an opportunity for students to experience and subsequently recognize challenges faced by patients with low-vision.

Skoy et al. (2016) employed an auditory hallucination simulation to assess student empathy for patients with mental illness. Participants listened to an audio recording while completing several stations that required various skills. Participants completed the Kiersma-Chen Empathy Scale (KCES), a 15-item empathy tool for health professions students, immediately following the simulation (Kiersma et al., 2013). Empathy increased significantly ($P < 0.05$) on 13 of the survey items.

Patient Counseling and Communication Skills

Pharmacists have long been considered one of the most accessible healthcare professionals and are often a primary point of information and presentation of health-related issues. Pharmacists must be prepared and willing to respond to a variety of patient inquiries including knowledge of pharmacotherapy, skills related to medication administration, and use of ancillary devices. Salter et al. (2014) conducted a study using simulated patients to evaluate community pharmacists manage patients with anaphylaxis. Specifically their preparedness to treat acute anaphylaxis and their willingness to engage patients to discuss their anaphylaxis was measured. This study indicated pharmacists had a reasonable knowledge of anaphylaxis symptoms and emergency care, but had poor epinephrine auto-injector technique. Additionally, pharmacists rarely discussed action plans in case of anaphylaxis with the simulated patients.

Dolovich et al. (2007) evaluated pharmacists' ability to facilitate an asthma action plan with a simulated patient following an asthma education program versus pharmacists in a control group. The program included didactic material and progressed to self-directed learning and role-playing with simulated patients. There was a statistically significant difference in the ability to facilitate an appropriate asthma plan for pharmacists who experienced the simulation intervention compared to the control group (44.8% and 29.3% respectively, $P = 0.004$). Pharmacists in the intervention group also demonstrated better overall communication skills

compared to the control group (Dolovich et al., 2007). In a related study, Schneider et al. (2009) used simulated patients to examine assessment and counseling practices by community pharmacists in relation to over-the-counter asthma reliever medications. Of note, pharmacies included were unaware of the study. The study found that in the simulated patient visits, some form of assessment was performed 84% of the time but counseling was only provided 24% of the time. These studies indicate opportunities to improve processes and the delivery of care related to asthma in the community pharmacy setting.

Simulation has also been utilized to assess patient counseling related to emergency contraception (EC). Access to EC without a prescription has become more readily available over the past decade. This has created an opportunity for pharmacists to provide patient education regarding appropriate use. Ragland et al. (2015) described the impact of counseling by student pharmacists in a retail setting on customer knowledge of EC and customer satisfaction with counseling. Participants completed a pre-test prior to a counseling session with a student pharmacist, which was followed by an identical post-test to assess for changes in knowledge and a follow-up test via telephone 1–3 months post-counseling session. This study showed an increased score on both the post-test and follow-up test compared to pre-test scores indicating knowledge was improved and retained.

Glasier et al. (2010) conducted a study using mystery shoppers to evaluate the quality of service provided by community pharmacies and measure the information provided to patients in regard to EC. Their research indicated that patient consultation regarding EC was generally good, but less than half provided education about contraception following EC use.

Patient Safety and Medication Errors

Medication errors have been ranked as the eighth leading cause of death in the United States (Aspden et al., 2006). Medication errors, also referred to as preventable adverse drug events, are linked to additional healthcare costs and harm to the patient (Samp et al., 2014). Given the magnitude of this safety issue and the pharmacist's role as the medication expert, it may be inferred that pharmacy education should measure a student's ability to identify medication errors.

While systems have been developed and implemented to report and analyze incidents and trends in patient safety, under-reporting jeopardizes the validity of these analyses. Estimates suggest that only 10%–20% of errors are actually reported (Griffin and Resar, 2009). Simulation allows individuals to work individually and as a healthcare team to identify and resolve potential and existing threats to patient safety. Hamman et al. (2009) implemented in situ simulation in a labor and delivery ward and found the training was helpful in identifying and resolving latent environmental threats to patient safety. SBT could be beneficial in making personnel more aware of what and how to report patient safety incidents.

Daupin et al. (2016) designed a medication errors room for an interprofessional simulation including medical, nursing, and pharmacy staffs. The primary objective was to assess staffs' ability to identify errors associated with the medication-use system. Simulated situations covered an array of medication errors. Overall, 67.5% of the errors were detected. The rate of correct responses was lower at some stations, including: (1) y-site compatibility; (2) hand hygiene practices; and (3) use of personal protective equipment when administering hazardous drugs. Participants also identified errors that the researchers had not planned. The majority of participants felt the simulation was effective for identifying errors and relevant to their practice.

Atayee et al. (2016) developed a simulation for first-professional year student pharmacists to improve their ability to identify medication errors. The simulation focused on the top 100 prescription medications and students reviewed prescriptions individually and in teams. The number or correctly checked prescriptions was evaluated at two time points. In this particular study, there was no significant change in individual student scores between the two assessments, but group scores significantly increased from, 79.1% to 98.6%, *P*-value = < 0.001.

A study by Warholak et al. (2011) evaluated medication error identification rates by pharmacy, medical, and nursing students. Participants evaluated three prescriptions for accuracy and indicated the type of error, if found. Student pharmacists identified the medication errors at a significantly higher rate than the other student groups ($P < 0.001$) and more frequently identified the type of error correctly.

Interprofessional Education

Since the publication of, *To Err is Human* and *Crossing the Quality Chasm*, by the Institute of Medicine (Institute of Medicine, 2000, 2001), there has been a growing demand for a transformation of healthcare education through the expansion of IPE opportunities to create a collaborative approach to delivering patient care (Institute of Medicine, 2000, 2001; Interprofessional Education Collaborative (IPEC), 2011; World Health Organization (WHO), 2010). These reports recognized that healthcare providers could no longer operate in disciplinary silos and expect to optimize patient care. They identified simulation training as a potential strategy and mechanism to improve patient safety (Institute of Medicine, 2000, 2001). A number of organizations, including the World Health Organization, the Interprofessional Education Collaborative (IPEC), and the International Nursing Association for Clinical Simulation and Learning (INASCL) have published guidelines and frameworks to aid in creating and implementing interprofessional learning opportunities (World Health Organization (WHO), 2010; Interprofessional Education Collaborative (IPEC), 2011; Decker et al., 2015).

While students in healthcare schools may be provided with a description of other professionals' roles within the healthcare team they may not have the opportunity to experience and apply interprofessional teamwork skills during their education. Patient simulation may be utilized for teaching and promoting interprofessional communication and teamwork to improve patient safety.

Ragucci et al. (2016) evaluated the interprofessional team disclosure of a medical error to a simulated patient. Students from up to four different disciplines (medicine, pharmacy, nursing, and physician assistant) participated in team simulated interprofessional rounds. This article focused primarily on the pharmacy students but all disciplines participated. The patient had a medical condition (i.e., gastrointestinal bleed) due to a medication error. Teams were expected to identify and communicate the error with the patient. The results of the study are limited because pharmacy students participated in a workshop whereas the other students did not. Interprofessional simulations such as this may improve knowledge of interprofessional roles and expertise which may in turn may improve patient safety.

Vyas et al. (2012) developed a patient simulation experience, utilizing five patient cases in a hospital emergency department, using both standardized patients and high-fidelity simulators. The scenarios integrated specific patient safety issues, but varied between the cases. The pharmacy student on each team was expected to ensure the appropriateness of the patient's drug therapy. Over 90% of participants agreed or strongly agreed that the simulation had increased understanding of importance of interprofessional communication and understanding roles of other healthcare professionals. Interestingly, while students' reported the simulation had increased their ability to recognize and respond to patient safety issues, they did not report feeling more confident reacting to patient safety issues after the simulation.

The Team Strategies and Tools to Enhance Performance Patient Safety (TeamSTEPPS) communication training program, developed by the Agency for Healthcare Quality and Research (AHRQ) is designed to improve communication and teamwork skills and has been used by multiple professions (Agency for Healthcare Research and Quality (AHRQ), 2012; Robertson et al., 2010). Brock et al. (2013) described the impact of an IPE team communication simulation focusing on student attitudes, knowledge, and skills. Fourth-year medicine, third-year nursing, and second-year pharmacy students participated in a TeamSTEPPS module, which included didactic and simulation training in practice areas of adult acute, pediatric, and obstetrics. Pre- and post-assessments measured changes in attitudes, beliefs and opportunities around team communication. Significant differences were found for several attitudinal measures, including team communication, motivation, utility of training and self-efficacy as well as changes in TeamSTEPPS skills such as team structure, situation monitoring, mutual support, and communication.

IPE simulation was also described by Bordley et al. (2018) to enhance recognition of latent patient safety issues in the Intensive Care Unit (ICU). Medical interns, nurses, and pharmacists in the ICU participated in a rounding simulation incorporating the review of a simulated electronic health record. Cases contained five days of patient data and embedded patient safety events. This exercise demonstrates an additional opportunity for evaluating the performance of interprofessional teams.

Discussion

Due to the evolving nature of the profession of pharmacy there has been an increase in demand for clinically competent pharmacists. Incorporation of simulation into pharmacy curriculum provides the opportunity for pharmacy students to actively engage through innovative simulated experiences, which they otherwise might not have been exposed to during experiential education.

Simulation framework includes pre-briefing, stimulation scenario, and debriefing. Facilitators should aim to have specific objectives prior to designing scenarios as well as to provide reliable and valid methods of assessment. Barriers to successful implementation of simulated experiences include, but are not limited to, budgetary restrictions, logistics, and faculty development.

A variety of simulation modalities can be used in training healthcare professions. Simulation exercises should incorporate a degree of fidelity (i.e., realism of event or environment) and technology (i.e., equipment and devices) to facilitate a robust training opportunities. Simulation exercises may include the use of standardized patients, patient stimulators, partial-task trainers, computerized models, and hybrid stimulations.

Simulation exercises have been incorporated across training medical, nursing, and pharmacy students mapped to a variety of skills and skill sets. Several studies have demonstrated students' appreciation of these processes as a means to increase confidence and clinical skills via integration of simulated scenarios in clinical education. The use of simulation in pharmacy education continues to experience dynamic growth. In conjunction with this growth, evaluation of these modalities—including comparative efficacy studies—is necessary to establish best practices for enhancing learning through these approaches.

Glossary

Debriefing: A formal, collaborative, reflective process facilitated or guided by a facilitator within or following a simulation activity (Fanning and Gaba, 2007; Lopreiato et al., 2016).
Facilitator: An individual who is involved in the implementation and/or delivery of simulation activities (Lopreiato et al., 2016).
Feedback: The relaying of information back to a learner (Lopreiato et al., 2016).
Fidelity: The realism of the simulation scenario, e.g., high-fidelity and low-fidelity (Lopreiato et al., 2016).
Frame: The perspectives through which individuals interpret new information and experiences for the purpose of decision-making (Lopreiato et al., 2016).

Healthcare Simulation: A technique that creates a situation or environment to allow persons to experience a representation of a real healthcare event for the purpose of practice, learning, evaluation, testing, or to gain an understanding of systems or human actions (Lopreiato et al., 2016).
Interprofessional Education (IPE): When students from two or more professions learn about, from, and with each other to enable effective collaboration and improve health outcomes (World Health Organization (WHO), 2010).
Medication Error: A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use (National Coordinating Council for Medication Error Reporting and Prevention, 2018).

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Pharmacist Workforce Issues

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Introduction

When one thinks of pharmacy, several concepts come to mind. Medications, kinetics, drug metabolism, and delivery mechanisms are some of them. Only after a while does the image of a pharmacist appear; yet the pharmacists are a vital component of the healthcare system. Without pharmacists medications would be used haphazardly, patients would not be counseled effectively, and drug-discovery and drug-utilization scientific advancement would be virtually nonexistent.

Pharmacists' functions and practices are as diverse as their culture and skills. These in turn are shaped by social, economic, political, and administrative structures conditioned by idiosyncrasies and national/regional pride carved by historical developments. Despite the differences, however, a common denominator binds them: the responsibility bestowed upon them to provide pharmaceutical care for effective and safe drug treatment and therapy.

The purpose of this chapter is to analyze pharmacist workforce issues that emerge in response to this responsibility. The issues are imbedded into the worldwide presence and composition of pharmacists and an analysis of the demand for their professional skills. The issues are by no means exhaustive, but are intended to highlight the complexities of studying the global pharmacist workforce and the circumstances that bring practitioners together or set them apart.

Overview of the Global Pharmacist Workforce

According to the International Pharmaceutical Federation (2017), which periodically provides reliable information on the global pharmacist workforce, approximately 2.82 million pharmacists practiced their profession in 2017 in 74 countries and territories comprising 76% of the world's population. Practicing pharmacists represented less than 70% of licensed/registered pharmacists identified in the survey; no explanation was given for the inactivity of the remaining pharmacists, but one might venture to identify separation from the labor force (i.e., retirement, child and elderly care) and working in nonpharmacy venues as important reasons. About 75% of practitioners worked in community pharmacies, 13% worked in hospital pharmacies, and 12% worked in industry, wholesaling, research and development, academia, and regulatory activities.

Community pharmacy practice constitutes the heart and soul of the profession and the most visible resource for patients (Health Care Intelligence Pty Ltd., 2003; Peter Bacon and Associates, 1999). Most community pharmacists spend a substantial portion of their time dispensing medications, counseling patients, compounding, and engaging in pharmacovigilance activities. In a growing number of countries their jobs encompass identification, resolution, and prevention of drug therapy problems through the evaluation of medication profiles, provision of patient education, and assessment of drug adherence patterns; administration of disease management programs (i.e., diabetes, hypertension); and measurement of clinical parameters (i.e., blood pressure, blood sugar, and body mass index). In addition, community pharmacy administrators normally supervise and coordinate the services rendered by the pharmacy, manage the acquisition of drugs and related products, and address human resource issues.

Hospital pharmacists also have a broad range of functions. Since the pharmacy is responsible for the safe and effective use of medications administered to patients during their hospital stay, the pharmacist's role is critical. McCarthy and Schafermeyer (2007)

have identified three major types of activities conducted by hospital pharmacists: drug product distribution, patient care or clinical services, and administrative duties. Distributive responsibilities are associated with medicines and include order entry and verification, checking medication carts, supervision of technicians, and preparation of sterile products. Patient care or clinical services include overseeing drug therapy quality, monitoring patient progress, looking for cost-effective therapy alternatives, providing education to discharged patients, managing adverse drug reaction programs, responding to drug information inquiries, and communicating with other healthcare providers for therapy coordination. Besides dealing with personnel issues, administrative responsibilities include managing the hospital's medication budget and serving as the pharmacy representative on multidisciplinary hospital committees. Practitioners' participation in these activities is influenced by hospital size; in larger institutions the responsibility may be shared by various persons, while in smaller institutions one pharmacist may carry out all activities. The functions also are influenced by the structure of the healthcare system, the hospital-ambulatory care balance, and accessibility to hospitals by the population.

Availability of Pharmacists

The International Pharmaceutical Federation (2017) has reported that in 2017 the worldwide pharmacists' median density was 5.09 per 10,000 population. Regionally, density varied from 8.28 in Europe to 4.96 in the Western Pacific, 4.67 in the Americas, 4.28 in the Eastern Mediterranean, 2.31 in Southeast Asia, and 0.61 in Africa. It also varied by countries' median income level: 7.61 for high income countries, 4.91 for upper-middle income countries, 3.80 for lower-middle income countries, and 0.60 for low income countries. (Bates et al., 2016) have found a positive association among pharmacist density, gross national income, and health spending per capita. In many low income countries, where shortages of pharmacists prevail, pharmacists prefer practicing in urban areas where they can earn more income, thus resulting in even greater pharmacist shortages in rural areas (Goel et al., 1996; Simpson and Wilkinson, 2002; Smith, 2004).

The global composition by type of practice setting also varies by world region and country income level (International Pharmaceutical Federation, 2017). The largest percentages of community pharmacists are recorded in Southeast Asia (81.1%), Europe (78.5%), the Western Pacific (75.0%), and the Americas (68.0%), with only 39.1% in the Eastern Mediterranean and 37.4% in Africa. The largest percentages of hospital pharmacists are found in Africa (29.1%) and the Americas (25.6%), followed by the Eastern Mediterranean (14.1%), the Western Pacific (11.9%), Southeast Asia (9.2%), and Europe (8.9%). The Eastern Mediterranean and Africa report larger percentages of pharmacists working in settings other than community or hospital (46.8% and 33.4%, respectively) than the other regions.

Variation patterns in practice setting by country income group are not clear cut. In low income countries, community pharmacists account for 39.2% of the workforce; this fraction increases to 79.1% in lower-middle income countries and 84.7% in upper-middle income countries, but declines to 67.6% in high income countries. Such discontinuity is not surprising given the changing role of pharmacists in more developed countries. The proportion of hospital pharmacists drops from 29.2% in low income countries to 9.3% in lower-middle income countries and 4.4% in upper-middle income countries, but increases to 21.5% in high income countries. The incidence of pharmacists practicing in settings other than community or hospital is greater in low income countries (31.6%) than in high income (11.9%), lower-middle income (11.6%), and upper-middle income countries (10.9%).

These erratic patterns in practice setting composition call for a further probe into separate density variations of community and hospital practitioners. Again, the information is provided by the International Pharmaceutical Federation (2017). Europe reports the highest density of community pharmacists (6.26 per 10,000 population), followed by the Western Pacific (4.55), the Americas (3.26), Europe (3.06), the Eastern Mediterranean (2.78), Southeast Asia (1.73), and Africa (1.04); the global median density is 4.22 community pharmacists per 10,000 population. The density of community pharmacists by country income group is as follows: 5.66 for high income countries, 3.58 for upper-middle income countries, 3.29 for lower-middle income countries, and 0.92 for low income countries.

Hospital pharmacists exhibit a different regional pattern. With a global median density of 4.52 hospital pharmacists per 100,000 population, the Western Pacific shows the highest density (10.45), followed by the Eastern Mediterranean (6.57), the Americas (5.04), Europe (4.08), Southeast Asia (3.51), and Africa (1.80). High income countries exhibit by far the greatest density (10.05) followed by lower-middle income countries (3.24), upper-middle income countries (2.54), and low income countries (0.69).

Education Trends

Increasing the worldwide presence of pharmacists requires improving professional training capabilities. This translates into more pharmacy schools with more students in lower income countries. The number of pharmacy schools throughout the world in 2017 was estimated to be 0.46 institutions, with an average of 28.3 graduates, per 1,000,000 population, which was equivalent to 63.3 graduates per pharmacy school per year (International Pharmaceutical Federation, 2017). While the number of schools may be sufficient to meet population needs in most high income countries (Arora et al., 2015; Knapp et al., 2010; Taylor et al., 2013), low income countries, especially in Africa, lack adequate pharmacy programs or are unable to accommodate enough candidates. For example, according to a World Health Organization (2011) report, only 11% of applicants in Nigeria are admitted into the Bachelor of Pharmacy programs despite a widespread shortage of pharmacists and a density below 1 practitioner per 10,000 population.

In most high income countries pharmacy education has moved away from a basic natural-sciences focus to include clinical, healthcare, economic, social, and administrative components. The Doctor of Pharmacy (Pharm.D.) degree, with an expanded

curriculum and more years of training, has replaced traditional baccalaureate degrees in the United States, the United Kingdom, Australia, Canada, New Zealand, and several European countries (Jamshed et al., 2007). Although, some low and middle income countries have tried to adopt pharmacy education models from high income countries, formal assessments of need and adaptation success of the new programs are lacking (Babar et al., 2013).

Recently Australia, Canada, Ireland, the United Kingdom, and the United States have experienced massive expansions in institutions and enrollment (Hawthorne and Anderson, 2009; Health Care Intelligence Pty Ltd., 2003; Jesson et al., 2001; Peter Bacon and Associates, 1999), and there is concern that the growth may have detrimental effects on the labor market's ability to accommodate the absorption of newly graduates in the short run and the sustainability of the profession in the long run (Covvey et al., 2015; Walton et al., 2010). In the United Kingdom and the United States some regions are experiencing a surplus of pharmacists, which has motivated some practitioners to seek additional professional training (McCarthy and Weber, 2013) and led to the recognition of advanced practice beyond what is expected from general practitioners (International Pharmaceutical Federation, 2015).

Another trend worth mentioning has been a move toward an international pharmacy education market and migration from lower income to higher income countries. India, for example, educates its pharmacists with the aim of meeting international standards; its graduates are equipped to sit for competency examinations that allow them to work in the United States (Ghilzai and Dutta, 2007). In response to political and economic problems, African community pharmacists have migrated to higher income countries. Historically, South Africa and Zimbabwe have been responsible for the education and training of pharmacists in the Southern African region; their pharmacy schools prepare graduates to practice overseas, especially in English-speaking countries (Katerere and Matowe, 2003). This practitioners flow aggravates the shortages experienced by lower income countries.

The Role of Pharmacists

The World Health Organization (1997) and the International Pharmaceutical Federation have developed the concept of "the seven-star pharmacist." The seven-star pharmacist is defined as a key member of the healthcare team responsible for providing pharmaceutical care and fulfilling the roles of caregiver, decision maker, communicator, manager, life-long learner, teacher, and leader. According to this view, a well-rounded pharmacist interacts with patients as an integral part of the healthcare team, ensures safe and cost-effective use of healthcare resources, facilitates communication between patients and physicians or other healthcare providers, assumes a leadership role in the healthcare system, participates in learning activities along his/her career, and helps train future generations of pharmacists. Recently these roles have been expanded to include comprehensive, patient-centered, and outcomes-oriented health care. Pharmacy throughout the world is becoming an increasingly clinical, patient-facing profession, and pharmacists are being endowed with expanding responsibilities and accountabilities for pharmaceutical care in clinical and domestic environments (International Pharmaceutical Federation, 2015).

Beyond the traditional roles of dispensing, counseling, compounding, and pharmacovigilance, several advanced services are provided (International Pharmaceutical Federation, 2017). These include drug utilization review, reported by 68% of countries; management programs for chronic diseases, reported by 47% of countries; and measurement of clinical parameters, reported by 62% of countries. Yet in rural areas of low income nations, pharmacists are the only healthcare professionals available, and it is not uncommon for them to assume the roles of other healthcare professionals for the sake of patients.

Preventive health care and cost reduction have become increasingly important as patients worldwide assume more responsibility for their health. Because of their expertise, accessibility, and close interaction with patients, community pharmacists are in a unique position to expand preventive care services and improve population health. This is especially true for vulnerable and isolated groups such as families with low income or living in remote areas. Pharmacists help directly by offering preventive care services (i.e., immunization and screening) and indirectly by providing education and referrals to primary care for follow-up, testing, and treatment (Kelling et al., 2016). In the United States, for example, the proportion of pharmacists rendering immunization services increased from 15% in 2004 to 53% in 2014; in 2014 almost one-half of chain pharmacists reported offering health screening services (Gaither et al., 2015). Several studies suggest that pharmacist-delivered preventive care is both safe and cost effective (Ayorinde et al., 2013; Edwards et al., 2012; Higginbotham et al., 2012; Otsuka et al., 2013).

Medication therapy management is another area in which community pharmacists recently have expanded their functions. Medication management provided by pharmacists improves drug adherence and clinical outcomes (Fox et al., 2009; Isetts et al., 2006; Robinson et al., 2010; Welch et al., 2009) and reduces healthcare costs, especially for chronic-disease patients (Isetts et al., 2008; Wittayanukorn et al., 2013). In the United States the proportion of pharmacists providing medication therapy management services jumped from 13% in 2004 to 60% in 2014 (Gaither et al., 2015); furthermore, pharmacists' evolving role has expanded to include drug reconciliation, which improves patient outcomes and reduces healthcare costs by lowering the incidence of adverse medication events (Delate et al., 2008; Israel et al., 2013; Schnipper et al., 2006).

Hospital pharmacists' roles are rapidly evolving, too. According to the International Pharmaceutical Federation (2017), the most widely rendered services are providing medications and support to emergency departments (96% of countries), reporting drug-adverse reaction events (95% of countries), and participating in therapeutic committees (95% of countries). Hospital pharmacists also provide services to improve responsible utilization of medications, including implementation of quality assurance strategies to reduce medication errors and antimicrobial drug stewardship programs to promote adequate use of antibiotics. In 88% of countries, hospital pharmacists' roles include drug consultation to other healthcare professionals.

Having access to patients' shared healthcare records is a prerequisite for improving pharmaceutical care in hospitals; in about four-fifths of the countries surveyed, hospital pharmacists have access to these records. Unfortunately, hospital pharmacists' roles have not evolved as fast in other areas. Only 31% of countries report that hospital pharmacists provide services related to pharmacogenomics testing, and a handful of countries report pharmacists engaging in collaborative or independent prescribing. Hospital pharmacists are allowed to provide immunization services in only 26% of countries.

While pharmacists' roles have expanded in higher income countries, pharmacy practice models elsewhere experience an absence of standard practice guidelines, scarcity of pharmacists, and no separation between prescribing and dispensing (Azhar et al., 2009). The main obstacle to expanding pharmacists' roles in lower income countries is a ubiquitous workforce shortage. In some countries like Malaysia, prescribing and dispensing are not separate practices. Separation is desirable because it prevents exploitation of the sick, controls drug expenditure growth, and encourages appropriate prescription of medications, but it has not occurred in Malaysia due to the shortage of pharmacists (Tiong et al., 2016). Consequently, both physicians and pharmacists have the legal right and responsibility to dispense medications. Something similar happens in China; due to the shortage of pharmacists, hospitals are the main outlet for the distribution of medications. In 2009 Chinese hospitals accounted for about three-quarters of total medication sales (Huang, 2007; Sun et al., 2008).

Diversity in the Pharmacist Workforce

Workforce diversity produces good results; men and women, practitioners from different ethnic groups, younger and older, as well as society as a whole, gain when the workforce becomes more heterogeneous and its distribution resembles the composition of the population being served (Ash, 2008; Otto and Gurbey, 2006). Diversity fosters variety in perceiving issues, analyzing alternative courses of action, and creating divergent processes, thus broadening the range of options to deal with problems and conflicts. It also promotes programming and implementation choices that may not be available otherwise. Three sources of pharmacist workforce diversity are apparent: gender, ethnic group, and age.

Differences between men and women transcend physical appearance and biological functions. According to Maier (1999), when men strive for success they engage in competition to win; women are more interested in attaining balance in life. Men's purpose in communication is to find solutions, gain status, and attain independence, while women's main motivation is to establish links and search for intimacy. He also points out that men's leadership image is framed within a hierarchical setting, while for women the concept of authority has a more personal nature, determined by competence and expertise. This dissimilarity of views has a profound impact on the reactions by male and female pharmacists to social, economic, and administrative stimuli.

Social structures throughout the world assign household and childcare responsibilities disproportionately to women. Women are expected to work more than men at home, so many end up not working, or working fewer hours, in the labor market (Carvajal and Hardigan, 2008; Cunningham, 2008; Fogli and Veldkamp, 2007; Mott, 2000; Poeschl et al., 2006; Quesenberry et al., 2006); this often leads to lower wages and salaries, fewer promotions, and less accessibility to managerial positions (Ahituv and Tienda, 2004; Blasius and Pae, 2005; Rad et al., 2016; Report of the ASHP Task Force on Pharmacy's Changing Demographics, 2007). These conditions also increase the potential for discrimination by employers and unequal treatment by managers who may believe that female pharmacists are less productive at work than male pharmacists because of their domestic commitments. The essence of gender discrimination and unequal treatment lies in the systematic, overt or covert preference by employers and managers to hire men when faced with a choice between equally qualified male and female candidates. Gender discrimination sets a higher performance goal for women than men, and women who are able to accomplish those goals and end up being hired (or promoted) frequently perform better than their male peers.

Recently the global pharmacist workforce has experienced a substantial influx of women. In the U.S. almost two-thirds of graduating students are women (American Association of Colleges of Pharmacy, 2016), and 84% of female pharmacists were practicing in 2014 (Gaither et al., 2015). Similar trends are observed in other countries (Brown et al., 2006; Gardner and Stowe, 2007; Health Care Intelligence Pty Ltd., 2003). Although male pharmacists outnumber female pharmacists in African and Eastern Mediterranean countries, globally women account for 59% of practicing pharmacists (International Pharmaceutical Federation, 2017). Female practitioners tend to be younger than male practitioners, which suggests a continued gender restructuring of the pharmacist workforce in the near future, as retiring older pharmacists are replaced by younger female pharmacists (Health Care Intelligence Pty Ltd., 2003).

Another form of workforce diversity pertains to ethnic classifications. Race and physical appearance play a major role in segregation, but the concept of ethnicity is more comprehensive as it includes language, religion, heritage, cultural identity, and other symbolic representations that people use to differentiate between themselves and others (Bissell et al., 2003). When the characteristics that set groups apart weigh more heavily than the commonalities bringing them together, competition for political control and access to economic resources often ensues and leads to dominance of some groups over others. The latter are frequently called minorities. Ethnic classifications within countries and regions are vast and complex; it is difficult to establish generalizations. Unlike differences by gender and age groupings, which are observable virtually everywhere, ethnic distinctions and comparisons, as well as relations among ethnic groups, are characterized by unique conditions forged by the specific geographic setting, historical development, and cultural context of each country or region. Consequently, lessons learned from ethnic interaction in one location may not be applicable to other locations.

Probes into ethnic composition and interaction are important because of patient and economic outcomes. Several studies suggest that minority patients receive better quality care and are more satisfied when healthcare services are provided by ethnically similar

practitioners; ethnic resemblance is conducive to improving communication and generating trust (Collins et al., 2002; LaVeist and Nuru-Jeter, 2002; Vanderpool, 2005). Minority healthcare providers are more likely than their non-minority counterparts to practice in medically underserved areas (Baldwin, 2003; Smedley et al., 2004; Weeks and Wallace, 2006).

Ethnic identification also has economic repercussions because the choice of cultural self-identity is closely related to the acceptance of, and acculturation into, the professional and social norms of the dominant group. Insofar as different ethnic groups have different beliefs and values that govern attitudes and expectations, they normally are expected to behave differently. A cultural self-identity may or may not be used by a minority person to distance himself/herself from a minority group to improve his/her chances of being accepted into the dominant group. Acculturation brings forth some degree of acceptance by the mainstream, which usually opens up economic opportunities, but it bears an implicit cost; by adopting the cultural norms of the dominant group, practitioners may alienate themselves from their own ethnic communities (Bodenhorn and Ruebeck, 2003). An effective ethnic acculturation into the mainstream depends not only on minority practitioners' actions, but also on the dominant group's receptiveness and willingness to accept minorities.

Last, but not less important, are age-group workforce diversity patterns. Younger-versus-older pharmacist comparisons possess an important perspective, namely, the role that work plays in people's lives. Younger pharmacists often express an interest in working more hours; they want to pay off loans, form families, and build estates. At the other end, many older pharmacists choose to remain active in the workplace on a part-time basis, frequently reducing the number of hours or days of work to engage in activities consistent with retirement. The conditions experienced by them may be of little or no concern to younger pharmacists. Some common motivating factors for older pharmacists to seek employment while in retirement include earning additional income, avoid depletion of savings, fight boredom, validation of personal worth, and coping with unanticipated care of dependents (Teeter, 2004). Understanding the similarities and differences in motivation to work underlying the various stages of pharmacists' work lifecycles improves communication, increases satisfaction, and raises productivity (Carvajal and Armayor, 2015b).

Generational differences affect pharmacists' behavior beyond their motivation to work (Carvajal and Armayor, 2015a). In many societies older workers exhibit a work ethic characterized by clearly defined professional goals, long hours of work, and commitment to their employers; they consider work a very important part of their lives and frequently define themselves in terms of what they do. Younger workers tend to hold different values; they prefer autonomy and flexible work schedules, are more interested in family and friends than in material success, are oriented toward technological innovation, place emphasis on personal growth and creativity, are more open toward diversity, and view organizations with cynicism and contempt (Jovic et al., 2006; Kennedy, 2003; Shields and Shields, 2003; Smola and Sutton, 2002; Southard and Lewis, 2004; Washburn, 2000). Conflicts inevitably arise between the different sets of values. Many older practitioners view their younger peers' attempts to balance work and leisure as an erosion of work ethics and lack of commitment, while younger practitioners criticize their older counterparts as being too competitive, overly cautious, and loyal to their jobs beyond reason.

Pharmacists aged 30–45 years comprise the largest segment of the global workforce, and male pharmacists outnumber female pharmacists over 50 years old (Cohen et al., 2000; Hawthorne and Anderson, 2009; Health Care Intelligence Pty Ltd., 2003; Mott et al., 2006; Peter Bacon and Associates, 1999). In the United States and other higher income countries, workforce participation by older pharmacists is expected to remain at unprecedented high levels (Knapp and Cultice, 2007), although a substantial portion may continue to work only part time (Carvajal and Popovici, 2016). Managing an age-diverse workforce is not easy; employers trying to maintain safety standards and patient satisfaction while finding suitable replacements for turnover employees, especially those who retire, often are challenged by the interaction of workers of all ages whose diversity of values, attitudes, opinions, expectations, and behavior may bring conflict to the workplace and jeopardize operations.

Demand for Pharmacist Services

Employment opportunities reflect the labor demand for pharmacists. They are set by business firms and government in response to people's demand for goods and services sold in pharmacies and other places where pharmacists practice their profession (i.e., universities, research laboratories). Thus, the demand for pharmacists is a derived demand influenced by employer-established job requirements (i.e., qualifications, skills, experience, and productivity) subject to social expectations and regulations, such as licensure and continuing education (Gabriel and Schmitz, 2007; Sørensen, 2007). If there were no demand for pharmacists-produced goods and services, there would be no demand for pharmacists; by the same token, the demand for pharmacists grows when more people demand more services. Understanding this labor demand structure requires knowledge of the ongoing relationships between the organizational environments and the motives for providing pharmacist-related services within the constraints limiting the ways in which they are allowed to function.

Labor Demand Curves

A labor demand curve depicts the number of pharmacist hours one or more organization(s) is (are) willing and able to hire at different wage rates in a given location and at a given time. Movements along the same curve occur because of wage-rate changes. When the wage rate increases, pharmacist's hours become more expensive for employers and organizations respond by hiring less labor; when the wage rate declines, organizations respond by hiring more labor. Thus, pharmacists' demand curves are normally negatively sloping, indicating that the wage rate and the number of pharmacist hours hired by employers vary inversely with each other.

Displacements of the curve to the right or left occur due to changes other than the wage rate. When pharmacist labor demand curves move to the right, labor demand is said to increase; organizations are willing and able to hire more pharmacist hours at the same wage rate. Conversely, when labor demand curves move to the left, pharmacist labor demand is said to decline; organizations are willing and able to hire fewer pharmacist hours at the same wage rate. These displacements explain why two organizations or groups of organizations, or the same organization or group at different times, may hire different amounts of pharmacist hours while paying the same wage rate.

The global demand for pharmacists has risen in recent decades and is likely to continue rising, thus pushing the demand curve to the right (Okunade, 2006). Several factors account for this push, including changes in population size and composition, increases in national and personal incomes, the rising prevalence of chronic disorders, the development of new pharmaceutical products and technological innovation, and the evolving roles of pharmacists.

Changes in Population Size and Composition

More people demand more pharmacist services. According to the United Nations (2017), the world population in 2017 consisted of approximately 7.6 billion persons, and was expected to increase to 8.6 billion in 2030 and 9.8 billion in 2050. This amounts to a 29% growth over a 33-year period. Most of the recent and projected expansion can be attributed to a steady rise of the elderly age group due to increases in life expectancy. Abubakar et al. (2015) have estimated that worldwide life expectancy has increased from 46.5 years in the 1950s to 65.3 years in 1990 and 71.5 years in 2013. The global population 60 years and older is expanding faster than any other age group. In 2017, at an estimated 962 million persons, they accounted for 13% of the total; they are expected to increase, at approximately 2.5% annually, to 1.4 billion persons in 2030 and 2.1 billion persons in 2050 (United Nations, 2017). Europe is the region with the greatest percentage of elderly population (about 25%), while Africa records the lowest percentage.

In the United States medications are used more frequently than in any other country; over 80% of adults take some form of medication and around 50% take at least one prescription drug (Kaufman et al., 2002). Individuals 65 years or older consume twice as many prescription medications as the rest of the population; they also purchase 40% of all nonprescription drugs, almost three times their share of the total population. More than five out of every six persons in this age bracket suffer from at least one chronic condition (i.e., cancer, heart disease, Alzheimer's disease) that requires continuous treatment, and over one-half take three or more prescription drugs (Manassee and Speedie, 2007; Report of the ASHP Task Force on Pharmacy's Changing Demographics, 2007). These indicators account for an increase of 44% in the number of new prescriptions generated through physician offices and hospital visits during 2005–30. As long as the population continues to grow and the elderly percentage increases, the demand for pharmacist services will continue to rise.

Increases in National and Personal Incomes

Prescription drugs are normal goods (e.g., their demand changes in the same direction, but less than proportionately, with income). The worldwide secular rise in national and personal incomes is another reason to expect increases in prescription drug use and the demand for pharmacist labor. Vandegrift and Datta (2006) and Suraratdecha (1996) have reported a strong, positive effect of real per capita income on per capita prescription drug spending in the United States. Their findings suggest that private, out-of-pocket pharmaceutical spending is procyclical, namely, people spend more on medications during periods of economic expansion and spend less in recessions.

Other studies, however, show that public-health expenditures are countercyclical or acyclical in more developed countries, but procyclical in developing countries (Chen et al., 2013; Lane, 2003). In a study of financial crises in Argentina, Indonesia, Thailand, and the Russian Federation, The World Bank has identified procyclical drops in health spending; both per capita out-of-pocket and public-health expenditures declined substantially during the crises in each country, and it took several years to achieve precrisis levels of expenditure (Gottret et al., 2009; Thomas et al., 2013). In another study, Del Granado et al. (2013) have concluded that public expenditure on healthcare is acyclical in more developed countries and procyclical in developing countries, and a World Health Organization report examining healthcare system responses to 2008–13 crises in Europe has found that several countries restricted drug benefits, introducing or increasing user charges for prescription drugs (Thomson et al., 2014).

Rising Prevalence of Various Disorders

Another development leading to increasing medication use, and consequently greater demand for pharmacist services, is the rising prevalence of chronic disorders. One of these disorders, obesity, is associated with hypertension, Type II diabetes, cardiovascular diseases, and cancer (Must et al., 1999). According to the World Health Organization (2017), the obesity worldwide prevalence has trebled in the last 40 years, and one-third of the population is currently obese or overweight; countries in the Middle East, North Africa, Central America, the Pacific Islands, and the Caribbean report obesity and overweight rates above 40% (Ng et al., 2014a). The rise in the prevalence of obesity over the last decades is associated with a 75% increase in prescription drug spending (Sturm 2002; Vandegrift and Datta, 2006).

The global prevalence of diabetes has risen from 4.7% in 1980 to 8.5% in 2014 (Ng et al., 2014a); the fastest increases are reported by low- and middle-income countries (Mathers and Loncar, 2006). Cancer is another chronic disease, and it becomes more

prevalent as life expectancy continues to rise; approximately 14.1 million new cases are reported globally every year (Stewart and Wild, 2014). Smoking also is associated with multiple health issues and risks (i.e., cancer, cardiovascular diseases, Alzheimer's disease); smoking increases average medication costs by 28%–30% (Sturm, 2002). While the incidence of global smoking has declined due to widespread smoking cessation campaigns, the number of cigarette smokers has increased between 1980 and 2012 because of population growth (Ng et al., 2014b).

Development of New Pharmaceutical Products and Technological Innovation

Advances in medical technology allow a greater array of health problems to be treated more aggressively, along with the development of pharmaceuticals designed to treat conditions previously considered untreatable. Both trends increase longevity and quality of life. About one-third of countries report that pharmacists provide technological innovation services (International Pharmaceutical Federation, 2017).

A rapidly evolving field is pharmacogenomics testing, a form of precision medicine that explores how genes affect the human body's response to medications. Blood or saliva tests are conducted to assess whether a medication is effective for specific individuals, optimal dosage, and potential adverse effects. The US Food and Drug Administration includes pharmacogenomics information on the labels of about 200 drugs.

Europe lags behind the United States in the use of pharmacogenomics testing, but this situation may change in the near future as a new consortium aims to make pharmacogenomics testing a routine part of clinical practice (Just et al., 2017). The Ubiquitous Pharmacogenomics Consortium (U-PGx) is a collaborative effort of experts from ten European countries seeking to make effective treatment optimization accessible for every European citizen. It is conducting a study funded by the European Commission of the European Union to implement preemptive pharmacogenomics testing at seven healthcare systems across the continent by 2020. Testing already is being conducted routinely for a limited number of health disorders, and the accelerated expansion of pharmacogenomics-related treatment is expected to include testing in managing asthma, cancer, depression, and other conditions.

While hospital pharmacists' role in pharmacogenomics testing is clear, its application is expected to pervade community pharmacies as well. There are already several laboratories in the United States working directly with pharmacists to offer testing in community pharmacies, and the trend is expected to rise. With greater contributions by pharmacists, demand curves will likely shift to the right.

Another innovation affecting the demand for pharmacist services is the emergence of mail/Internet-ordered distribution of prescription drugs, which is becoming increasingly popular in higher income countries whose physical infrastructure can support this practice. In the United States Internet/online pharmacies started operating in the 1990s. Websites such as Drugstore.com provide prescription-drug services using Internet-based platforms to fill prescriptions that are delivered to patients by mail. This practice has flourished over the last 20 years, and today mail-order and Internet pharmacies account for approximately 20% of total retail medicine sales. They are used mostly by patients with chronic disorders who take drugs on a continuous basis (IMS Institute for Health Informatics, 2011). About 30% of chronic-disease prescriptions in the United States are filled by mail, replacing a substantial portion of the local retail-pharmacy medication distribution system and shifting to the left the demand curve for pharmacists. The mail-order and Internet pharmacies business is likely to continue expanding for two reasons: they are price competitive and they are appealing to younger patients, who feel comfortable purchasing goods and services online.

Other Considerations

The demand for pharmacist labor is projected to grow in the near future based on four basic forecasts: a global ageing population requiring more health care, especially because of the rising prevalence of various disorders; a wealthier population that can afford more and better healthcare services; advances in medical technology that continue to reduce both morbidity and mortality and improve patients' quality of life; and diversification in the roles that pharmacists play to make patients' lives better. These additional roles were addressed in the previous section of this chapter–drug utilization review, disease management programs, measuring clinical parameters, rendering immunization services, providing education and referral to primary care providers, monitoring medication adherence and therapeutic response to drugs, medication reconciliation, informatics, and collaborative team-based care, among others (Avalere Health, 2014; International Pharmaceutical Federation, 2017).

In some countries competition in the community pharmacy marketplace has led to the coexistence of chain and individually-owned pharmacies. Philipsen (2014) argues that whenever chain pharmacies are allowed to exist (e.g., the Baltic States, Belgium, Ireland, the Netherlands, Poland, the United Kingdom, and the United States), the average price of medications drops. The shift from independent to chain pharmacies also increases the demand for practitioners; chain pharmacies need more staff because their employees work fewer hours, thus requiring more practitioners to serve each store. In addition, whenever permitted to do so, chain pharmacies commonly expand hours of operation, which further raises the demand for pharmacists.

Conclusions

The issues reviewed in this chapter reveal the intricate nature of worldwide pharmacist workforce analysis. Despite obvious social, economic, and political differences across continents, practitioners and researchers address multiple common concerns: the

expanding roles of pharmacists, the demand for pharmacists' services, the emergence of new products and therapies, and the changing needs of populations being served, to name a few. Regardless of cultural setting, availability of resources, or technological infrastructure, these issues affect the way pharmacists practice their profession. It is important to understand that pharmacists' mission, to provide pharmaceutical care for effective and safe drug treatment and therapy, constitutes a common bond that transcends language, practice site, and other specifics, and unites practitioners and researchers into a clearly identified profession and an essential component of healthcare-providing teams.

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Pharmacometrics and its Application in Clinical Practice

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Background

Ensuring the five rights of the medication use, that the right patient receives the right drug in the right dose at the right time and by the right route is classically included in the clinical decision making (CDM) goals of the pharmacist (Reynolds and Rupp, 2017). Once the choice of drug has been made, the process of the decision making shifts the selection of dosage regimen, which is governed by the pharmacokinetics of the drugs and the intended therapeutic goals. Variations in the patient's physiological conditions by factors like age, ethnicity, gender, and presence of other conditions like concomitant drugs or a disease state can alter the pharmacokinetics [i.e., absorption, distribution, metabolism, and elimination (ADME)] of the drug and hence can affect the amount and the rate at which the drug is available to the target site in the body. Identification of the factors that affect these key pharmacokinetic parameters and provision of an easy to use mathematical equation are crucial aids in CDM for selecting an individualized/optimized dosage regimen for the patient. This optimization of the dosage regimen is targeted at ensuring the safety and efficacy of medicine by keeping the drug levels in its therapeutic window (i.e., within the minimum effective and toxic concentrations).

The pharmacokinetics of drugs may be influenced by a variety of pathophysiological conditions, which can alter the renal and hepatic functions of the patients and ultimately affecting the drug activity. Patients with augmented renal or hepatic clearance (as in case of increased cardiac output in early state of severe sepsis) are at increased risk of subtherapeutic plasma concentrations which may result in therapeutic failure. On the other hand, patients with decreased renal or hepatic clearance (which can occur in case of end stage-organ dysfunction) are at risk of drug accumulation and toxicity (Taccone et al., 2011; Varghese et al., 2011). This problem becomes more pronounced in case of narrow therapeutic index drugs as slight change in dose can lead to either toxicity or therapeutic failure.

In addition to other factors, age is also an important factor for drug clearance because renal and hepatic functions decrease progressively with increasing age (Verhave et al., 2005). Therefore, the kidney and liver status must be considered for maintaining plasma concentrations of drugs at the required level in order to achieve therapeutic success on one side and also to ensure safety and cost effectiveness on the other side. Ethnicity can also be linked with modified pharmacokinetics of drugs as the distribution of cytochrome P450 (CYP450) isoenzymes is varied among people of different ethnic origins. For example, the occurrence of warfarin toxicity prevails more in white as compared to black individuals due to poor metabolism through CYP2C9 enzyme. Similarly, the risk of angioedema associated with angiotensin converting enzyme (ACE) inhibitors is high in black Africans (McDowell et al., 2006). Genetic variation among individuals for the metabolism of warfarin has also made it a target for pharmacogenetics research. In 2007, the US Food and Drug Administration (FDA) advised a lower initial dose of warfarin in patients with certain genetic variability (Laurence, 2009). Therefore, individualized dosage regimen is necessary for safe and effective administration of

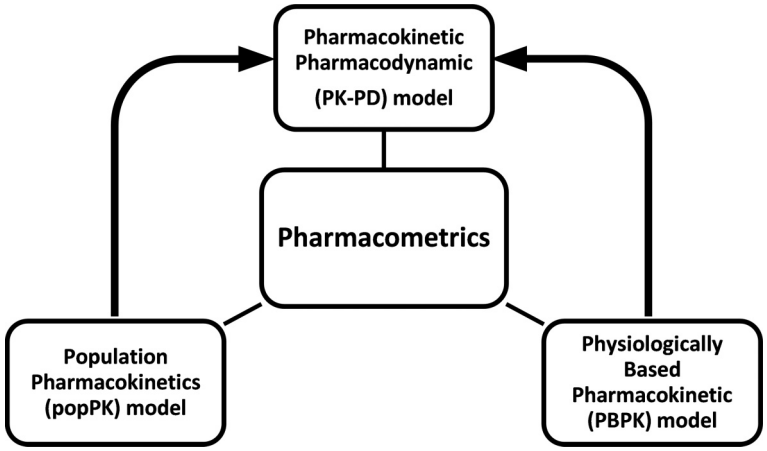

Figure 1 Components of pharmacometrics.

drugs. The selection of rational dosage regimen for individual patient is also inevitable for antibiotics, because subtherapeutic levels of antibiotics can cause development of resistance by pathogenic bacteria.

Pharmacokinetic modeling approaches such as physiologically based pharmacokinetic (PBPK), population pharmacokinetics (popPK), and pharmacokinetic/pharmacodynamic (PK-PD) can help in provision of critical information needed for the CDM regarding dosage regimen. As stated earlier, the information includes identification of physiological or genetic factors which have influence on pharmacokinetic parameters and derivation of the mathematical expression through which the drug dosage can be calculated. The advancement in the field of pharmacometrics is a key tool to establish this relationship and can be useful for tailored dosing through simulation of different dosage regimens.

Introduction to Pharmacometrics

The development in the field of pharmacokinetics accelerated greatly due to the availability of computer applications and advancement in the field of bioanalysis. The complex calculations of pharmacokinetic parameters are simplified by different software programs which allow rapid pharmacokinetic modeling and quick solutions to complex equations. Moreover, these software are also used for designing experimental studies, statistical analysis of data, graphical interpretation of results, dosing simulations, and prediction of drug effects (Shargel and Yu, 2015). The term "pharmacometrics" was first used in 1982 by *Journal of Pharmacokinetics and Biopharmaceutics* and can be briefly described as the science that deals with the use of computer programs to work with mathematical and statistical models in order to characterize, understand, and predict the pharmacokinetic, pharmacodynamic, and biomarker outcome behavior of drugs (Ene and Ette, 2007). This is a relatively new bridging science that describes the PK-PD behavior of drugs by the application of quantitative models representing pharmacology, physiology, and disease progression in relation to the effects and possibility of adverse drug reactions in patients (Barrett et al., 2008). The Division of Pharmacometrics has become an important part of regulatory affairs for decision making and establishing the product labels in new drug applications (NDAs) in US FDA (Gobburu, 2010). The modeling approaches in pharmacometrics are shown in Fig. 1.

The commonly used software available for pharmacokinetic modeling and simulation are listed below:

- NONMEM® 7.4 by ICON
- Phoenix WinNonlin NLME™ by CERTARA
- Simcyp® by CERTARA
- PK-Sim® by BAYER, Germany

Physiologically Based Pharmacokinetics

Pathophysiological changes due to chronic diseases could have significant effects on the pharmacokinetics of drugs, requiring the need for modification in drug therapy (Boucher et al., 2006). It is essential to state that most patients with chronic diseases are mostly suffering from multiple comorbidities. The development of drug-disease models due to the advancements in the field of PBPK modeling as well as the quantitative understanding of disease-related physiological changes, can be helpful in predicting the pharmacokinetic impact of these changes (Sayama et al., 2014). The major advantage of PBPK model is that it can be extrapolated to other populations and conditions (Tsamandouras et al., 2015). Therefore, a PBPK model that is developed for healthy individual with normal physiology can be modified according to the pathophysiology of a disease.

The developed PBPK model after incorporation of diseased condition, can be extended to a wide variety of drugs and can also be extrapolated from adult patients to special populations such as children and elderly (Rasool et al., 2015). Furthermore, the pharmacokinetics of drugs can also be altered due to incorporation of artificial organs to patients with organ failure such as extracorporeal membrane oxygenation (ECMO), which provides cardiac and pulmonary support to critically ill patients with cardiorespiratory failure. The PBPK models are also flexible to include the artificial organ as additional compartment and can be utilized to predict the change in pharmacokinetics of drugs for ultimate application to dose optimization (Watt et al., 2018).

Population Pharmacokinetics

Population pharmacokinetics is the study of variability among individuals with respect to drug concentrations after the administration of clinically relevant dosage regimens (Aarons, 1991). The selection of dosage regimen is most important for safe and effective use of drugs in a target patient population or more specifically in an individual patient (Joel and Owen, 2014). Population pharmacokinetic models are utilized for the construction of dosing strategies and play an important role for safe use of drugs (Ette and Williams, 2004). A sufficient number of samples are required to perform the traditional pharmacokinetic analysis whether the analysis is simple calculation of pharmacokinetic parameters through nonlinear regression or estimation of noncompartmental parameters on an individual subject basis. The population pharmacokinetic modeling approach extends the traditional individual subject model by addition of models that take into account the sources and magnitude of interindividual variability in model parameters and also the intraindividual variability within an individual (Joel and Owen, 2014). The pharmacometrics model parameters are of two types:

- Fixed effect parameters
  Fixed effect parameters are the model elements that take a particular or a scalar value. In a pharmacokinetic model, these represent the average population parameters such as clearance and volume of distribution (Kiang et al., 2012).
- Random effect parameters
  Random effect parameters are related to population models and include the interindividual variability on specific pharmacokinetic parameters as well as the errors that are related to the sampling and bioanalytical techniques.

Nonlinear Mixed Effect Modeling

The development of Nonlinear Mixed Effect Modeling (NONMEM®) software has tremendously enhanced the ability to analyze sparse data, to pool and analyze data from different studies and experimental conditions, and also to simulate new dosage regimens and conditions of drug use. The ability to analyze sparse data was a strong motivational factor for the development of NONMEM® approach, because the patients for whom dose selection is critical are frequently the ones from whom data collection is difficult. With the development of NONMEM® software in 1980s (Sheiner and Beal, 1980), population pharmacokinetic analysis has become extremely useful not only for the development of new drugs (Stone et al., 2010), but also for the improvement of already approved drugs (Zandvliet et al., 2008). Although other modeling software are also available, NONMEM® is still considered as gold standard in pharmacometrics (Keizer et al., 2013).

Use of NONMEM® for Population Pharmacokinetic Modeling

The major components of this system are NONMEM® the engine, subroutines for the PREdiction of Population Pharmacokinetic parameters (PREDPP) and NonMem TRANSlator (NM-TRAN). The estimation of parameters is governed by NONMEM® through FORTRAN subroutines. Multiple prewritten subroutines are available in PREDPP library for most of the common pharmacokinetic models. However, these subroutines can be customized according to specific needs of the modeler (Joel and Owen, 2014). The NM-TRANS provides the language used by modelers for model specification and interaction with the system (Beal et al., 1989–2011). The basic steps for the development of popPK model are described below (Joel and Owen, 2014). The schematic diagram for popPK modeling is presented in Fig. 2.

Analysis Planning

Data analysis planning (DAP) is a very important step in any kind of data analysis and modeling. In pharmacometrics, it is critical to complete this step before the start of actual modeling process in order to increase the credibility of the model to the reviewers. A good DAP provides a detailed information about analysis procedures and results interpretation and it should enable two independent modelers to come to the same conclusion after following the plan.

Dataset Creation

The construction of a dataset should be done before the actual modeling work. A pharmacometrics dataset is a complex set of information arranged in a format that is compatible with the software. The dataset usually requires the information of

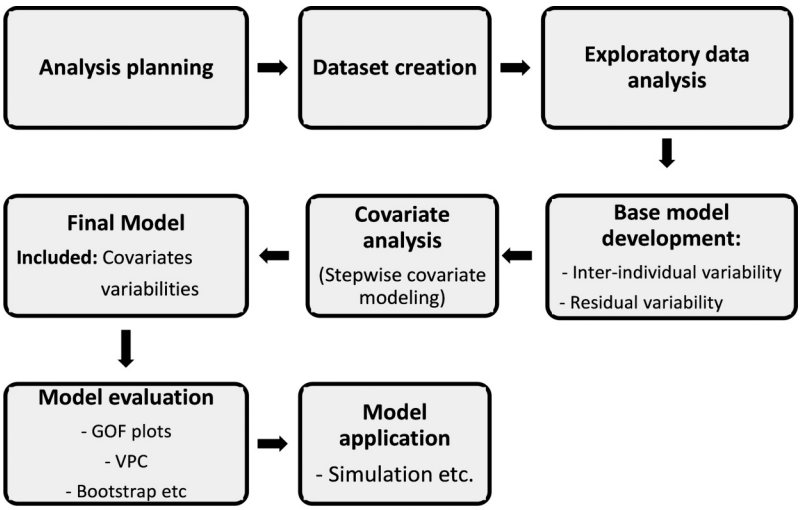

Figure 2 Schematic plan for population pharmacokinetic modeling.

dosing events, plasma concentration-time data, and patients' demographics (e.g., age, body weight, height, gender, etc.). Different data management packages can be used for generating data files which include spreadsheets, text editors, or programming languages such as SAS (Statistical Analysis Software) or R (R development Core Team 2013). A quality control review of the dataset with focus on individual fields and a structure of dataset should be performed when the dataset is not created by the modeler.

Exploratory Data Analysis (EDA)

Prior to running the initial model, an exploratory review of the data should be performed with the help of graphical and tabular summaries in order to explore the relation between the information available and the models to be evaluated. These summaries may also help in identifying extreme values in datasets, obvious trends in data, and outliers required for exclusion. The large complicated datasets can be analyzed by different scatterplots, boxplots, and frequency distributions of population related, dose related, and concentration related data to get the understanding of the available information in the data.

Development of Base Model

After getting the complete information of the dataset to be used for population pharmacokinetic modeling, model fitting may be started with a simplest model in order to portray the overall nature of the data, then proceeding to more complex model as long as more variability is explained and more information is gained. Therefore, the base model can be defined as the model that can appropriately describe the basic pharmacokinetic characteristics including between subject variability estimation on limited parameters and residual variability by using the simplest error model. Usually, a base model does not contain the influence of any covariate on pharmacokinetic parameters. However, the covariates with highly significant influence are necessary to obtain a base model. Several model diagnostic plots can be used to interpret the results of model fit. A table file is generated by NONMEM® after the successful run which includes the values of dependent variable (DV), population predictions (PRED), individual predictions (IPRED), residuals (RES), and weighted residuals (WRES) in addition to requested values. DV is the value of observed concentration included in the dataset. PRED is the model-predicted concentration of population corresponding to DV. The IPRED is the predicted concentration calculated once the effect of individual-specific random effects is taken into account. The RES is the difference between DV and PRED and is calculated as:

$$RES = DV - PRED \tag{1}$$

If the value of RES is positive, it indicates the points where the population concentrations are underpredicted (DV > PRED) and negative values represent the points of overestimation of PRED (PRED > DV). The WRES is the weighted difference between DV and PRED (Hooker et al., 2007). This can be calculated as:

$$WRES = \frac{DV - PRED}{\text{Residual error}} \tag{2}$$

Hooker et al. in 2007 (Hooker et al., 2007) illustrated that WRES are calculated by First Order (FO) approximation even if First Order Conditional Estimation (FOCE) method was used for estimation purpose which can lead to misguided diagnostic plots. They introduced conditional weighted residual (CWRES) which is calculated by using FOCE method and is a more appropriate model

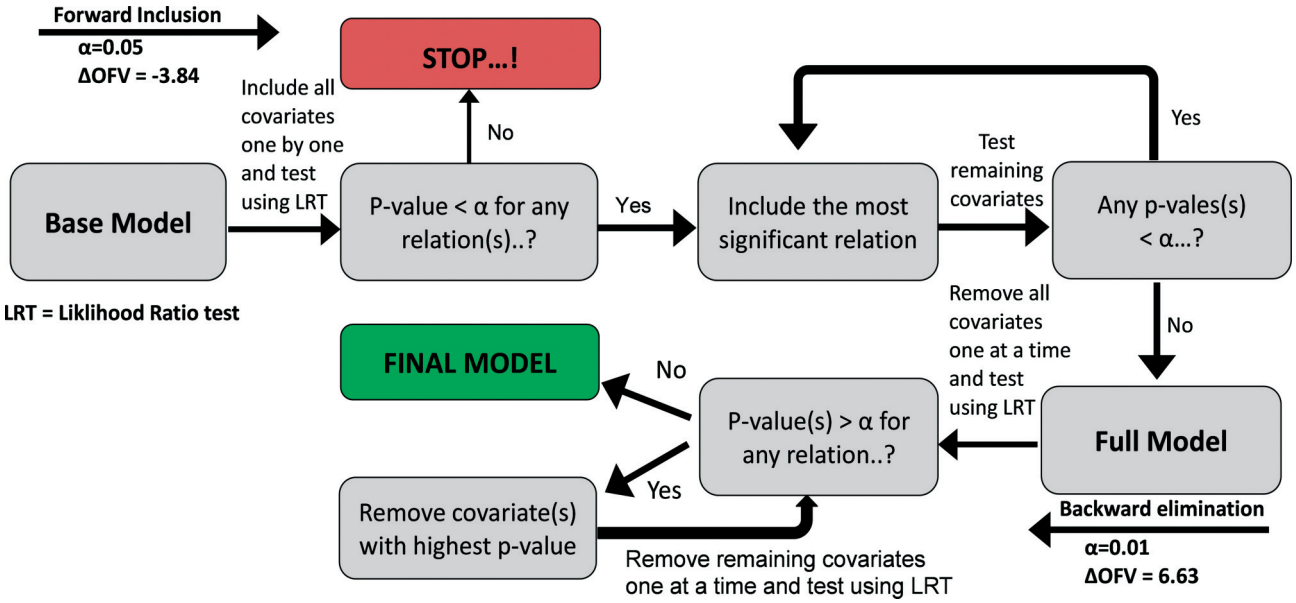

Figure 3 Stepwise covariate modeling—a forward inclusion process followed by a backward elimination process. Source: Adapted from NONMEM Workshop held in Köln, Germany on 11–12 Oct. 2014. Courtesy Dr. Ahmed Abbas Suleiman.

diagnostic for model performance. Moreover, CWRES can also be calculated by FO method combined with a post hoc step. The value of CWRES should be equally distributed around a mean 0 and are expected between −3 to +3, higher values indicate worse fitting points (Joel and Owen, 2014).

Covariate Analysis

Many methods describe the process for the evaluation of between-subject and within-subject variability with respect to patient-related factors. A covariate can be described as a patient specific variable that can influence the pharmacokinetics or pharmacodynamics of drugs and can be categorized as continuous covariates (age, weight, height, etc.), dichotomous covariates (e.g., gender), or polychotomous covariates (race, smoking habit, etc.) (Bonate, 2011). The influence of a covariate on the improvement of a model can be measured by several ways. The most desirable tool for decision making is the statistical measure of improvement in model. The addition of the influence of a covariate to the model must decrease the objective function value (OFV = −2 × log of likelihood; −2LL) to a significant level. The selection of the covariates in final model can be made by stepwise covariate modeling (scm) on the basis of forward inclusion process and backward elimination process. During forward inclusion, all the covariates are added one by one and a covariate is included to the model if a significant ($P < 0.05$) drop in OFV (≥3.84) is observed between two nested models after inclusion of that covariate. The importance of included covariates should be reassessed by backward elimination process by using a stricter criterion ($P < 0.01$) in which a covariate is removed if a significant increase in objective function value (ΔOFV ≥ 6.63) is not observed after elimination of that covariate. The resulting model can be considered as the final model. Fig. 3 illustrates the scm.

Model Evaluation

Model evaluation is the assessment of its predictive performance or the determination of model deficiencies on substantive conclusions (Yano et al., 2001). The FDA guidance for population pharmacokinetics describe several methods for model validation which include internal and external validation, assessment of predictive performance, objective function evaluation, goodness of fit plots, bootstrapping, visual predictive checks, etc. (Food and Drug Administration, 1999).

Internal validation

Internal validation procedure should be planned carefully and should be described in DAP. For internal validation, a randomly selected portion of dataset (validation dataset) is set aside and model development should be performed with remainder dataset. After the development of final model, it should be used for the prediction of observations in the validation dataset in order to observe whether the model is appropriate for the characterization of data (Sheiner, 1982).

External validation

In external validation procedures, the developed model is validated against the validation dataset similarly as in internal validation. The difference is the source of validation dataset which is obtained from a study independent of the study used for model development.

Predictive performance assessment

The predictive performance of models can be assessed by using easy statistics by comparing the observed values in a validation dataset to the model predicted values in order to assess the bias and precision of the model (Sheiner and Beal, 1981). This can be performed by calculating the prediction error (PE) as follow:

$$PE_j = pred_j - obs_j \tag{3}$$

where $pred_j$ is the predicted value and obs_j is observed value of jth individual. The positive and negative values of PE indicate the overprediction and underprediction by the model, respectively. The overall bias in the model can be predicted by calculating the mean prediction error (MPE) in which the mean of PE are calculated as:

$$MPE = \frac{\sum(PE)}{N} \tag{4}$$

where N is the total number of observation. Similar to PE, MPE is also either positive or negative indicating, overprediction or underprediction respectively. The positive or negative signs from the PE can be removed by calculating absolute prediction error (APE) as;

$$APE_j = |PE_j| \tag{5}$$

For expression of these statistics in percentage units, it should be mentioned whether the percentage is calculated relative to observed value or predicted value. Eq. (6) shows the calculation of mean absolute prediction error (MAPE).

$$MAPE = \frac{1}{N}\sum_{j=1}^{N}\left[\left(\frac{|pred_j - obs_j|}{obs_j}\right)\times 100\right] \tag{6}$$

A prior criteria (e.g., $<\pm$10% for MPE and $<$25% for MAPE) must be mentioned in the analysis plan in order to assess the model validity.

Goodness of fit plots

Goodness of fit (GOF) plots are the analysis of the different scatterplots based on their graphical nature or by use of metrics in order to demonstrate the validity of a model. The most common parameters used in diagnostic plots include DV, PRED, IPRED, RES, WRES, and CWRES. The commonly used diagnostic plots described in literature are as follow:

- DV versus PRED
- DV versus IPRED
- CWRES versus PRED
- CWRES versus Time after Dose

Bootstrap analysis

Internal validation of a model by using a validation dataset, where a portion of dataset is kept aside, may prove ineffective when only limited data is available for modeling (Parke et al., 1999). Bootstrap is another technique used for internal validation of the model with the advantage of using the entire dataset. It involves creation of multiple new datasets of the same size as an original dataset, with different combinations of the subjects, by intensive and effective resampling from original dataset and fitting the model to each dataset in order to assess the accuracy of parameter estimation in a wider population (Parke and Charles, 2000). A large number of datasets are generated by repeating this process for many hundreds or thousands of times (at least 500 times) (Joel and Owen, 2014). The FDA proposed at least 200 replicates (Food and Drug Administration, 1999). The summary statistics (median, mean, maximum, minimum, and 95% confidence interval based on 2.5th and 97.5th percentile of distribution) are calculated for each parameter across the bootstrap estimates and compared with the final parameter estimates of the original model in a tabulated form (Joel and Owen, 2014). The convergence criteria for acceptability of bootstrap should also be specified in the analysis plan (e.g., 945 samples successfully minimized out of 1000 samples indicates 94.5% rate of convergence). In addition to the comparison of bootstrap and final model parameter estimates, a predefined convergence criterion should also be met for the acceptance of bootstrap results (Joel and Owen, 2014).

Visual predictive checks

Karlsson and Savic in 2007 proposed the visual predictive check (VPC) procedures for model evaluation. The theory behind this technique is that if the model is a correct description of data, then the simulations performed on the basis of developed model will produce a very similar simulated data as the original data used for the model development (Karlsson and Savic, 2007). This means that the plasma concentrations of a patient are simulated for hundreds or thousands (usually 1000) of times and then compared with the original observations. Typically, the results of VPC are presented graphically where the median and the 5th and 95th percentile (90% CI) of the simulation are shown in a graph with the observed data. If the observed data are within the simulated percentile, the predictive power of the model can be considered as good (Post et al., 2008).

Table 1 Advantages of NONMEM

1.	Data originated from patients in clinical settings
2.	Involves diverse demography and patient profile variation
3.	Accounts for concomitant drug and disease
4.	Noninterventional
5.	Sparse data including TDM
6.	Ideal for neonates, children, and geriatrics
7.	Useful for understanding pharmacokinetics of orphan drug
8.	Provides a clinically applicable expression for dose correction
9.	Devoid of ethical issues related with interventional studies and clinical trials

Model Application

A normal extension of a developed model is its use for simulation to get the answers of various questions regarding study design conditions. The simulation conditions are used to find the effect of these conditions on study outcomes which are further used for subsequent decision-making regarding clinical aspects (i.e., dose optimization) or regulatory affairs (i.e., drug approval) (Joel and Owen, 2014). The scope of this chapter is restricted to the role of pharmacometrics in CDM, discussed in the following section.

Advantages of NONMEM

Table 1 shows the key advantages of pharmacometrics over the conventional PK data originated from clinical trials.

Role of Pharmacometrics in Clinical Decision Making

The role of pharmacometrics in CDM is pivotal. It can also be used in dose optimization for individual patients and for prevention of adverse drug reactions and drug interactions through pharmacokinetic modeling. In modern practice, computerized decision-making systems known as clinical decision support systems (CDSS) are used for ensuring incorporation of critical information on clinical decisions (Sim et al., 2001). Fig. 4 describes how the patient data can be modeled using popPK to identify risk factors and then feeding this information to the CDSS can enhance the achievement of intended kinetic profiles avoiding therapeutic failure and

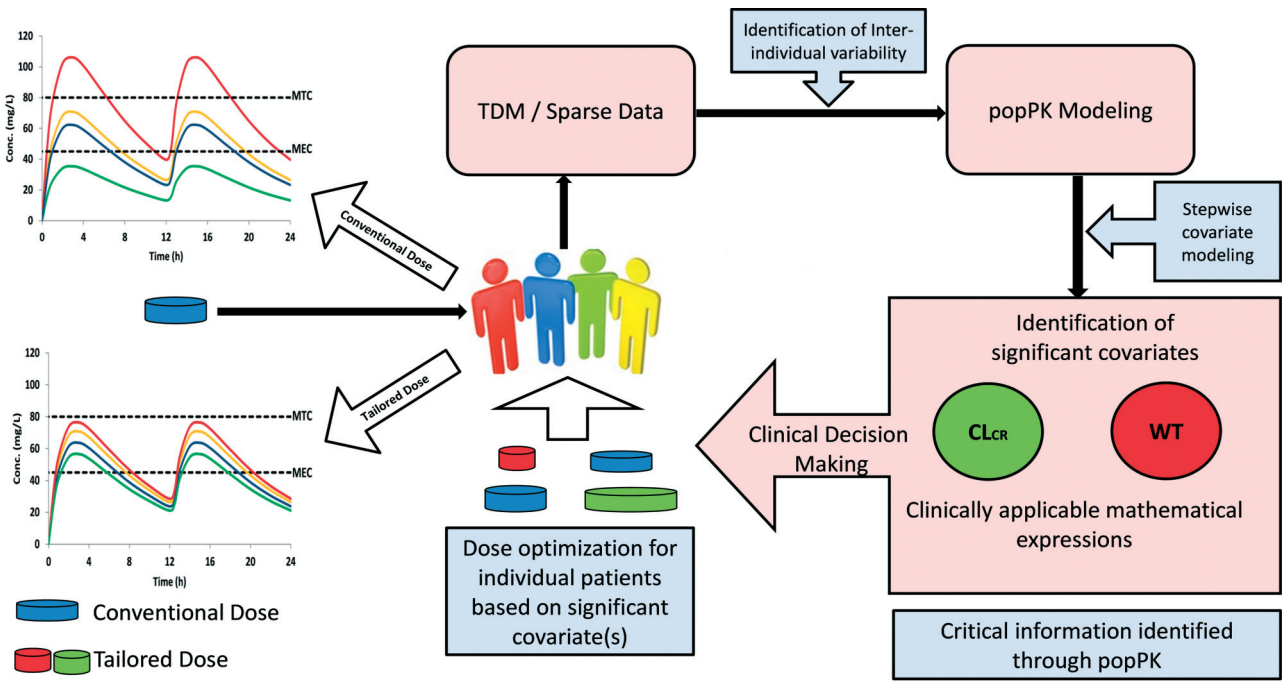

Figure 4 Schematic flow showing patient data using conventional dosing (*solid blue line*) and its application to produce information for use in clinical decision-making systems and the expected outcome.

toxicity. CDSS are used for prescription alerts on the dose adjustment for the potentially toxic medicines like anticancer drugs in case of renal impairment (Krens and Damhof, 2016).

Dose Optimization

The term "precision medicine," as described by the US FDA, is an innovative approach for the prevention and treatment of diseases by taking into account the variability among individuals based on genetic makeup, lifestyle, and environment (US Food and Drug Administration). Hence, it can be used for tailoring the dose for individual patients in order to ensure the administration of right drug to right patient in right dose. With the advancements in the field of bioinformatics along with the availability of large scale biologic databases, patient characterizations methods, and computational techniques for mathematical and statistical analysis of big data has led to the application of precision medicine to the clinical settings (Collins and Varmus, 2015). Antimicrobial agents are good candidates for dose optimization through modeling and simulation technique (Zhao et al., 2014) in order to enhance the therapeutic success on one hand and also to prevent the incidents of therapeutics failure and development of antimicrobial resistance on the other hand. Dose optimization is also necessary to reduce the "financial toxicity" to the patients and caregivers (Nair and Kong, 2018).

The lack of guidance documents and information tools regarding the selection of dosage regimen for antimicrobial agents is a big challenge being faced by antimicrobial stewardship programs. The appropriate dosage regimen can be evaluated by taking into account the patient demographics, susceptibility of pathogenic microbes, and pharmacokinetic—pharmacodynamic targets for antimicrobial agents. This unmet need was addressed by development of an educational mobile application consisting of Monte Carlo simulation algorithm integrating the patients' demographics, pathogenic susceptibility, and assessment of PK-PD target attainment for 35 antimicrobial agents against 29 infection categories. Population pharmacokinetic models were developed, evaluated, and refined for each antimicrobial agent. The susceptibility breakpoints for the pathogenic microorganism were defined based on guideline of US FDA, Clinical Laboratory Standards Institute (CLSI), and European Committee of Antimicrobial Susceptibility Testing (EUCAST). These information were incorporated to one interface, enabling the clinicians to select the antimicrobial agent of interest, target pathogen and infection type in order to obtain the percentage probability of target attainment (PTA%) for each dosage regimen based on patient's characteristics. Such algorithm can be helpful for the clinicians in selection of optimized dosage regimens of antimicrobial agents through the lens of PK-PD (Bulik et al., 2017). The commonly used PK-PD indices include the percentage of time above MIC of pathogenic bacteria (%$T >$ MIC), the ratio of maximum plasma concentration to MIC of bacteria (C_{max}/MIC), the ratio of minimum plasma concentration of the drug to MIC (C_{min}/MIC), and the ratio of area under the serum concentration time curve to MIC (AUC/MIC). The most commonly used PK-PD index is the %$T >$ MIC as this is attributed to the antibacterial possessing time dependent antibacterial activity (Zhou et al., 2011).

Clinical settings with small number of patients and drugs with complex pharmacokinetics hinder the conduct of clinical trials for dose optimization. The model-based simulation approach has played tremendous role in CDM for designing the tailoring dosage regimens based on the pathophysiological conditions of the patients, particularly in vulnerable populations such as children and elderly.

Sample popPK Profiles of Critical Medicines

Drugs with narrow therapeutic indices and the antibiotics of WATCH and RESERVE group (World Health of Organization, 2017) are of critical interest to pharmacists for their application in CDM because of their potential to produce toxicity and antimicrobial resistance in case of subtherapeutic doses, respectively. Some examples of these medicines are discussed below for sharing the information needed for dose optimization.

Vancomycin

Vancomycin is included in WHO's WATCH group antibiotics and the emerging resistant of MRSA to vancomycin is a huge concern globally. Inappropriate dosing of antibiotics can lead to subtherapeutic drug levels resulting in development of antibiotic resistant. Vancomycin is widely used in neonates, critically ill patients, and other vulnerable groups and therefore had been studied for dose optimization using popPK modeling.

An easy-to-use chart was developed for clinicians in order to adapt the schedule for dosing of vancomycin in pediatric cancer patients (Guilhaumou et al., 2016). A method for dose adjustment of vancomycin based on renal status in ICU neonates has also been reported (Li et al., 2018). Application of modeling and simulation-based dosing compared to mg/kg dosing in children with malignant hematological disease reduced the variability in AUC and Css/min values, resulting in improved therapeutic outcomes (Zhao et al., 2014). A higher dose of vancomycin was also recommended to achieve therapeutic concentration in patients during high-volume hemofiltration (Escobar et al., 2014). An important finding for vancomycin is that unlike renal clearance in adults, the body weight of neonates is identified as the significant covariate determining the pharmacokinetics of vancomycin (Anderson et al., 2007; Lo et al., 2010; Zhao et al., 2014). Similarly, dose optimization for vancomycin has been reported in different clinical conditions such as in trauma patients (Medellin-Garibay et al., 2016), postoperative neurosurgical patients (Li et al., 2016), and patients undergoing hemodialysis (Gunning et al., 2016).

Patient case studies have also been reported for individualized dose optimization after taking into account all the significant covariates affecting the clearance of vancomycin in Chinese patients (Lin et al., 2016).

Case study 1

A 69-year-old female patient developed high grade fever, neck stiffness, and headache 2 days after undergoing acoustic neuroma surgery. She was diagnosed with postcraniotomy meningitis (PCM) based on the presence of *Staphylococcus capitis* in cerebrospinal fluid (CSF) and blood cultures. Administration of vancomycin every 12 h was recommended to combat the infection. The clearance of creatinine for the patient was 40.6 mL/min and her body weight was 65 kg. The pharmacist simulated the vancomycin trough concentration by using the developed popPK model and taking into account the demographics of the patient based on significant covariates. The estimated trough concentrations were 8.5, 12.8, 17.0, 21.3, and 25.5 mg/L, respectively for the dose of 500, 750, 1000, 1250, and 1500 mg vancomycin administered every 12 h through i.v. infusion. The target trough concentration range (TTCR) was selected as 15–20 mg/L keeping in view the severity of the infection. Therefore, a dosage regimen of 1000 mg vancomycin every 12 h was administered to the patient. After 2 days, the blood samples were collected 5 min before the drug administration in order to observe the trough concentration, which was 15.7 mg/L. The body temperature of the patient returned to normal and the reports for her CSF and blood culture were negative after 10 days of treatment with recommended dose of vancomycin.

Case study 2

A 62-year-old male patient developed high fever, neck stiffness, and headache 3 days after undergoing glioma operation. He was diagnosed with PCM due to the presence of *Staphylococcus capitis* in cerebrospinal fluid (CSF) and blood cultures. Administration of vancomycin and meropenem every 12 h was recommended for the treatment of the infection. The creatinine clearance of the patient was 45.7 mL/min and his body weight was 68 kg. The pharmacist simulated the vancomycin trough concentration by using the developed popPK model and taking into account the demographics of patient based on significant covariates. The estimated trough concentrations were 7.8, 11.7, 15.7, 19.6, and 23.5 mg/L for the dose of 500, 750, 1000, 1250, and 1500 mg vancomycin administered every 12 h through i.v. infusion, respectively. A 1000 mg dose every 12 h was selected to maintain the target trough concentration range (TTCR) between 15 and 20 mg/L keeping in view the severity of infection. The TDM report revealed the trough concentration as 26 mg/L, which was above the required trough level. Given the possible risk associated with this high trough level, the pharmacist estimated the concentration once again by incorporating all the significant covariates in popPK model. The Bayesian method was used to acquire the TDM results in order to lower the trough concentration levels of vancomycin for ensuring patient's safety. The new predicted trough concentrations were 18.1, 23.3, 28.5, 33.7, and 38.9 mg/L, respectively for 500, 750, 1000, 1250, and 1500 mg of vancomycin as an i.v. infusion every 12 h. Based on this prediction, 500 mg of dose was selected to be administered every 12 h. This time the trough concentration from TDM record was observed as 19.6 mg/L. The body temperature of the patient returned to normal after 8 days of treatment with simulation-based recommended dose of vancomycin and meropenem.

Valproic acid

Valproic acid, an antiepileptic drug, is being used for the treatment of both partial and generalized seizures. A number of popPK models have been developed for identification of significant covariates on pharmacokinetics of valproic acid among which body weight, dose, coadministered drugs, age, and gender proved to be significant covariates for valproic acid clearance while weight and dose significantly influenced volume of distribution (Methaneethorn, 2018). Lin et al. have developed a popPK model in Chinese population and have used their model for individualized dosing of patients in their affiliated hospital (Lin et al., 2015). They reported a case as follows:

Case study 3

A 23-year-old male patient suffering from complex partial secondarily generalized seizures had been receiving carbamazepine 300 mg TID, clonazepam 1 mg TID, and valproic acid 500 mg BID. However, he was still having seizures 1–2 times daily. In popPK model, carbamazepine was a significant covariate for clearance of valproic acid. Thus, the level of valproic acid may not be reaching to the minimum effective concentration when coadministered with carbamazepine. The trough concentration of valproic acid was estimated using the established popPK model by taking into account the demographics of patient medication information. The predicted trough concentrations with dose of 250, 500, 750, 1000, and 1250 mg BID were 27.57, 45.83, 61.49, 75.61, and 88.61 mg/mL, respectively. A 500 mg BID dose of valproic acid may not be sufficient to achieve the target concentration within the therapeutic window (50–100 mg/mL), while 750 mg BID will likely achieve the target despite coadministration with carbamazepine. Therefore, 750 mg BID dose was selected for this patient with continued administration of other medications. The TDM report, after 3 months of continuous treatment with simulation-based dose selection, showed the trough concentration of valproic acid as 60 mg/mL. The frequencies of seizures decreased gradually, and the patient had no seizures attack for approximately 2 months in addition to normal liver function.

Meropenem

Meropenem, a potent carbapenem, is effective against a variety of bacteria including gram positive and gram negative anaerobes, Enterobacteriaceae, and Pseudomonas species. In popPK studies of meropenem, CL_{CR} is the most consistent covariate for meropenem clearance (Kees et al., 2016; Ulldemolins et al., 2015; Usman et al., 2017). In a popPK model of meropenem, different dosage regimens of meropenem, based on dose and dosage intervals, were simulated keeping in view the renal status of the patients. The most appropriate dosage regimens were defined and tailored dosage regimens were recommended for patients with different renal status (Usman et al., 2017).

Phenobarbital

The TDM data of 53 neonates was obtained and used for the development of popPK model by using NONMEM® software. The effect of different covariates was observed on clearance and volume of distribution of phenobarbital. The birth weight and postnatal age (PNA) were the most significant covariates for phenobarbital clearance. The dose optimization of phenobarbital based on PNA and birth weight was recommended for term and preterm neonates (Voller et al., 2017).

Prevention of Drug Interactions

Drug interaction is a primary cause of adverse drug reactions and is a significant challenge in current clinical practice. The extraction of pharmacovigilance data and pharmacokinetic modeling are computational tools for integration of drug interaction knowledge and generation of drug interaction hypothesis (Zhang et al., 2018). The major areas where pharmacometrics has a vital role is drug interaction research where the numerous patient databases such as electronic medical records, electronic health records, and spontaneous reporting systems are being maintained for epidemiological studies and post marketing surveillance by different hospitals, regulatory agencies, and research organizations. Drug-drug interactions (DDIs) are being identified and prioritized through the development of computational models based on data obtained from research communities and hospitals (Harpaz et al., 2012).

The pharmacokinetic DDIs are also being predicted by the use of modeling approaches like stepwise covariate modeling in popPK and PBPK. A popPK-based simulation study recommended a dose reduction or increase in dosage interval of vancomycin when coadministered with frusemide (Medellin-Garibay et al., 2016). In another study, the coadministration of spironolactone decreased while amoxicillin-clavulanic acid increased the clearance of vancomycin (Marques-Minana et al., 2010). The interaction of carbamazepine, phenobarbital, and phenytoin with clearance of valproic acid was identified and this information was used for designing the individualized dosing regimens for valproic acid as described in case study 2 above (Lin et al., 2015).

Conclusion

Pharmacometrics is a novel science that quantifies the interaction between drugs and patients by interlinking the biology, physiology, and pharmacology with disease condition through mathematical models. The data and information collected from different sources are linked together quantitatively. The quantitative answers are required for the questions raised during clinical use regarding safety, efficacy, and dosage regimen or more specifically to design individualized dosage regimen of pharmaceutical products. Pharmacometric analysis can provide arguably better insight than any other available tool to answer these questions when utilized by trained clinician or researcher. Nonlinear mixed effect models (NONMEM) have been commonly used for the population-based pharmacometric analysis. Furthermore, the US FDA considers modeling technique utilizing NONMEM software as a gold standard. The analysis of sparse data is a unique feature of NONMEM, offering a valuable advantage for patients from whom sample collection is difficult including neonates and other critically ill pediatric and geriatric patients. These vulnerable patient groups are also the ones for whom the appropriate dose selection is critical. The development of PK model and establishment of relationships between the PK parameters and patient's demographics can enable the clinicians to devise the appropriate dosage regimen for individual patients ensuring the safe and effective treatment of underlying clinical conditions.

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Dynamic Relationship Between Education, Regulation, and Practice: Case Studies and Examples

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Introduction

This chapter presents eight case studies that provide a more detailed description of a conceptual framework which describes the dynamic relationship between education, regulation and practice. The conceptual framework describes that in any professional arena, there is a dynamic relationship between three interrelated professional sectors: practice, education, and regulation (International Pharmaceutical Federation (FIP), 2008, 2014) (**Fig. 1**).

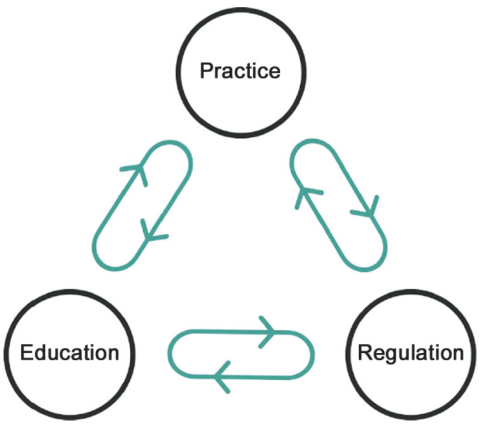

Figure 1 A conceptual framework depicting the dynamic relationships between practice, regulation, and education. *Source: Adapted with permission from International Pharmaceutical Federation, 2014.*

The framework was first developed by author Rouse in the early 2000s as a result of his work with the Accreditation Council for Pharmacy Education (ACPE), the U.S. national accreditation agency for pharmacy education. The framework was first published in the Global Framework for Quality Assurance of Pharmacy Education (Version 1), which was adopted in 2008 by the International Pharmaceutical Federation (FIP)—the global leadership body for the pharmaceutical workforce worldwide (International Pharmaceutical Federation (FIP), 2008, 14).

Between 2013 and 2014, the framework was validated and used in a country-level study in Jordan. Preliminary research resulted in the identification of eight major challenges facing the professional arena in Jordan. National stakeholders used the framework to map each of the challenges to the primary sector-to-sector disconnect that they perceived to explain it (Bader et al., 2017). Between 2017 and 2018, the authors collected country and regional case studies using the tool for publication in the Encyclopedia. The purpose of this was to further utilize the tool's descriptive and prescriptive purposes in other countries around the world and to help national stakeholders reflect on successful developments and assess any existing challenges. An initial scoping survey was distributed to the authors' contacts around the world. The scoping survey served to identify preliminary case studies that were evaluated by the authors for inclusion in the chapter. A total of 10 initial submissions spanning 10 countries were received. In-depth case study templates were then sent to these country contacts and reminders were distributed. From this scoping survey, seven full case studies were received and included in the chapter; these case studies span the following countries and regions: Brazil, Europe (with specific examples from Spain), Japan, Nigeria, Oman, Romania, and Taiwan. With the exception of South East Asia, all World Health Organization (WHO) regions are represented in this study. One additional case study from the United States was then purposively identified to provide an example of a country where a structure had been established to promote and facilitate active and ongoing communication, interaction and collaboration between the practice, education, and regulation sectors within the profession, thereby illustrating how the conceptual framework can and should work in a country. The case studies describe varying issues that touch on different sectors—demonstrating the usability of the whole conceptual framework.

This chapter reports on these case studies. Each case study is accompanied by a descriptive, contextual background on education, regulation, and practice in the country or region and an analysis of the dynamic sectoral relationship(s) reported by the case study authors. Drivers and barriers to advancement, lessons learned, and implications for future planning are also discussed. The chapter authors carefully reviewed the case studies, edited them, and returned them back to their original authors for validation. The authors of the case studies are acknowledged at the end of the chapter.

Case Studies

Using the conceptual framework, Fig. 2 provides an illustrative summary of the case studies and where the dynamic relationship(s) reported in each case study lies.

Brazil

Background

Education and training of pharmacists

Entry for students to pharmacy school occurs via an entrance examination or a national test for high school students (National High School Examination—ENEM). Pharmacy graduation requires a minimum study load of 4000 h distributed over 5 years. After graduation, pharmacists must register with the Regional Council of Pharmacy of their state to obtain a professional registration, and

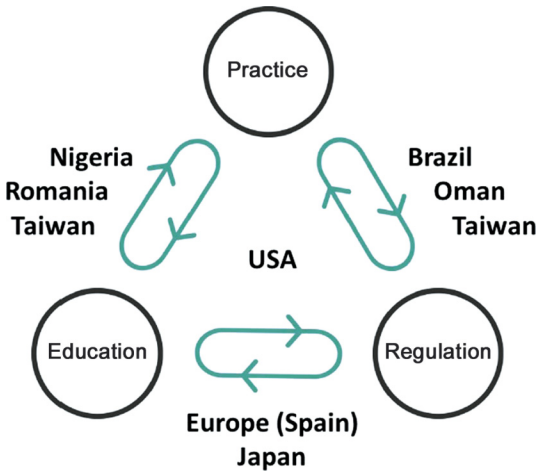

Figure 2 Summary of the dynamic relationships reported by the eight case studies.

they enter the labor market to practice in their area of interest. The pharmacists are not evaluated again to verify the maintenance or improvement of their professional competencies. Two types of postgraduate programs exist in Brazil: one at higher education institutions, with an academic purpose (postgraduate programs, *sensu stricto*), and the other aimed at professional qualifications (postgraduate programs, *sensu lato*), including residencies.

Regulation of Practice

Pharmacy practice is regulated through legislation by the Brazilian Government, regulations of the agency for control of health products and services (Brazilian Health Regulatory Agency, ANVISA), and Federal and Regional Council Resolutions. These laws provide for the education/training of pharmacists, registration, and professional responsibilities in the various areas and rules/procedures for the functioning of the Councils and establishment of pharmaceutical practice.

Oversight and Quality Assurance of Education

Higher education is regulated by the Conselho Federal de Farmácia (CFF, Brazilian Federal Council of Pharmacy) Resolutions and the Brazilian Ministry of Education legislation. Specialization courses and Master's-level, doctoral and post-doctoral programs exist, and they are subject to authorization requirements and accreditation provided through legislation of the Ministry of Education. Residency programs were created by Federal Law in 2005.

Pharmacy Practice

Pharmacy practice is structured along the following axes: health-care provision, management, and technology/innovation. Health-care provision is the set of actions and services offered to the individual, family, and community, conducted through the promotion, protection, and recovery of health, along with disease prevention. Management encompasses technical, political, and social processes and the ability to integrate resources and actions to achieve results. Technology practice is the organized use of scientific knowledge in the research, development, production, quality assurance, and provision of goods and services; whereas, health innovation is related to the introduction or improvement of processes, products, strategies, or services, with positive repercussions on individual and collective health. In Brazil, the main challenge is related to clinical pharmacy, because it is not yet consolidated to the same extent as in other countries.

The Relationship Between Practice and Regulation

The pharmacy profession in Brazil has undergone continual transformations over the last two centuries and has excelled in many fields of activity due to the ability of the profession to renew and adapt to the market. In some areas of practice, the regulatory sector stands out as a positive driver for change in the practice sector, particularly in clinical pharmacy and professional education (Fig. 3). The Federal Council of Pharmacy (CFF) is a member of the Brazilian executive branch, with full autonomy, officially in charge of professional regulation and pharmacy licensing, including pharmacists and companies that perform activities related to the pharmacy. Therefore, important professional legislation is published by the CFF, while other regulations derived from the Brazilian government and the agency responsible for control of health products and services (ANVISA).

Particularly in clinical pharmacy, some of this legislation broadened the scope of the profession. For example, the publication of Federal Law 13.021 innovated by transforming pharmacies and drugstores into health units and by authorizing the administration of vaccines in these establishments. The impact of this law has brought about the need for change in many other resolutions, which will probably expand pharmacists' health-care services. Published CFF legislation has also contributed to the expansion of the scope of the profession, for example, CFF Resolution 585/2013 (Conselho Federal de Farmácia (CFF), 2013d), which establishes the clinical attributions (rights and responsibilities) of the pharmaceutical profession, and CFF Resolution 586/2013 (Conselho Federal de Farmácia (CFF), 2013e), which regulates pharmacist prescribing.

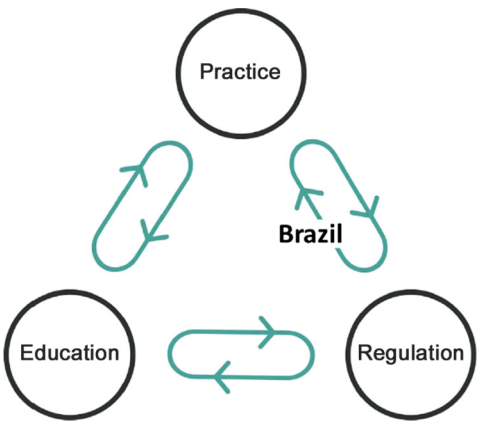

Figure 3 The regulatory sector is a positive driver for practice change in Brazil.

Legislation enacted in education was also a factor that contributed to change of the professional training model and to meeting the demands generated by the updating of the professional practice resolutions. The new curriculum guidelines published in 2017 (Ministério da Educação (MS), 2017) represent a major advance for the professional training of pharmacists and reshaped the training of pharmacists based on three axes: health care, technology, and innovation in health and health management. Notably, 50% of the course workload is now targeted for health care. The CFF also published important resolutions in the area of education, such as CFF Resolution 581 (Conselho Federal de Farmácia (CFF), 2013b), which established the title of professional pharmaceutical specialist, without academic characterization, and CFF Resolution 582 (Conselho Federal de Farmácia (CFF), 2013c), which regulates the recognition of courses for professional pharmaceutical specialization.

However, in the field of esthetic health (National Center for Biotechnology Information (NCBI), 2018), resolutions were passed to regulate procedures already performed by pharmacists in practice. This situation is also common to other health professions, which have also broadened their scope to encompass esthetic health, for example, nursing, dentistry, and biomedicine. Accordingly, the CFF published three resolutions. In 2013, esthetic health was recognized as within the pharmacist's scope of practice, through Resolution 573 (Conselho Federal de Farmácia (CFF), 2013a). This resolution regulates the duties of the pharmacist in the practice of esthetic health and technical responsibility for the establishment that performs related activities. The publication of this resolution also consolidates an important market activity. Additionally, CFF Resolution 616 (Conselho Federal de Farmácia (CFF), 2015) emerged, which defines the technical requirements for the pharmacist's practice in esthetic health and expands the number of techniques and therapeutic resources used by the pharmacist in esthetic health establishments. This resolution was amended by CFF Resolution 645 (Conselho Federal de Farmácia (CFF), 2017).

Although the regulatory sector stands out as a positive driver in specific areas of the profession, it is possible to observe the dynamics and synergies among the practice sectors, regulation, and education in Brazil. The professional practice advances strongly supported in the elaboration of guidelines of clinical practice and in the systematization of the continuing education of pharmacists. In the field of education of new pharmacists, advances have been made in the unification of the two national entities for pharmaceutical education. There is a long way to go with respect to teacher development to design and delivery a competency-based educational program, as well as the use active teaching-learning methods. Despite these challenges, in the field of education, there is a national perception of what is the way forward in educational processes.

Drivers for Advancement

Four important drivers exist in Brazil for this practice:

1. state policies and health legislation;
2. the social needs of individuals and clients;
3. the marketplace and social division of labor; and
4. the internal processes of regulation and professional ideology

Barriers to Advancement

- Legislators and government technocrats: they are sensitive to lobbying and the lobbying of interest groups, including the pharmaceutical market. They are also sensitive to public opinion, and their decisions directly interfere with the laws that regulate the profession.
- Archaic and contradictory legislation: these are complex and sometimes raise conflicts between the allocation of pharmaceutical professionals and other health professionals.
- Health legislation: it is fairly dated and incomplete. The updating of professional legislation and terminology occurred mainly in the scope of professional practice (Brazilian Federal Council of Pharmacy). However, in the areas of health regulation (Health Surveillance) and health (Department of Pharmaceutical Assistance)—both within the Ministry of Health—progress is slow; for example, the misalignment between terms and techniques that have evolved over the years.
- Owners of pharmacies and drugstores do not value the pharmacist in the pharmacy.
- Some pharmacists who do not want to improve or be part of the change.
- Conflicts and legal disputes between professions: The Brazilian Federal Medical Council has filed several injunctions against the Brazilian Federal Council of Pharmacy. Until now, court decisions have been favorable to pharmacists. Other professional councils (Nutrition, Nursing, and Biomedicine), on a smaller scale, took legal action to prevent the expansion of pharmacy professional practice. To the same extent, they have not been successful with legal proceedings, although some demands are still under judicial review.

Important Lessons Learned

- A need exists to build a national professional initiative of Brazilian pharmacists in the coming years. These advances require an essential foundation of technical knowledge and important social and political strategies, which involve different areas. The first step is to build national unity in the pharmacy professional domain and prepare a strategic plan; specifically, the need to strengthen the "Fórum de Valorização da Profissão Farmacêutica" (Forum for Valuing the Pharmaceutical Profession). This Forum was established in 2014 and aims to identify strategic priorities for the development of the profession, as well as to integrate different sectors of society, such as councils, federations, labor unions, to achieve this.

- An evaluation of clinical services impact in Brazil is necessary. Research is highly important to the implementation of the services or products in practice. "Implementation science and sustainability" will comprise an important discussion within the next few years.

Implications and Future Planning

This case study allows reflection on the development of the pharmaceutical profession in various aspects. It also identifies breakthroughs, gaps, and challenges that still need to be overcome. The way forward is to consolidate the importance of pharmacists in Brazilian society; highlighting this for the population. In addition, stimulating research in the area as well as the dissemination of the results will contribute to the relevance of professional development. Finally, another important point is the need to encourage the continuous training of pharmaceutical professionals, in order to achieve excellence in practice.

Europe (With Specific Examples From Spain)

Background

Education and training of pharmacists

In Spain, as well as in all the European Union countries, the requirements are as follows:

1. 4 years of full-time theoretical and practical training at a university or at a higher institute of a level recognized as equivalent, or under the supervision of a university.
2. during or at the end of the theoretical and practical training, a 6-month traineeship in a pharmacy that is open to the public or in a hospital under the supervision of that hospital's pharmaceutical department.

Most countries have adopted a 5-year course, which in accordance with the European Higher Education Area Framework of Qualifications (European Commission, 2018) has a Master's level (Ministerio de Educación Cultura y Deporte, 2015).

Regulation of Practice

Regulation in Europe is according to European Directives 2005/36/CE and 2013/55/UE (European Parliament and Council, 2005, 2013), and Pharmacists can be established in any of the European Union countries in accordance with the principle of free movement of people. In general, community pharmacies are private health-care establishments of public interest, subject to the health-care planning established by the national or regional authorities.

Oversight and Quality Assurance of Education

In each country, there are national and regional agencies of accreditation. In Spain, for example, the agency is The National Agency for Evaluation of Quality and Accreditation (ANECA) (The National Agency for Evaluation of Quality and Accreditation (ANECA)). ANECA is a state foundation for the evaluation, certification, and accreditation of courses, programs, teachers, and institutions. There are recognized agencies in many "autonomic" (regional) communities that work in collaboration with the national agency, ANECA. Both national and autonomic agencies are recognized by the European Association for Quality Assurance in Higher Education (ENQA) (European Association for Quality Assurance in Higher Education (ENQA)). These agencies follow the directives of the European Higher Education Area (EHEA) member states.

Pharmacy Practice

According to European Directives 2005/36/CE and 2013/55/UE, the roles of pharmacists are as follows:

1. preparation of the pharmaceutical form of medicinal products
2. manufacture and testing of medicinal products
3. testing of medicinal products in a laboratory for the testing of medicinal products
4. storage, preservation, and distribution of medicinal products at the wholesale stage
5. supply, preparation, testing, storage, distribution, and dispensing of safe and efficacious medicinal products of the required quality in pharmacies open to the public
6. preparation, testing, storage, and dispensing of safe and efficacious medicinal products of the required quality in hospitals
7. provision of information and advice on medicinal products as such, including on their appropriate use
8. reporting of adverse reactions of pharmaceutical products to the competent authorities
9. personalized support for patients who administer their medication; and
10. contribution to local or national public health campaigns.

In Spain, the primary practice sectors are community pharmacy (regulated; i.e., restricted to pharmacists), distribution, hospital (regulated), pharmaceutical industry, other industries (including food, dietetics, and cosmetics), biological and chemical analysis, and others including public organizations and health administration services.

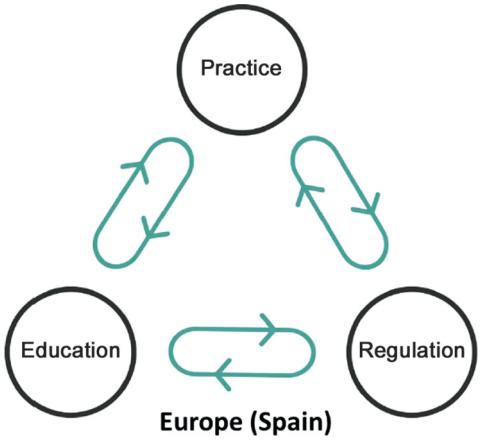

Figure 4 The beneficial effects of regulation on education in the case of Spain, Europe.

The Main Challenges Facing Pharmacy Practice in General

The economics and organization of health-care systems, with community and hospital pharmacists playing an increasingly important role in health-care systems: dispensing alone is no longer a sustainable economic retail model; to compete, pharmacies need to promote and expand their service offerings, get closer to consumers, and reduce economic and logistical inefficiencies. Pharmacogenomics may be one of the services to be incorporated soon, as the use of genetic testing offerings is becoming available within retail pharmacy settings, or it will be done by other professionals.

Advances in the pharmaceutical and biotechnology industries, with a move from small molecule medicines to therapies of biomedical origin: this has increased the growth of the specialty market, which will require special handling, administration, or monitoring.

The Relationship Between Regulation and Education

In this case study, we analyze the beneficial effects of "soft regulations," such as the European Directives (ED) and the EHEA's agreements on the changes in pharmacy education using, as an example, the case of Spain. See Fig. 4 for an illustrative description of the relationship between regulation and education reported in this case study.

Directives and EHEA are soft regulations, as they can be implemented in the different countries in accordance with their own laws. The result, however, has been that they have been adopted by most of the countries with little changes. Implementation is going on, although with a considerable delay. For example, in Spain, ED 2013/55/UE was incorporated into Spanish law as Royal Decree 581/2017 (Agencia Estatal Boletin Oficial del Estado, 2017).

The European Directives established the conditions for the activity in pharmacy and other health care professions, indicating the core elements and the education and training needed. As noted, countries are free to take these recommendations or not, but the result has been that at least for pharmacy programs, all faculties in Europe include the recommendations in their study plans. Harmonization is now the key word and there are many successful initiatives such as the European Community Pharmacy Blueprint. Professional chambers and professional associations are negotiating a new model for pharmacy based on competences (Consejo General de Colegios Oficiales de Farmaceuticos et al., 2018). Furthermore, in cases such as Spain and other Latin countries, the professional organizations are in the process of debating with the governments in order to prepare the profession for these principles. The abolishment of barriers together with easier recognition has significantly increased professional mobility. Currently, the implementation of a professional card is in process.

Starting with the so-called Bologna Process, universities and countries all around Europe agreed to increase the compatibility and comparability of their higher education systems, while at the same time respecting their diversity. The result has been the development of the European Higher Education Area (EHEA), based on institutional autonomy, academic freedom, equal opportunities, and democratic principles that will facilitate mobility, increase employability, and strengthen Europe's attractiveness and competitiveness.

The variability in Europe regarding degrees is high; however, two initiatives have reduced the problem considerably. The first is the adoption of the European Credit Transfer and Accumulation System (ECTS) (European Commission), which eliminates the ambiguity of the years of duration by introducing the estimated student workload. The second is the European Framework of Qualifications (EFQ) (European Commission, 2018), which establishes up to seven levels according with knowledge, skills, and responsibilities, and allows each country to find the equivalence. For example, the Spanish system (MECES) (Ministerio de Educación Cultura y Deporte, 2015) establishes four levels, and the degree in pharmacy MECES Level 3 (Master's degree) corresponds to Level 7 of the EQF. Another tool that helps recognition is the Diploma Supplement, which explains the degrees in more detail (European Commission et al.).

Finally, as a result of the increasing harmonization and to guarantee the quality of the studies, in all countries the accreditation processes have been implemented following the recommendation of the European Agency, ENQA.

Drivers for Advancement

The main drivers for the change in Spain have been the recognition of studies and professionals and the European mobility programs, such as Erasmus. The globalization in all fields goes in parallel with mobility and it requires recognition. This is especially true for health professionals, who clearly are a global workforce.

Barriers to Advancement

First, the main barrier is the lack of flexibility in the management of the changes, second, the lack of resources in some cases, and hird, the low level of recognition of the efforts made by educational professionals for their career promotion.

Important Lessons Learned

A "soft regulation" shared by the different actors can promote big changes in education.

Implications and Future Planning

- Implementation of competences and learning outcomes in all degrees: This is necessary in order to facilitate the rapid changes in the profession and to increase recognition. This applies both academically (as it is easier to recognize previous study based on achievement of competences rather than on content) and socially, especially in Spain, where the role of pharmacists is under-recognized. In this regard, the Pharmine and PHAR-QA projects have establish a framework of competences for use in community pharmacy (Pharmine; Pharmine).
- Recognition of specialties is needed in Europe: Pharmacy, like medicine, has the possibility for specialty curricula development, otherwise recognition would decrease. In the case of hospital pharmacy and, in general, in the development and recognition of pharmacy specialties, a good example is the Common Training Framework for Hospital Pharmacy (European Association of Hospital Pharmacists), a first step to the recognition of this specialty in Europe.

Japan

Background

Education and training of pharmacists

The Japanese School Education Act was revised in 2004, and the new 6-year initial pharmacy education program was implemented in 2006 (Ministry of Education Culture Sports Science and Technology, 2004). This substantial reform indicated that becoming a pharmacist requires not only sufficient practical training but also specialization and a demonstrated sense of humanity (Inui et al., 2016). Since this model core curriculum was implemented; however, several problems have been described (Inui et al., 2016). The model core curriculum was, therefore, revised, and the revised model core curriculum was implemented in 2015 (Inui et al., 2016). The basic policy of the revised model core curriculum was to foster "Professional Competencies for Pharmacists," which were stipulated as follows: (1) professionalism, (2) patient-oriented attitude, (3) communication skills, (4) interprofessional collaboration, (5) basic sciences, (6) medication therapy management, (7) community health and medical care, (8) research competency, (9) lifelong learning, and (10) education and training (Inui et al., 2016). In addition, the revised model core curriculum includes pharmacy practice training for 22 weeks (11 weeks in hospital and 11 weeks in community settings) and establishes some new criteria that prevent differences in practical training content by facilities, etc. (Ministry of Education Culture Sports Science and Technology, 2015).

Regulation of Practice

The systems currently in place in Japan issue various credentials to pharmacists (Yasuhara, 2016; International Pharmaceutical Federation (FIP), 2015; Araki, 2016):

- Certified pharmacists for pharmacy practical training (in hospital or in pharmacy) for students in a 6-year initial pharmacy education program
- Certified pharmacists through a continuing education program
- Certified pharmacists through related "specialty" societies such as the Japanese Society of Pharmaceutical Health Care and Sciences, the Japanese Society of Clinical Pharmacology and Therapeutics, the Japanese Society for Emergency Medicine, and the Japanese Society of Chemotherapy. Other certified pharmacists include "sports pharmacists," who play a role in helping to prevent doping in athletes; and
- Specialized pharmacists certified by the Japanese Society of Hospital Pharmacists in fields, such as oncology, infection control, psychiatry, HIV infection, pregnancy, and lactation.

Recently, the types of certified or specialized pharmacists were also increasing; some of these relate to the medical fee. These medical added fees can be calculated in cases where certified pharmacists or specialized pharmacists contribute to drug management, etc. (Araki, 2016).

Oversight and Quality Assurance of Education

The establishment of all universities or colleges is controlled by set standards of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) (Ministry of Education Culture Sports Science and Technology, 2002). These standards differ between public or private, department and junior university. In accredited universities and colleges, self-assessment was in place since 1991, and it was mandated since 2004. The Japan Institution for Higher Education Evaluation (JIHEE) was founded in 2004, and has been authorized by MEXT as a certified evaluation and accreditation agency for universities and junior colleges, etc. (Ministry of Education Culture Sports Science and Technology, 2002; Japan Institution for Higher Education Evaluation, 2004). All universities or colleges must be evaluated on a 7-year cycle. The evaluation results are indicated by "conformity," "nonconformity," and "hold" and are publically disclosed. Universities or colleges that were evaluated as "nonconformity" and "hold" are required by MEXT to demonstrate improvement.

Pharmacy Practice

The nature of pharmacy practice is dispensing, instruction on dosage, and administration for patients, medication therapy management (prescription analysis, prescription proposal, and therapeutic drug monitoring), and home medical care in the community (Mochizuki, 2014). The main challenge is community health medical care in Japan (Saito, 2016; Tamiya, 2016).

The Relationship Between Regulation (Accreditation) and Education

In 2004, the Japanese School Education Act was revised, and the new 6-year initial pharmacy education program was implemented in 2006 (Inui et al., 2016; Ministry of Education Culture Sports Science and Technology, 2004). This substantial reform indicated that becoming a pharmacist requires not only sufficient practical training but also specialization and a demonstrated sense of humanity. The 6-year initial pharmacy education program was created based on the following policies (Inui et al., 2016):

- Training pharmacists suitable for current social and health-care needs;
- Students being the center of learning, and hence how they should achieve their goals must be clearly explained;
- Assessing whether students reach their educational goal;
- The balance between basic scientific and clinical subjects is maintained; and
- Practical professional training is comprehensive.

In these various changes, to assure quality of pharmacy education, the Japan Accreditation Board for Pharmaceutical Education established the Third-Party Pharmaceutical Education Evaluation in 2008 (Japan Accreditation Board for Pharmaceutical Education, 2018). This organization, which is the first to specifically evaluate colleges or universities of pharmacy in Japan, has been evaluating all such institutions with a 6-year initial pharmacy education program since 2012. The purposes of the evaluation are to ensure the quality of education programs, to promote their improvement, and to provide support for actively obtaining public understanding and cooperation (Hirata, 2015; Japan Accreditation Board for Pharmaceutical Education, 2018).

Evaluations are performed on the students and structure of each education program, and as of March 2018, 48 of the 74 universities have been evaluated. The evaluation has eight areas that comprise 57 standards and 176 viewpoints (Hirata, 2015; Japan Accreditation Board for Pharmaceutical Education, 2018). All evaluated universities or colleges would have self-assessed against the standards for the first time to check if their curricula, methods of evaluation of students' outcomes, and systems, etc. are appropriate. Each university or college of pharmacy, therefore, would have identified their problems, and the problems must be improved by the deadline set by Third-party Pharmaceutical Education Evaluation. Third-party Pharmaceutical Education Evaluation may serve to assure the quality of Japanese pharmacy education; however, since evaluation of graduates is not included in this system, most universities and colleges of pharmacy are not evaluating graduates (Hirata, 2015; Japan Accreditation Board for Pharmaceutical Education, 2018). The outcomes of pharmacy education are reflected by the quality and competence of graduates; therefore, the assessment system should include evaluation of the graduates in the near future. Regulation in the form of accreditation, therefore, drives changes in education (**Fig. 5**).

Drivers for Advancement

Third-party Pharmaceutical Education Evaluation: This organization, which is the first system to specifically evaluate colleges or universities of pharmacy in Japan, has been evaluating all such facilities with a 6-year initial pharmacy education program (Hirata, 2015; Japan Accreditation Board for Pharmaceutical Education, 2018). Assessments are performed on the students and the structure of each education program, and, the first cycle of assessment of all universities will be finished by 2019. Assessments will restart in 2020, and this audit will improve eight items that comprise 19 standards and 53 viewpoints; accordingly, assessment in the second cycle will be more in-depth than in the first cycle (Japan Accreditation Board for Pharmaceutical Education, 2018). All universities or colleges of pharmacy will self-assess against the evaluation items again. The QA of Japanese pharmacy education might be improved as a result in the future. On the other hand, it has already been decided that new universities and colleges of pharmacy will be established after 2018 (Ministry of Education Culture Sports Science and Technology, 2018). Universities and colleges of pharmacy, therefore, will require QA of pharmacy education more than now and will have to work on QA by themselves.

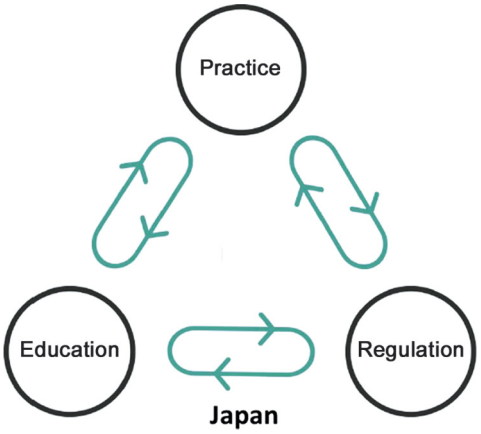

Figure 5 The relationship between regulation, in the form of accreditation, and education in Japan.

Barriers to Advancement

Universities and colleges of pharmacy depend on the Third-Party Pharmaceutical Education Evaluation.

Standards for the establishment of universities in Japan were revised and were deregulated since 1991 (Ministry of Education Culture Sports Science and Technology, 1991). The number of colleges and universities of pharmacy was rapidly increased from 46 (2002) to 74 (2017) (Ministry of Education Culture Sports Science and Technology; Japan Pharmaceutical Association). As a result, faculty members spend a lot of time on basic education of students in many private colleges or universities of pharmacy and also spend a lot of time responding to the education reforms in all colleges and universities of pharmacy (Koyama and Kodama, 2014; Ozawa, 2012; Wada and Yoshimura, 2015). For these reasons, universities or colleges of pharmacy might not have a clear vision about QA and the need for good internal QA systems, and might depend too much on assessment (QA) by the Third-party Pharmaceutical Education Evaluation, which has its limitations.

There is no nationally adopted list of educational outcomes (competencies) for graduates for pharmacy degree programs, as exists in some other countries. Such a list could provide valuable guidance to colleges and universities and provide a standardized point-of-reference for the evaluation of graduates.

Important Lessons Learned

When quality is evaluated, evaluation criteria and standards are most important for appropriate evaluation; therefore, if something is missing from the evaluation criteria and standards, appropriate evaluation cannot be performed. Moreover, the university or college itself must constantly evaluate the outcomes of the education for assurance of quality.

Implications and Future Planning

The university or college itself must also evaluate the outcomes of the education program, including the evaluation of graduates. Appropriate evaluation criteria and standards must be in place to ensure effective evaluation.

Nigeria

Background

Education and training of pharmacists

Educational requirements for registration as a pharmacist in Nigeria are either a 5-year Bachelor of Pharmacy or a 6-year Doctor of Pharmacy undergraduate degree covering the basic sciences, pharmacy, and biomedical sciences. A 1-year mandatory internship training follows under a registered pharmacist in an accredited institution.

Foreign pharmacy graduates (FPG) must be from institutions recognized by the Pharmacists Council of Nigeria (PCN) and satisfy the following requirements: (1) at least 4 years of undergraduate pharmacy education; (2) degree content should be equivalent to the Nigerian program; and (3) the graduate must participate in a 5-week FPG Orientation Program (FPGOP) that tests knowledge of pharmacy, educates on the laws and ethics of pharmacy practice in Nigeria and on tropical diseases and medicines.

With success in the FPGOP, applicants can enter the mandatory 1-year internship program, which is waived for those with evidence of registration in their country of study.

All pharmacists must pass a Pre-Registration Examination (PEP) set by the PCN and participate in the Mandatory Continuing Professional Development (MCPD) program.

Regulation of Practice

Practice regulation falls under the "4P components": the practitioner, practice, premises, and the product. The PCN regulates the practitioner, the practice, and the premises, while the National Agency for Food Drug Administration and Control (NAFDAC) regulates the product.

The PCN uses its prescription of training curricula, graduate induction/oath taking, provisional registration, internship, full registration, annual licensure, and MCPD to regulate the practitioner based on the Pharmacy and Drug Laws, e.g., the PCN publication—"A Four-Part Compendium of Minimum Standards for the Assurance of Pharmaceutical Care in Nigeria." PCN uses its instruments of inspection, approval, registration, and annual licensure to regulate the premises.

NAFDAC controls the registration, manufacture, importations, export, advertisement sale, and distribution of drug products. Routine monitoring is conducted to ensure compliance to preset standards.

Oversight and Quality Assurance of Education

The PCN regulates pharmacy education in conjunction with the National Universities Commission (NUC). Benchmark standard requirements are stipulated by the PCN to the NUC as packaged minimum academic standards.

Pharmacy Practice

The primary pharmacy practice sectors in Nigeria include the community, hospital, and industrial sectors, as well as pharmacy administration/regulation, academia, publishing, research, and the emerging public health pharmacy sector. The community and hospital pharmacy sectors have witnessed significant improvement in practice following the concerted attention clinical pharmacy education has received in line with global trends.

The main challenge confronting pharmacy practice in Nigeria is the disconnect between the training received in pharmacy school and what is practical in the work environment that the pharmacist meets upon graduation. Key components of this environment include competition with medical colleagues and lay businessmen in the control of drug distribution activities, poor remuneration, hitherto weak regulatory activities, poor understanding of pharmacists' role in patient care by the public, and the low pharmacists to patient ratio resulting in increased workload.

The Relationship Between Education and Practice

Pharmacy education in Nigeria has served as a positive driver for change in practice (Fig. 6). Its impact can be viewed from two perspectives—the roles played by pharmacy regulators and the universities (formal sector), and the contributions of implementing partners in public health programs supported with donor funds (informal sector).

The formal sector witnessed a gradual shift from the traditional product-centered practice to patient-focused practice over the past 25 years with the promotion of clinical pharmacy education. The shift started in 1992 with the Pharmacists Board of Nigeria (PCN's predecessor) approving two separate delegations (each consisting of Deans of pharmacy faculties and the PCN Registrar) to the United States and the United Kingdom to understudy clinical pharmacy education and practice. The objective was to determine applicability to Nigerian pharmacy education. In 2002, PCN approved the Pharmaceutical Society of Nigeria's proposal to officially adopt the Doctor of Pharmacy degree (PharmD) program in Nigeria, which had commenced in 2001 in the University of Benin.

Today, all faculties of pharmacy in Nigeria offer clinical pharmacy courses and their undergraduate students participate in clinical clerkships in hospitals for hands-on experience as part of their training. The knowledge so gained enables pharmacists to be more proactive in providing pharmaceutical care as well as collaborating with other health professionals in medication management, as opposed to only serving as a medication dispensing point in the clinical care process. The second pharmacists' summit in Nigeria held in 2012 made a landmark recommendation that the PharmD degree should be the minimum registrable qualification for the profession by 2023, and that all accredited pharmacy schools in Nigeria should commence admission of students for the PharmD degree program from 2016/2017 academic year.

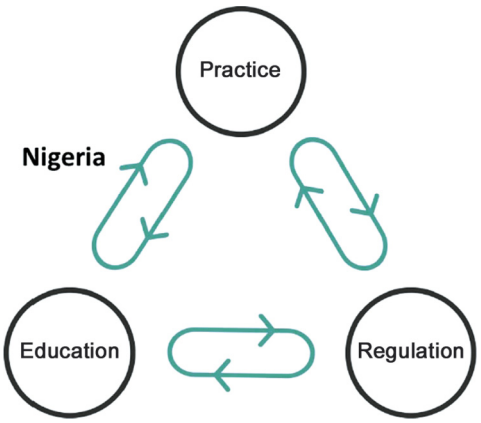

Figure 6 Education as a positive driver for practice changes in Nigeria.

A major catalyst that facilitated the achievement of PCN and Nigerian universities' drive for a patient-focused pharmacy practice is the contributions of United States Government (USG) funded Implementing Partners programme. Notable among the partners is Howard University Pharmaceutical Care and Continuing Education Centre (HU-PACE), which was given the dual mandate under two USG funded projects (GHAIN and SIDHAS) to promote quality care for the patients by strengthening the pharmacy systems, and enhancing the pharmacists' capacity to provide pharmaceutical care in all supported hospital and community pharmacies. Since 2004, HU-PACE has been setting up structures and processes for providing, documenting, and monitoring pharmaceutical care implementation across Nigeria through some of the following activities:

- Conducting didactic pharmaceutical care training/retraining in Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome/Tuberculosis (HIV/AIDS/TB) for 2151 Pharmacists between 2004 and July 2017. Trainings are usually followed by onsite, hands-on mentoring in the hospitals to institutionalize the eight elements of Pharmacy Best Practice and by Skill Certification workshops for community pharmacists (Oqua et al., 2013);
- Developing and rolling out various pharmaceutical care tools to support the provision and documentation of pharmaceutical care services by pharmacists;
- Providing support to PCN to develop pharmaceutical care modules on HIV/AIDS for its MCPD program and to the National Pharmacovigilance Centre (NPC) in NAFDAC to develop adverse drug reaction (ADR) screening and reporting forms;
- Setting up structures for support of confidential counseling, as well as processes for routine assessment and interventions for ADR manifestations and medication adherence problems, and patients and prescription screening for medication errors;
- Enlisting community pharmacists into the national HIV and TB case findings and providing a continuum of care in the community including anti-retroviral therapy refills for HIV-positive clients discharged from public hospitals; and
- Setting up new, and strengthening existing Drug and Therapeutic Committees/Pharmacovigilance Committees to demand and use pharmaceutical care data for clinical decision making in supported hospitals.

Drivers for Advancement

In addition to named factors above, drivers for the impact pharmacy education has had on patient-centered pharmacy practice include the following:

- The global paradigm shift toward patient-centered pharmacy practice with the resultant realignment of pharmacy education in Nigeria;
- Consistency in PCN's support for pharmacy education that shifted its focus over the years;
- The platform provided by USG funded HIV/AIDS/TB projects in Nigeria, which has helped to strengthen the pharmacy system and the pharmacists' capacity to provide pharmaceutical care; and
- The preexisting yearning of Nigerian pharmacists who have consistently complained of being over educated and underutilized.

Barriers to Advancement

Barriers to the advancement of this relationship include the following:

- Poor remuneration has caused many pharmacists to seek fulfilment in other sectors, with some exporting their services to other countries (brain drain);
- Ongoing inter-professional friction with other medical colleagues, who see the increasing patient-centered role of pharmacists as an encroachment into their areas of clinical practice; and
- Inadequate or complete absence of pharmacists in many hospitals, especially in privately owned hospitals, to provide pharmaceutical care.

Important Lessons Learned

The positive impact pharmacy education has had on practice has shown clearly that:

- Concerted collaborative efforts of key stakeholders in pharmacy education (PCN, PSN, academia, and NGOs) are instrumental in achieving the pharmacy practice that meets the needs of the people; and
- When pharmaceutical care is practiced at the community and hospital levels, it has the potential to increase public understanding of pharmacists' roles in safeguarding their health, bring recognition to the pharmacy profession, create demands for pharmaceutical care, and ultimately fetch greater benefits to the profession, the health-care system and the entire citizenry.

Implications and Future Planning

The case has demonstrated clearly that forward planning is critical to the achievement of any desired goal. The next steps for further improvement in pharmaceutical care in Nigeria include the following:

- Implementation of more synergistic activities that promote pharmacy practice by the key stakeholders (PCN, PSN, Academia, and NGOs) such as joint use of data collection and reporting formats, use of project-based training materials as part of the national professional continuing education program; and

- Improved data collection on pharmaceutical care practice in Nigeria and dissemination to increase public awareness of its benefits, thereby creating demand for the practice.

Additional Reading:

1. World Health Organization and International Pharmaceutical Federation Handbook; *Developing pharmacy practice: a focus on patient care 2006*.
2. Erah P. *The changing roles of pharmacists in hospital and community pharmacy practice in Nigeria.* Tropical Journal of Pharmaceutical Research. 2003; 2 (2): 195-196.
3. Oji V, Weaver SB, Falade D, Fagbemi B. *Emerging roles of U.S. Pharmacists in global health and Africa.* J Biosafety Health Educ. 2013. 1: 108. doi:10.4172/2332-0893.1000108.

Oman

Background

Education and training of pharmacists

In Oman, pharmacists and assistant pharmacists are the two pharmacy practitioners who can practice the pharmacy profession. Pharmacists should complete a Bachelor's degree in pharmacy or equivalent, e.g., PharmD. Assistant pharmacists should obtain a Diploma in Pharmacy (minimum 2 years) and work under pharmacists' supervision. They are equated to pharmacy technicians in some developed countries, except they have had comprehensive academic courses in pharmacology and pharmacy practice (Higher College of Technology, 2016). Pharmacists are required to complete a Master's degree in clinical pharmacy to practice in inpatient settings.

Pharmacists and assistant pharmacists should fulfil the pharmacy licensing conditions to practice in the country; this includes:

1. completing a Bachelor's degree or equivalent for pharmacists, or diploma in pharmacy for assistant pharmacists;
2. passing the licensing exam;
3. completing the training hours for Oman graduates

Overseas applicants must be registered with the pharmacy council or association in the country of origin and have at least 3 years of practice experience (Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&DC)).

Regulation of Practice

The Directorate General of Pharmaceutical Affairs and Drug Control (DGPA & DC) under the Ministry of Health (MOH) governs pharmacy practice. It is the main regulatory organization responsible for pharmaceutical law and its implementation. One of its responsible duties is licensing and inspection of pharmaceutical establishments and for registration and licensure of pharmacy staff. There is no independent regulatory pharmacy council or pharmaceutical association in Oman.

The Department of Pharmaceutical Care under the Directorate General of Medical Supplies (DGMS) is responsible for identifying and facilitating the training and support of the pharmacy workforce for better delivery of pharmaceutical care and services.

Oversight and Quality Assurance of Education

The Ministry of Higher Education and MOH license pharmacy academic degrees in the country. The Oman Academic Accreditation Authority regulates the quality of higher education in Oman (Oman Academic Accreditation Authority, 2018). The Bachelor of Pharmacy degree program provided by Oman Medical College is affiliated with West Virginia University in the United States (Oman Medical College (OMC), 2015). The provision of pharmacy education is limited in the country, as no school of pharmacy provides postgraduate degrees.

Pharmacy Practice

The services provided by community pharmacies are traditional services, i.e., product-oriented rather than patient-centered. Clinical pharmacy services are limited and usually associated with a hospital setting, where staff are clinically trained and supported by clinical pharmacists. With no clinical pharmacists working in the primary health-care sector or private community pharmacies, clinical pharmacy services are very limited and highly dependent on individual initiatives (Al-Abdullatif, 2014). The concept of pharmaceutical care, therefore, is not fully and effectively developed, and the clinical pharmacy services can vary between different health sectors.

The challenge faced is the lack of a national policy and/or guideline on good pharmacy practice that can maintain a standard in the quality of pharmacy services between the two pharmacy sectors. Thus, the main challenge is the suboptimal standard of pharmacy practice in the primary health-care sector.

The Relationship Between Practice and Regulation

The case study describes how effective enforcement of regulation positively impacted practice in one sector in Oman while lack of effective enforcement in another sector was a barrier to advancing practice (Fig. 7).

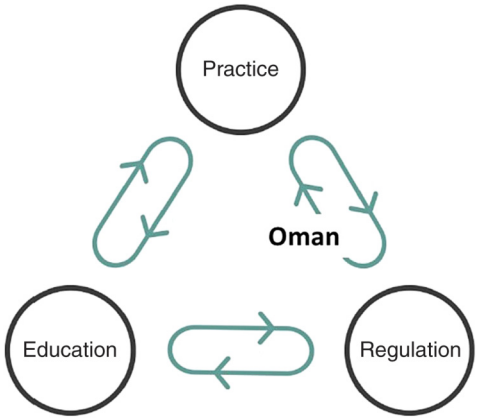

Figure 7 The effect of enforcement of regulation on the advancement of practice in Oman.

The administration of pharmacy practice varies significantly in Oman. The Ministry of Health (MOH) regulates both the public and the private (community) health sectors, but variation in the clinical practice between the two sectors is observed. Using semi-structured interviews carried out in a PhD candidate's qualitative study, community pharmacy staff were asked about their dispensing practice and role in patient care (Al Juma, 2017). The study identified that most of the community pharmacy staff adhere only to MOH regulations when practicing pharmacy. One community pharmacist stated: "Here, almost we are following the Ministry rules only, almost we are not violating and that is actually good only for customers and for the community." Furthermore, a variation in perceptions and practice was observed among the community pharmacy staff; some explained that they would refuse to supply prescription-only-medicine (POM) without a prescription while others agreed to supply without a prescription, especially for chronic medications. The difference in approach was perceived to be influenced by the profit motive *versus* the professional obligation. Some pharmacists suggested that enforcement of the law is required. A community pharmacist explained: "First of all, the pharmacist should feel the importance and commitment to it, and this will only come either by enforcing the law or by feeling a good conscience, to take into account every simple (sic) thing in their profession."

The Oman Pharmacy Law was updated in 2015; however, the prohibition of supplying POMs without a prescription has recently been added to the draft version of the good pharmacy practice (GPP) bylaw. Moreover, the bylaw does not clearly stipulate the minimum international standards for medicine labeling (GSD; **g**eneric name, **s**trength of medicine, individual **d**osage instructions) or counseling (International Pharmaceutical Federation (FIP), 2001; International Pharmaceutical Federation (FIP), 2012). Labeling of medicines and patient's counseling are standard procedures to be performed in most of hospitals' pharmacies in the country, but they are lacking in community pharmacies. Consequently, no integrated labeling system is available in most of the private sector pharmacies. The observed current practice is handwritten dosage instructions on the box itself using abbreviations, for example, the Latin number is used to indicate dose and frequency, i.e., "II–II" is the instruction to take two tablets, twice daily.

People acknowledge pharmacists' expertise in medicines, although some people observed a variation of the pharmacy staff who are working in the community compared to those working in a hospital setting. People indicated that most community pharmacies supply the medicines without providing adequate counseling: "I cannot trust the pharmacist, he may issue a medicine without explaining the benefits and side effects." A member of the public, who had a positive experience with a community pharmacy in an overseas country, questioned the competency of local community pharmacy staff to provide health advice, which raised concern of patient safety: "In [Country X] they will ask you: Is it for you? How old are you? What is your weight? and will explain for you how much dosage, within how many hours, and so on, but here they just give it to you without asking. The pharmacy here is like a shop to buy from, and not a place to be treated" (Al Juma, 2017).

Drivers for Advancement

- Under the national health strategy "Health Vision 2050," there are plans to privatize some of the health-care services to overcome the challenges of demand (Ministry of Health, 2014). There is a national need to standardize and close the gap between the two sectors with regard to patient care and the quality of pharmaceutical care services provided.
- Identify and recognize the importance of the pharmacy profession in optimizing medicine use and patient education in hospitals
- Stress the need to develop a national strategy to improve the clinical role of the pharmacy profession in the private sector for safe and effective involvement in patient care and medicine use.

Barriers to Advancement

- The good pharmacy practice law lacks the elements related to the clinical role of the pharmacy profession and patient care. There is, therefore, no clear minimum national standard established for activities related to either labeling of dispensed medicines or provision of effective medication therapy management.

- The absence of a clear implementation strategy of pharmacy law and inefficient enforcement of regulation are barriers for the advancement of pharmacy practice to comply with the international standards of GPP.
- The absence of an independent body to monitor compliance of pharmacy staff to the Law and to provide professional support to reduce variation in practice between both sectors or among the overseas pharmacy workforce.

Important Lessons Learned

- Weakness of regulation (scope of regulation and/or effective enforcement) is a threat for advancement of the pharmacy profession in the country.
- Absence of a clear professional strategy or guidelines results in incapacity of the profession to meet international standards.
- Individual initiatives and efforts can improve practice, but they are not sustainable if the system does not support this advancement.
- Adherence to some regulation was observed after enforcement by sending reminding circulars, regular inspection, and requests to maintain documented evidence. Since the MOH has not identified labeling and therapy management as a requirement to meet the GPP standards, this will not be adhered to by the community pharmacies.

Implications and Future Planning

- Set clear national minimum standards of GPP related to the clinical role of the pharmacy profession, including medicine labeling, patient counseling, and supply of POM. Identify a mechanism or key indicators for GPP implementation, assessment, and monitoring in community pharmacy.
- Develop a clear professional strategy to support the implementation of Oman national health policy and set a framework/roadmap for the pharmacy profession in the new health vision of the country.
- Enhance the governing role of the Oman Pharmaceutical Society to act as an independent body responsible for practice and training in the pharmacy profession.

Romania

Background

Education and training of pharmacists

Pharmacists during the period 1998 through 2002, before Romania joined the European Union, could register through the professional association, the College of Pharmacists, if they possessed a pharmacist diploma (degree) delivered by a Higher Education Institution accredited in Romania or abroad (if recognized according to the law). In this period, pharmacy education was organized in a 5-year curriculum that included all disciplines required by the European standards (but not specific training on contraception and family planning) as well as a period of 4 months of in-service training. Diplomas were delivered after the validation of each individual's program, and a graduation exam that included both a theoretical component as well as the defence of a degree thesis.

Regulation of Practice

The practice of pharmacy was regulated in this period by Law 81/1997 and was based on a free practice authorization delivered by the Ministry of Health, with the concurrence of the College of Pharmacists. All practicing pharmacists were enrolled in the College of Pharmacists, whose role was to defend and promote the rights and interests of its members, as well as to ensure that professional obligations, the norms, and code of ethics (Deontology code) were respected. The College was also involved in the creation of new pharmacies, warehouses or laboratories, as well as the continuing education of practitioners. The practice in pharmacies was regulated by norms approved by the Ministry of Health.

Oversight and Quality Assurance of Education

Higher education institutions delivering pharmacist diplomas had to have a pharmacy program accredited by the National Council of Academic Evaluation and Accreditation, based on the quality of the curriculum, the faculty, and on teaching facilities and resources.

Pharmacy Practice

At that time, pharmacy practice was mostly in the private sector, with the exception of hospital pharmacies, as they were just beginning. The practice sectors included: public pharmacies, pharmacies in polyclinics, in diagnostic and treatment centers open to the public, hospital pharmacies, warehouses, and units for the synthesis and production of pharmaceutical products. The main challenges at that time were related to the rapid growth in the number of public pharmacies. This led to a high demand for pharmacists in the labor market, to an increase of industrial preparations available and by consequence the need for more time available for pharmacists to interact with their patients. This was coupled with the increasing recognition of their role

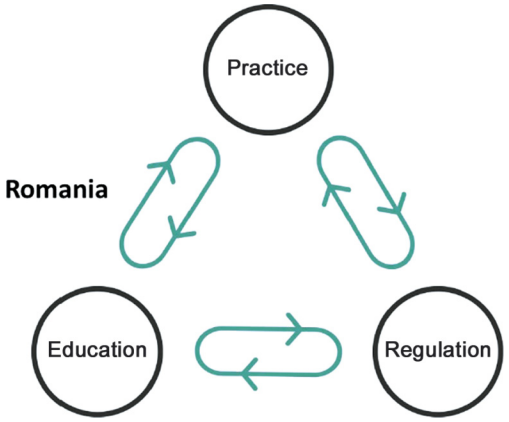

Figure 8 The relationship between education and practice in Romania.

in primary health care and increasing need for continuing education in this respect, especially for the pharmacists who graduated prior to 1989.

The Relationship Between Education and Practice

Demonstrating a dynamic relationship between education and practice (Fig. 8), this case study refers to the segment of pharmacy practice in Romania that was a part of the partnership begun in 1998 with a focus on expanding primary health care in the pharmacy curriculum and continued with the TrainPharm Project (1999–2002).

The role of the pharmacist in Romania was under transformation since the change in the political system in 1989 served as a motivator for reform in the health-care system. As in many other countries, pharmacists were educated with an emphasis on preparing and dispensing medicines. As the health-care system reformed, the training of health-care professionals shifted toward the improvement of primary health care (PHC) delivery including family planning. Pharmacists were placed in a position to strengthen their service and expand the scope of their practice. Universities wanted to mount more formal continuing education programs for practitioners to provide them with updated information and skills enhancement.

Recognizing the potential of pharmacists to make a significant contribution to women's health services, the United States Agency for International Development (USAID) in Romania entered into a cooperative agreement with Howard University's Pharmacists and Continuing Education (PACE) Centre for 1 year (1999–2000) to support USAID/Romania's Strategic Objective *"Improved Welfare of Women and Children in Romania."* The initiative had a primary emphasis on Women's Health Services—Reproductive Health and Family Planning. The TrainPharm Project was designed to support this objective through the provision of training and skills enhancement for pharmacists, who would be enabled to increase their contribution and expand their roles in primary health care delivery to women and their families. Pharmacists gained knowledge and skills related to shifting their practice from primarily drug manufacturing and distribution to a more patient-care centered focus within the health-care system. Additional project goals in Phase I were to:

- assist the University of Medicine and Pharmacy in Cluj (UMF-Cluj) to develop, organize, and conduct a training process for 300 pharmacist practitioners from three judets (counties), Cluj, Constanta, and Iasi
- assist UMF-Cluj with the development of a sustainable capacity to plan, implement, and evaluate continuing education (CE) services for pharmacists.

In the second phase (2000–02), the training was conducted in target counties using the methods and model of instruction from the first phase of the TrainPharm Project but with improvements based on feedback, evaluations, and lessons learned in the first phase. This phase of the TrainPharm Project was structured to increase the cadre of pharmacist practitioners who were better prepared to participate in health reform in general and assure wider access of women and couples to reproductive health services. Due to practitioner's interest, the second phase, initially planned for seven judets, accommodated pharmacists in nine judets: Alba, Botoşani, Călăraşi, Dolj, Ialomiţa, Sălaj, Suveava, Tulcea, and Vâlcea. Project results yielded training of 1026 pharmacists representing over 500 pharmacies in 30% of the judets of Romania. As a result of training, a technical expert assessed the effectiveness of the workshops that revealed the following:

- A high level of participant satisfaction with the training
- Measurable growth in pharmacists' knowledge of family planning methods and their professional role in primary health-care delivery
- Acceptance of an interactive training method
- Change in the pharmacists' method of practice to incorporate skills acquired in patient interaction and education

Drivers for Advancement

A key driver toward advancement of the relationship of education and practice change was the international partnership between UMF-CLUJ & HU-PACE as supported by funding of the local USAID Mission. The international partnership exhibited many successful principles:

- Shared mission, goals, and measurable outcomes
- Positive relationship characterized by respect, congeniality, commitment, and mutual trust
- Roles, responsibilities, and processes identified with agreement of all partners
- Mutual benefit, with sharing of credit for joint accomplishments, but highly focused on the trainees' needs and attainments
- An evolving partnership that built upon the strengths of each partner
- Balanced, clear, and open communication
- Key personnel remained committed over time

Barriers to Advancement

Barriers to this relationship included distance between educator and practitioner, inability to accommodate all of the pharmacists who wished to be participants in the training so that they could change their practice appropriately, as well as the need to produce some material in English for later translation and use.

Important Lessons Learned

The main lessons learnt from this case were as follows:

- mutuality of vision, goals, and understanding is essential to the ease of forward planning
- a wide inclusion of practitioners helps to generate a high level of interest in change
- the engagement of practitioners from several geographic practice settings and cultural (e.g., urban/rural) perspectives contributed greatly in effecting change. These lessons also serve as a basis for the evaluation of future planning and practice change efforts. Furthermore, it assists a diffusion of the ideas and practices into those areas where actual training could not take place.

Implications and Future Planning

The implications of this case include recognition of the importance of maintaining clear communication between the relevant component participants, e.g., university, practitioners, and resource agency. In this case, an outcome of the TrainPharm Project was the expansion of the internal drug information system to permit practitioners to enact evidenced-based changes. For this reason, among others, the first drug information center in Romania was established at the University of Medicine and Pharmacy in Cluj. This site was designed to be a resource for physicians as well as pharmacists and continues to this day. Its role was expanded to research and educational purposes in the field of pharmacovigilance.

Additional Reading:

1. King RC, Marius B (Eds). Skills Certification Workshop. *TrainPharm Participant's and Trainer's Manuals.* Phase II. 2001.
2. Carson R, King RC, Marius B (Eds). *TrainPharm Manual.* Phase I. 1999. (Romanian).
3. Pharmacists and Continuing Education (PACE) Center. *Capsule Newsletter* (Edit). 1999, 2000, 2003.
4. *Developing the patient-care focus of pharmacists through continuing education* (Romanian). Global Health Council. 2004.
5. King RC. *A Look at the Role of the Pharmacist in Primary Health Care*: Proceedings of the First International Conference on Primary Health Care in Romania. *Applied Medical Informatics*. Vol 2, 12/96, 15-22.

Taiwan

Background

Education and training of pharmacists

Taiwan has nine schools of pharmacy. With the progression of the Doctor of Pharmacy (PharmD) degree program, the number of years of study required for graduation and the conduct of the licensure examination became complicated. Some schools kept the traditional 4-year curriculum; some added Chinese herbal medicine and adopted a 5-year curriculum; and some adopted a 6-year PharmD program. Regardless of the number of years of study, students need to complete at least 132 credits of coursework and 640 h of hospital internship in order to graduate from the school of pharmacy. Before 2015, students who graduated from a school of pharmacy could take the licensure exam. The rules changed, however, and after 2015, the licensure exam became a two-stage exam—the basic exam and the clinical exam. Those who do not pass the first stage cannot take the second stage. The licensure exam is governed and managed by the Ministry of Examination. Pharmacists need to take 120 continuing education (CE) hours in 5 years to renew their practice license.

Regulation of Practice

The Ministry of Examination has a committee to determine the rules and contents of licensure examination. The Taiwan Food and Drug Administration (TFDA) sets the rules for pharmacy practice; however, pharmacist workforce issues are regulated by the Department of Medical Affairs under the Ministry of Health and Welfare. The Taiwan Pharmacist Association (TPA) is the contact organization for the government to discuss any issues related to pharmacy practice.

Oversight and Quality Assurance of Education

The Department of Higher Education in the Ministry of Education organizes a committee from professors of the nine schools of pharmacy to decide the requirements of pharmacy education and graduation. In 2005, the Higher Education Evaluation and Accreditation Council of Taiwan was established to conduct accreditation on the university level, including medical universities. Pharmacy education is included under the university level and Taiwan does not have the school or programmatic level of pharmacy accreditation. The Pharmaceutical Society of Taiwan is the contact organization for issues about pharmacy education.

Pharmacy Practice

In the health sector, pharmacists can practice in hospital or community pharmacies, or pharmacies in primary care clinics. Prescription dispensing is the major task; however, many clinical and drug use quality management services were conducted in hospital pharmacy. Starting in 2010, TPA in collaboration with the National Health Insurance Administration (NHIA) started a pharmacist home care program for high users of medical resources; this started the direct patient care services conducted by community pharmacists. Thereafter, TPA received research funding from TFDA and the Nursing and Health Care Administration to develop more services for patients at home, in long-term care facilities, or in community pharmacies. The challenges are that pharmacists do not receive competent training on direct patient care while at pharmacy school; therefore, they are not used to being responsible for interventions or documentation, do not have confidence in communication with physicians, and even do not have the concept of the patient care process.

The Relationships Between Education/Practice and Practice/Regulation

In this case study, two relationships are reported by Taiwan: education and practice and practice and regulation (Fig. 9).

Regulation has been a positive driver for innovation and changed the practice by community pharmacists. In 2007, the Pharmacist Law added a new responsibility of pharmacists to provide pharmaceutical care related activities. At that time, the concept of pharmaceutical care was to conduct clinical services in the hospital setting. However, in 2009, when TPA requested the Ministry of Health to create new roles for pharmacists to practice in the long-term care environment, the NHIA responded that a group of high users of medical resources might need help from pharmacists. Physicians and nurses tried to manage those high users but in vain. NHIA provided a budget and drafted a plan for pharmacists to manage the high users, with the goals to decrease their number of outpatient department (OPD) visits and reduce outpatient health-care expenditure. The author was invited by TPA in late 2009 to lead the training, qualification, implementation, monitoring, and presentation of outcomes to the NHIA in 2010.

The first year pilot study had very positive outcomes. Later, the project expanded from eight cities to the total 24 cities in Taiwan, and the budget was increased four times higher in 2011. In addition, from 2011 to 2015, TPA applied funding from TFDA to conduct more trainings and developed standard operating procedures (SOPs) for different kinds of services that can be conducted in community pharmacies, such as cognitive services, adherence counseling services, and the PharmaCloud drug integration service (Yan and Lu, 2016). The NHIA created the PharmaCloud system, putting all prescription information for every citizen for the past 3 months into the system; physicians and pharmacists can access the information via the Internet with the patient's agreement. In 2014, TPA also applied for funding from the Health Promotion Administration (HPA) to conduct a Diabetes Management Program. From 2010 to 2018, the NHIA project continued.

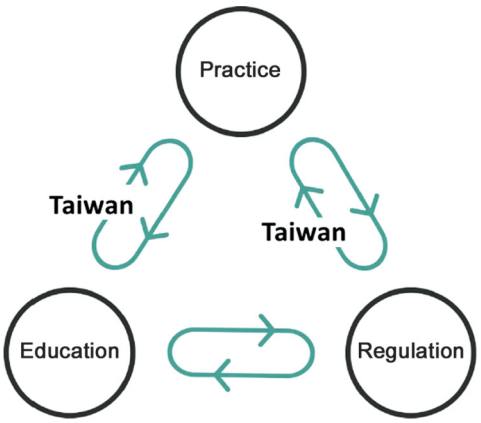

Figure 9 The relationship between practice and education, and practice and regulation in Taiwan.

Practice and pharmacists' education did not go hand-in-hand. The pharmaceutical care process taught and practiced by community pharmacists includes assessment of patient information and medication used, development and implementation of a care plan, and follow-up evaluation.[2] The author also created an AABBCC coding and documentation system for drug therapy problems identified (AA code), resolution recommended to the physician or patient (BB code), and follow-up of the changes of prescription or patient behavior (CC code).[3] The computer system for documentation was developed using the same philosophy. The above-mentioned NHIA home care services can only be conducted by community pharmacists due to the claiming process, and most of the other projects were conducted mainly by community pharmacists. With the total annual budget for projects of nearly (New Taiwan Dollar) NT$80 million, not many hospital pharmacists can take it up because the claiming process needs to go through contracted community pharmacies and some are specifically designed for community pharmacists. Clinically oriented teachers in the schools of pharmacy mostly have experience in hospital practice, using SOAP format (**s**ubjective, **o**bjective, **a**ssessment, and **p**lan) to take care of patients in the acute environment. They were, therefore, not involved in the training and practice in the TPA projects. They still teach the patient care process using SOAP format and ignore the practices developed in the community pharmacy sector for the holistic care of patients (Cipolle et al., 2012; Joint Commission of Pharmacy Practitioners (JCPP), 2014; Tarn and Li, 2017).

Graduates from schools of pharmacy still do not have the competency to conduct patient-centered care for patients with chronic diseases, illustrating a disconnect between education and practice. Community pharmacists need to take 31 Credit CE hours and pass the written exam developed by TPA, practice on five real patient cases, and then pass the oral test in order to get the certificate to join all the home pharmaceutical projects. Every 4 years, they need 48 CE hours and other requirements (proof of taking care of at least 15 patients, etc.) to continue their qualification; however, those CE courses did not invite faculty members from pharmacy schools to teach. It is hoped that the new PharmD program in the schools of pharmacy may change the Education–Practice relationship.

Drivers for Advancement

- Due to the needs of complex patients, the leaders of the TPA believe pharmaceutical care is the future. They persuaded the NHIA, TFDA, and HPA to provide funding for pharmacists to help those patients identified with multiple chronic diseases, polypharmacy, and poor adherence.
- The longevity of members of the population and the move in the health-care environment pushing toward long-term care that is more community-based practice, and not hospital services.
- The waste of medications, and the fact that drug expenditure accounts for ±25% of total health-care expenditure in NHIA, contributes to the need of having pharmacists improve the rational and safe use of medications.

Barriers to Advancement

- Community pharmacists were not trained to conduct patient-centered care.
- Few knowledge-based drug or decision-support information resources could be accessed in the community pharmacy.
- More professional services should be developed and receive remuneration so that more efficient hospital pharmacists can be attracted to conduct ambulatory care practice.
- Taiwan does not have pharmacy technician training programs to assist pharmacists to practice at a higher level.
- The schools of pharmacy is still debating having a 4, 5, or 6-year education and are missing on competency requirements.
- Only candidates with a PhD degree can be recruited as a professor to teach in pharmacy schools, and they are not familiar with professional practice.

Important Lessons Learned

- Schools of pharmacy are research-oriented institutions and not a place to prepare professionals who can improve patient health through the provision of pharmaceutical care.
- Pharmacists are used as "technicians," and there is not a plan to create a technician workforce.
- The professors who teach clinical pharmacy mainly focus on hospital practice and ignore community practice, and the patient care process does not follow the model promoted by the Joint Commission of Pharmacy Practitioners (Joint Commission of Pharmacy Practitioners (JCPP), 2014).
- The future for pharmacists will be direct patient care, holistic care, and not only disease management for those in need.
- Schools of pharmacy need to change how they recruit faculty members and focus more on professional practice, not only publications on basic or applied sciences.

Implications and Future Planning

Recently, NHIA asked TPA to propose pharmacist services that can add to the physician home visit for those who cannot go to clinics or hospital for medical care. Four more services, in addition to home pharmaceutical care, were developed and proposed with remuneration. Another TPA campaign requested a budget from NHIA to reimburse clinical services conducted by hospital pharmacists, especially in the intensive care unit. Although this would be difficult, it is a message sent to the government that pharmacists have value and can do more in the patient care environment. Achieving good collaboration between hospital and community pharmacists will be the major task for TPA to revise future professional practice.

USA

Background

The final case study provides an example of a country, the United States of America, where a structure has been established to promote and facilitate dynamic relationships between the practice, education, and regulation sectors of the profession, which has been the focus of this chapter. The Joint Commission of Pharmacy Practitioners (JCPP) was established in 1977 and now comprises practitioner member organizations and liaison member organizations from pharmacy education, regulation, and accreditation. (Joint Commission of Pharmacy Practitioners, 2018) Through JCPP, active and ongoing interaction, communication, and collaboration have been achieved within the profession, resulting in several notable advances for the profession, which have ultimately served the best interests of patients.

Education and training of pharmacists

To optimize pharmacy practice and the role of pharmacists within the health-care system requires that pharmacists are educated to meet society's care expectations for today and the future. In 2004, with the final graduates of Bachelor of Science degree programs, the transition to a single accredited entry-level degree—the Doctor of Pharmacy (PharmD) degree program—was completed.

The PharmD degree is a 4-year professional degree program completed after a minimum of 2 years of prerequisite undergraduate coursework. Some US colleges and schools of pharmacy require completion of a baccalaureate (BS) degree prior to admission to their PharmD program. Accordingly, a PharmD degree typically takes between 6 and 8 years to complete. The PharmD curriculum consists of didactic and experiential education that meets the accreditation standards of the Accreditation Council for Pharmacy Education (ACPE). In 2016, ACPE released new degree program standards that incorporated or expanded expectations for patient-centered care, working in interprofessional teams, evidence-based practice, quality improvement, public health, and transforming activities of pharmacists. Successful completion of both the didactic and experiential pharmacy curriculum prepares students to apply for pharmacist licensure. Post-graduate education and training of pharmacists support pharmacists' ability to enhance skills, knowledge, and abilities to advance patient care. All pharmacists are required by state regulations to complete a number of hours of approved or accredited continuing education (National Association of Board of Pharmacy, 2017). Many pharmacists complete post-graduate training programs and achieve other credentials, including certificate training programs, 1 or 2-year residency programs, fellowship programs, specialty certifications for pharmacists (12 different specialties), and interdisciplinary certifications.

Regulation of Practice

Pharmacist licensure and relicensure, as well as scope of practice, are governed at the state level by individual boards of pharmacy. Licensure indicates that state requirements to practice pharmacy have been met. US candidates for licensure in all states must have graduated an ACPE-accredited pharmacy degree program and pass the North American Pharmacist Licensure Examination (NAPLEX). This competency-based examination applies knowledge gained in pharmacy education to real-life practice situations. All states also require a law examination incorporating both federal and state laws. Foreign pharmacy graduates are required to achieve Foreign Pharmacy Graduate Equivalency Certification (FPGEC), which includes among other requirements an evaluation of the graduate's curriculum, assessment of competence in the English language, and passing of the Foreign Pharmacy Graduate Equivalency Examination (FPGEE) before being eligible to sit for the NAPLEX. Additional details can be obtained from the NABP website (National Association of Board of Pharmacy, 2018)

The federal Food and Drug Administration (FDA) regulates pharmaceutical manufacturing. However, states are the primary regulator of pharmacies. Every state has laws and regulations guiding pharmacy standards and requirements, addressing issues such as required licenses for each facility and for the credentialed pharmacists and other employees who work there. Virtually every state also has requirements for storage, recordkeeping, prescription requirements, labeling, and patient safety among others. The annual NABP Surveys of Pharmacy Law provide a comprehensive summary of state requirements for pharmacy practice and facilities (National Association of Board of Pharmacy, 2017). The practice of pharmacy as governed under state sovereignty is influenced by state legislators and advocacy at the local level.

Oversight (State and Federal) and Quality Assurance (Accreditation) of Education

ACPE provides public recognition that a professional degree program leading to the Doctor of Pharmacy degree is judged to meet established qualifications and educational standards through initial and subsequent periodic evaluations. Accreditation is of educational programs and is different from licensure, which applies to individuals. A directory of programs accredited by ACPE is published and maintained on ACPE's website (Accreditation Council for Pharmacy Education, 2018). The directory includes the accreditation history of the program, the term of accreditation, scheduled monitoring, and any special certification status of the program, such as Probation. ACPE accreditation does not imply or infer that all Doctor of Pharmacy programs are equivalent beyond meeting the expectations of the accreditation standards. Accreditation standards include both quantitative and qualitative parameters.

A professional program is evaluated on the extent to which it accomplishes its stated mission and goals and is consistent with the concept that pharmacy is a unique, personal service profession in the health science field. ACPE is an independent, autonomous, not-for-profit agency, which is recognized by the US Department of Education (USDE) for the accreditation and preaccreditation,

within the United States, of professional degree programs in pharmacy leading to the degree of Doctor of Pharmacy, including those programs offered via distance education.

Pharmacy Practice

Since 1977, the Joint Commission of Pharmacy Practitioners (JCPP) has served as a forum for US pharmacy on matters of common interest and concern to US-based, national organizations of pharmacy practitioners and invited liaison members on professional, educational, legislative, and regulatory issues through analysis, interpretation, communication, and exchange of views on relevant issues. JCPP is where the cross-section of pharmacy organizations occurs. These organizations are focused on achieving the JCPP Vision for Pharmacists' Practice (adopted in 2013): *Patients achieve optimal health and medication outcomes with pharmacists as essential and accountable providers within patient-centered, team-based health care.*

Where able, the Joint Commission has issued position statements to communicate its position on contemporary issues impacting the profession and health-care system. Representatives to the Joint Commission consist of the chief elected and executive officials of the member organizations. During the history of the Commission, this process has allowed participating organizations to adopt identical positions on several major issues. These identical positions are significant because practitioner organizations of the Commission represent pharmacy practitioners from the community and institutional environments, the two largest practice sectors. Where appropriate and feasible, organizations collaborate on cross-profession issues, as well as interprofessional issues working with medicine, nursing, public health, etc.

In 2014, JCPP developed and adopted the *Pharmacists' Patient Care Process* (Joint Commission of Pharmacy Practitioners, 2014). The goal of high quality, cost-effective, and accessible health care for patients is achieved through team-based patient-centered care. Pharmacists are essential members of the health care team. As a result of the profession's evolution, the importance of, and need for, a consistent process of care in the delivery of patient care services has been recognized by the profession. This led JCPP to the development of the patient care process document.

The Relationship Between Practice, Education, and Regulation (Fig. 10)

Obtaining authority, recognition, and coverage for pharmacists' patient care services is a critical element of JCPP's Vision for Pharmacy Practice and has driven collaboration among the various sectors of the profession and health care. Advancements in pharmacist education, credentialing, and certification have positioned pharmacists with the ability to assume greater roles on patients' health-care teams (Council on Credentialing in Pharmacy, 2014). Innovations in practice have supported the advancement of pharmacist education to where expanded pharmacist-provided patient care services have been integrated within school and college accreditation standards and post-graduate continuing education. This has also influenced pharmacy practice laws, regulations and policies on the national, state, and local levels that empower pharmacists to assume expanded roles in patient care. Examples of where this has occurred are medication therapy management (American Pharmacists Association, 2008; Bluml 2005; Cipolle et al., 2012; McInnis et al., 2012) pharmacy-based immunizations, and collaborative practice activities. Several collaborations have been formed by JCPP member organizations and other stakeholders, within and outside of the profession to advance progress toward JCPP's vision. Collaborations within health information (pharmacy-HIT collaborative), quality (PQA—pharmacy quality alliance), and the Patient Access to Pharmacists' Care Coalition (PAPCC) support pharmacists' efforts to attain recognition for and coverage of their quality patient care services.

Resources

- Patient Access to Pharmacists' Patient Care Services: https://pharmacistscare.org/
- Pharmacy Health Information Technology Collaborative: www.pharmacyhit.org
- Pharmacy Quality Alliance (PQA): https://www.pqaalliance.org/

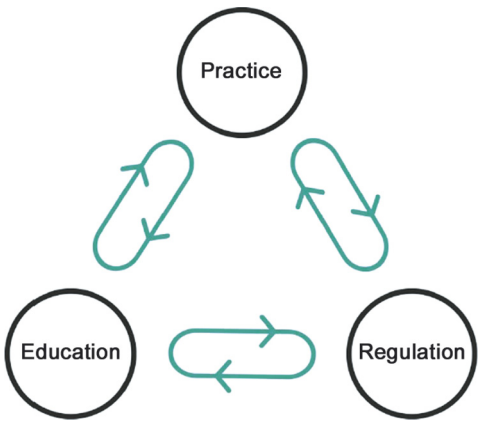

Figure 10 The relationship between practice, education and regulation in the USA.

Drivers for Advancement

- Increased need for improved medication use and outcomes.
- Pharmacists' unique training and expertise.
- Health-care provider shortages and gaps in healthcare service access.
- Collaborative practice agreements and expanding authority.
- Health information technology provides tools that support pharmacist integration in team-based care.
- Collaboration, coordination, and communication among health-care providers.

Barriers to Advancement

- Inconsistency across states and other jurisdictions regarding the practice authority of pharmacists.
- Lack of recognition by other health-care providers, payers, the public and other decision makers regarding pharmacists' delivery of meaningful patient care services.
- Lack of coverage for pharmacists' patient care services and a business model supporting the provision of patient care services.
- Reimbursement of pharmaceutical products has tightened and increased pressure on provider provision of medication use and management services.
- Manpower issues.
- Pharmacist well-being.
- Lack of read/write access to patients' health records.

Important Lessons Learned

- Keep patient needs and desire as the focal point
- Use consistent and understood terminology for describing patient care services provided by pharmacists
- Pharmacists must demonstrate their value
- Pharmacists must document their services
- Educate decision makers regarding pharmacists' education, training, and skillsets and alignment with other health-care team members
- Obtain multidirectional access to patients' health records

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INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

P

Q

R

S

T

U

V

W

X

Y

Z

Page left intentionally blank

AUTHOR INDEX

T

U

V

W

Y

Z